



Ministério da Saúde
Secretaria Executiva
Departamento de Logística em Saúde
Coordenação-Geral de Aquisições de Insumos Estratégicos para Saúde
Coordenação de Licitações e Análise de Mercado de Insumos Estratégicos para Saúde
Divisão de Análise das Aquisições de Insumos Estratégicos para Saúde

CONTRATO Nº 29/2021

Processo nº 25000.175250/2020-85

CONTRATO QUE ENTRE SI
CELEBRAM A UNIÃO, POR
INTERMÉDIO DO DEPARTAMENTO
DE LOGÍSTICA EM SAÚDE DA
SECRETARIA EXECUTIVA DO
MINISTÉRIO DA SAÚDE E A BHARAT
BIOTECH LIMITED INTERNATIONAL,
REPRESENTADA PELA EMPRESA
PRECISA COMERCIALIZAÇÃO DE
MEDICAMENTOS LTDA.

A **UNIÃO** por intermédio do Departamento de Logística em Saúde da Secretaria Executiva do Ministério da Saúde, inscrita no CNPJ sob o nº 00.394.544/0008-51, com sede em Brasília – DF, neste ato representada por seu Diretor, Sr. **ROBERTO FERREIRA DIAS**, portador da Carteira de Identidade RG nº 152.991.800, expedida pela SSP/PR, e inscrito no CPF sob o nº 086.758.087-98, em conformidade com a Portaria nº 262, de 08/01/2019, publicada no Diário Oficial da União nº 6, de 09/01/2019, doravante denominada CONTRATANTE, e de outro lado a empresa **BHARAT BIOTECH LIMITED INTERNATIONAL**, representada pela empresa **PRECISA COMERCIALIZAÇÃO DE MEDICAMENTOS LTDA**, CNPJ: 03.394.819/0005-00, com sede na Avenida Portugal nº 1100, Rua 5, Parte A-14-B, Itaquí, Itapevi/SP, CEP: 06.696-060, doravante denominada CONTRATADA, neste ato representada por **EMANUELA BATISTA DE SOUZA MEDRADES**, portadora da Carteira de Identidade RG nº 354.357.591, expedida pela SSP/SP, e inscrita no CPF nº 330.976.208-42, de acordo com o constante no Processo Eletrônico nº 25000.175250/2020-85, em observância às disposições da Lei nº 8.666, de 21 de junho de 1993 e da Medida Provisória nº 1.026, de 6 de janeiro de 2021, resolvem celebrar o presente Termo de Contrato, por meio da **Dispensa de Licitação nº 10/2021**, com fundamento no Artigo 2º, inciso I, da Medida Provisória nº 1.026/2021 e mediante as cláusulas e condições a seguir enunciadas:

1. CLÁUSULA PRIMEIRA – DO OBJETO

1.1. O objeto do presente Termo de Contrato é a aquisição de VACINA, COVID-19 (CORONAVÍRUS, SARS-COV-2), INJETÁVEL (Covaxin/BBV152), conforme especificações estabelecidas no Termo de Referência e na proposta final, as quais integram este instrumento, independente de transcrição.

1.2. Discriminação do objeto:

| Item | Descrição do Item (Objeto) | CATMAT | Unidade de Medida | Quantidade | Valor unitário |
|------|--|-----------|-------------------|------------|----------------|
| 1 | VACINA, COVID-19 (CORONAVÍRUS, SARS-COV-2), INJETÁVEL (Covaxin/BBV152) | BR0475096 | Doses | 20.000.000 | US\$ 15,00 |

1.3. A CONTRATANTE terá o direito de exclusividade/preferência na aquisição de doses da VACINA, COVID-19 (CORONAVÍRUS, SARS-COV-2), INJETÁVEL (Covaxin/BBV152), produzidas ou importadas pela Contratada em todo o território nacional, enquanto durar a pandemia.

1.4. A CONTRATANTE poderá autorizar em caráter excepcional a comercialização pela Contratada de doses da VACINA, COVID-19 (CORONAVÍRUS, SARS-COV-2), INJETÁVEL (Covaxin/BBV152), devendo, para tanto, ser notificada formalmente sobre a intenção de venda com antecedência mínima de 20 (vinte) dias da data prevista para contratação junto a outro ente, sobre a intenção de venda, com a devida justificativa.

1.5. A CONTRATANTE deverá se manifestar sobre a autorização de comercialização/venda no prazo máximo de 05 (cinco) dias a contar da data do protocolo da notificação formal.

2. CLÁUSULA SEGUNDA – DA FORMA DE FORNECIMENTO

2.1. Cronograma de entrega:

| VACINA, COVID-19 (CORONAVÍRUS, SARS-COV-2), INJETÁVEL | | |
|---|----------------------|---------------------------------------|
| PARCELA | QUANTITATIVO (DOSES) | PRAZO MÁXIMO DE ENTREGA (ATÉ) |
| 1ª | 4.000.000 | 20 dias após a assinatura do Contrato |
| 2ª | 4.000.000 | 30 dias após a assinatura do Contrato |
| 3ª | 4.000.000 | 45 dias após a assinatura do Contrato |
| 4ª | 4.000.000 | 60 dias após a assinatura do Contrato |
| 5ª | 4.000.000 | 70 dias após a assinatura do Contrato |
| TOTAL | 20.000.000 | |

2.2. A CONTRATANTE poderá anuir com a alteração do cronograma, desde que verificada a ausência de culpa da CONTRATADA em possível atraso injustificado.

2.3. Havendo necessidade de prorrogação ou antecipação no cronograma, ou do quantitativo da respectiva parcela de entrega, caberá à CONTRATADA encaminhar ofício com embasamento técnico e justificativas, incumbindo à CONTRATANTE se manifestar quanto ao impacto da alteração e o aceite ou não da nova proposta, de acordo com o interesse da Administração.

2.4. Os ofícios de prorrogação dos cronogramas, ou de alteração dos quantitativos das parcelas, somente serão apreciados se encaminhados com antecedência mínima de 30 (trinta) dias da data prevista para a entrega de cada parcela, ressalvados os casos fortuitos ou de força maior.

2.5. O quantitativo final do lote a ser entregue deverá ser confirmado por ofício ao Ministério da Saúde com a antecedência mínima de dois dias úteis antes da data de entrega, sem prejuízo ao exposto do item anterior.

3. **CLÁUSULA TERCEIRA – DA VIGÊNCIA**

3.1. O prazo de vigência deste Termo de Contrato inicia-se na data de sua assinatura e vigorará por 12 (doze) meses, prorrogáveis, nos termos do artigo 57, §1º, da Lei nº 8.666 de 1993.

4. **CLÁUSULA QUARTA – DO PREÇO**

4.1. O valor total do presente Termo de Contrato é de US\$ 300.000.000,00 (trezentos milhões de dólares americanos), que convertidos na hipótese de US\$ 1,00 para R\$ 5,38 perfaz o valor total estimado de R\$ 1.614.000.000,00 (um bilhão, seiscentos e quatorze milhões de reais).

4.2. No valor acima estão incluídas todas as despesas ordinárias diretas e indiretas decorrentes da execução contratual, inclusive tributos e/ou impostos, encargos sociais, trabalhistas, previdenciários, fiscais e comerciais incidentes, taxa de administração, frete, seguro e outros necessários ao cumprimento integral do objeto da contratação.

5. **CLÁUSULA QUINTA – DA DOTAÇÃO ORÇAMENTÁRIA**

5.1. As despesas decorrentes desta contratação estão programadas em dotação orçamentária própria, prevista no orçamento da União, para o exercício de 2021, na classificação abaixo:

Gestão/Unidade: 00001/250005

Fonte: Decreto nº 10.595 de 07/01/2021.

Programa de Trabalho: 10.122.5018.21C0.6500

Elemento de Despesas: 33.90.30.

5.2. No exercício seguinte, se for o caso, as despesas correrão à conta dos recursos próprios para atender às despesas da mesma natureza, cuja alocação será feita no início de cada exercício financeiro, recursos já destacados e aprovados por Medida Provisória no exercício de 2020.

6. **CLÁUSULA SEXTA – DO PAGAMENTO**

6.1. O pagamento só será feito uma vez concluída a análise e a eventual aprovação integral pela Anvisa, para uso emergencial e temporário e/ou registro definitivo.

6.2. O pagamento à CONTRATADA, que apresentar proposta de preço em moeda estrangeira, será realizado no prazo máximo de até 30 (trinta) dias, contados a partir da apresentação dos documentos que comprovem a efetiva entrega do objeto contratado (AWB, Invoice, Packing-list) na Coordenação de Execução Orçamentária e Financeira – CEOF, que providenciará a autorização do

responsável pelo Departamento de Logística em Saúde - DLOG, de acordo com as normas internas em vigor.

6.2.1. No caso de entregas efetuadas antes da aprovação integral pela Anvisa, para uso emergencial e temporário e/ou registro definitivo, o prazo de que trata o subitem anterior somente será iniciado após, cumulativamente, serem efetivadas tanto a aprovação em questão, em qualquer modalidade, quanto a entrega do objeto a ser pago.

6.3. Para cada parcela liquidada, será pago pela CONTRATANTE à Instituição Financeira, responsável pela realização da operação de contratação cambial, comissão bancária sobre o valor da operação a ser realizada.

6.4. A CONTRATADA brasileira que apresentar proposta de preço em moeda estrangeira terá o pagamento efetuado em moeda brasileira à taxa de câmbio vigente, PTAX, fornecida pelo Banco Central do Brasil (www.bcb.gov.br) no dia útil imediatamente anterior à data do efetivo pagamento. Para tal, se fará necessária a apresentação de uma nova Nota Fiscal Complementar contemplando a diferença decorrente da variação cambial a maior. Na hipótese de o câmbio estar a menor, será necessária a glosa do valor.

6.5. Os pagamentos decorrentes de despesas cujos valores não ultrapassem o limite de que trata o inciso II do art. 24 da Lei 8.666, de 1993, deverão ser efetuados no prazo de até 5 (cinco) dias úteis, contados da data da apresentação da Nota Fiscal, nos termos do art. 5º, § 3º, da Lei nº 8.666, de 1993.

6.6. Considera-se ocorrido o recebimento da nota fiscal ou fatura no momento em que o órgão contratante atestar a execução do objeto do contrato.

6.7. A Nota Fiscal ou Fatura deverá ser obrigatoriamente acompanhada da comprovação da regularidade fiscal, constatada por meio de consulta on-line ao SICAF ou, na impossibilidade de acesso ao referido Sistema, mediante consulta aos sítios eletrônicos oficiais ou à documentação mencionada no art. 29 da Lei nº 8.666, de 1993.

6.8. Constatando-se, junto ao SICAF, a situação de irregularidade do fornecedor contratado, deverão ser tomadas as providências previstas no art. 31 da Instrução Normativa nº 3, de 26 de abril de 2018.

6.9. Havendo erro na apresentação da Nota Fiscal ou dos documentos pertinentes à contratação, ou, ainda, circunstância que impeça a liquidação da despesa, como, por exemplo, obrigação financeira pendente, decorrente de penalidade imposta ou inadimplência, o pagamento ficará sobrestado até que a Contratada providencie as medidas saneadoras. Nesta hipótese, o prazo para pagamento iniciar-se-á após a comprovação da regularização da situação, não acarretando qualquer ônus para a Contratante.

6.10. Será considerada data do pagamento o dia em que constar como emitida a ordem bancária para pagamento.

6.11. Antes de cada pagamento à contratada, será realizada consulta ao SICAF para verificar a manutenção das condições de habilitação exigidas no TR.

6.12. Constatando-se, junto ao SICAF, a situação de irregularidade da contratada, será providenciada sua notificação, por escrito, para que, no prazo de 5 (cinco) dias úteis, regularize sua situação ou, no mesmo prazo, apresente sua defesa. O prazo poderá ser prorrogado uma vez, por igual período, a critério da contratante.

6.13. Previamente à emissão de nota de empenho e a cada pagamento, a Administração deverá realizar consulta ao SICAF para identificar possível suspensão temporária de participação em licitação, no âmbito do órgão ou entidade, proibição de contratar com o Poder Público, bem como ocorrências

impeditivas indiretas, observado o disposto no art. 29, da Instrução Normativa nº 3, de 26 de abril de 2018.

6.14. Não havendo regularização ou sendo a defesa considerada improcedente, a contratante deverá comunicar aos órgãos responsáveis pela fiscalização da regularidade fiscal quanto à inadimplência da contratada, bem como quanto à existência de pagamento a ser efetuado, para que sejam acionados os meios pertinentes e necessários para garantir o recebimento de seus créditos.

6.15. Persistindo a irregularidade, a contratante deverá adotar as medidas necessárias à rescisão contratual nos autos do processo administrativo correspondente, assegurada à contratada a ampla defesa.

6.16. Havendo a efetiva execução do objeto, os pagamentos serão realizados normalmente, até que se decida pela rescisão do contrato, caso a contratada não regularize sua situação junto ao SICAF.

6.17. Será rescindido o contrato em execução com a contratada inadimplente no SICAF, salvo por motivo de economicidade, segurança nacional ou outro de interesse público de alta relevância, devidamente justificado, em qualquer caso, pela máxima autoridade da contratante.

6.18. Quando do pagamento, será efetuada a retenção tributária prevista na legislação aplicável.

6.19. A Contratada regularmente optante pelo Simples Nacional, nos termos da Lei Complementar nº 123, de 2006, não sofrerá a retenção tributária quanto aos impostos e contribuições abrangidos por aquele regime. No entanto, o pagamento ficará condicionado à apresentação de comprovação, por meio de documento oficial, de que faz jus ao tratamento tributário favorecido previsto na referida Lei Complementar.

6.20. Nos casos de eventuais atrasos de pagamento, desde que a Contratada não tenha concorrido, de alguma forma, para tanto, fica convencionado que a taxa de compensação financeira devida pela Contratante, entre a data do vencimento e o efetivo adimplemento da parcela, é calculada mediante a aplicação da seguinte fórmula:

$EM = I \times N \times VP$, sendo:

EM = Encargos moratórios;

N = Número de dias entre a data prevista para o pagamento e a do efetivo pagamento;

VP = Valor da parcela a ser paga.

I = Índice de compensação financeira = 0,00016438, assim apurado:

| | | |
|------------|--|--|
| $I = (TX)$ | $I = \left(\frac{6}{100} \right) \frac{1}{365}$ | $I = 0,00016438$ $TX = \text{Percentual da taxa anual} = 6\%$ |
|------------|--|--|

7. CLÁUSULA SÉTIMA - DA GARANTIA DE EXECUÇÃO

7.1. A CONTRATADA, no prazo de 10 dias após a assinatura do Termo de Contrato ou aceite do instrumento equivalente, prestará garantia no valor de US\$ 15.000.000,00 (quinze milhões de dólares americanos), que convertidos na hipótese de US\$ 1,00 para R\$ 5,38 perfaz o valor total estimado de R\$ 80.700.000,00 (oitenta milhões e setecentos mil reais) correspondente a 5% do valor do Contrato, que será liberada de acordo com as condições previstas no Termo de Referência, conforme disposto no art. 56 da Lei nº 8.666, de 1993, desde que cumpridas as obrigações contratuais.

7.2. Caberá ao contratado optar por uma das seguintes modalidades de garantia:

7.2.1. Caução em dinheiro ou em títulos da dívida pública, devendo estes ter sido emitidos sob a forma escritural, mediante registro em sistema centralizado de liquidação e de custódia autorizado pelo Banco Central do Brasil e avaliados pelos seus valores econômicos, conforme definido pelo Ministério da Fazenda;

7.2.2. Seguro-garantia;

7.2.3. Fiança bancária.

7.3. A garantia em dinheiro deverá ser efetuada em favor da Contratante, na Caixa Econômica Federal, com correção monetária, em favor do contratante.

7.4. No caso de alteração do valor do contrato, ou prorrogação de sua vigência, a garantia deverá ser readequada ou renovada nas mesmas condições.

7.5. Se o valor da garantia for utilizado total ou parcialmente em pagamento de qualquer obrigação, a Contratada obriga-se a fazer a respectiva reposição no prazo máximo de 10 dias úteis, contados da data em que for notificada.

7.6. A Contratante executará a garantia na forma prevista na legislação que rege a matéria.

7.7. A garantia prestada pelo contratado será liberada ou restituída após a execução do contrato e, quando em dinheiro, atualizada monetariamente. (artigo 56, §4º da Lei nº 8666/93).

8. **CLÁUSULA OITAVA – DO REAJUSTE**

8.1. As regras acerca do reajuste do valor contratual são as estabelecidas no Termo de Referência.

9. **CLÁUSULA NONA – DAS ALTERAÇÕES**

9.1. Eventuais alterações contratuais reger-se-ão pela disciplina do art. 65 da Lei nº 8.666, de 1993.

9.2. A CONTRATADA é obrigada a aceitar, nas mesmas condições contratuais, os acréscimos ou supressões que se fizerem necessários, até o limite de 50% (cinquenta por cento) do valor inicial atualizado do contrato, conforme o art. 9º da MP 1.026 de 2021.

10. **CLÁUSULA DÉCIMA – CRITÉRIO DE ACEITAÇÃO DO OBJETO, ENTREGA E RECEBIMENTO**

10.1. OS CRITÉRIOS DE ACEITAÇÃO DO OBJETO são aqueles previstos no Termo de Referência.

10.2. DO LOCAL DE ENTREGA:

10.2.1. As entregas das parcelas deverão ser realizadas de forma centralizada no Almoxarifado do Ministério da Saúde em São Paulo no endereço abaixo:

a) Produtos FÁRMACO (Medicamentos/Vacinas/insumos relacionados):

b) Endereço: Rua Jamil João Zarif, nº 684, Jardim Santa Vicência, UNIDADES 11 A 17 e 18ª –Guarulhos – SP

c) CEP: 07.143-000.

d) E-mail para agendamento: c_glog.agendamento@saude.gov.br

10.2.2. A Contratada deverá agendar cada entrega, entrando em contato com a área responsável através do telefone: (61) 3315-7770 ou (61) 3315.3582.

10.3. DO RECEBIMENTO DO OBJETO:

10.3.1. Nos termos do art. 73, inciso II, alíneas a e b da lei nº 8.666/93, os imunobiológicos, objeto desta aquisição, serão recebidos da seguinte forma:

10.3.2. Os bens serão recebidos provisoriamente no prazo de 1 dia, pelo(a) responsável pelo acompanhamento e fiscalização do contrato, para efeito de posterior verificação de sua conformidade com as especificações constantes neste Termo de Referência e na proposta.

10.3.3. Os bens poderão ser rejeitados, no todo ou em parte, quando em desacordo com as especificações constantes neste Termo de Referência e na proposta, devendo ser substituídos no prazo de 15 dias, a contar da notificação da contratada, às suas custas, sem prejuízo da aplicação das penalidades.

10.3.4. Os bens serão recebidos definitivamente no prazo de 15 dias, contados do recebimento provisório, após a verificação da qualidade pelo INCQS e quantidade do material e consequente aceitação mediante termo circunstanciado.

10.3.5. Na hipótese de a verificação a que se refere o subitem anterior não ser procedida dentro do prazo fixado, reputar-se-á como realizada, consumando-se o recebimento definitivo no dia do esgotamento do prazo.

10.3.6. O recebimento provisório ou definitivo do objeto não exclui a responsabilidade da contratada pelos prejuízos resultantes da incorreta execução do contrato.

11. CLÁUSULA DÉCIMA PRIMEIRA – DO CONTROLE E DA FISCALIZAÇÃO (CRITÉRIO DE MEDIÇÃO)

11.1. Nos termos do art. 67 Lei nº 8.666, de 1993, será designado representante para acompanhar e fiscalizar a entrega dos bens, anotando em registro próprio todas as ocorrências relacionadas com a execução e determinando o que for necessário à regularização de falhas ou defeitos observados.

11.2. O recebimento de material de valor superior a R\$ 176.000,00 (cento e setenta e seis mil reais) será confiado a uma comissão de, no mínimo, 3 (três) membros, designados pela autoridade competente.

11.3. A CONTRATANTE indicará um fiscal de contrato ou comissão, que será responsável pelo acompanhamento e fiscalização da execução, conforme Portaria GM nº 78/2006 e Circular MS/SE/GAB nº 40, emitida pelo Gabinete da Secretaria Executiva, assim como artigos. 67 e 73 da Lei nº 8.666/1993. 9.3.

11.4. O Fiscal/comissão do contrato deverá manter permanente vigilância sobre as obrigações da CONTRATADA, definidas nos dispositivos contratuais e condições do Termo de Referência e, fundamentalmente, quanto à inarredável observância aos princípios e preceitos consubstanciados na Lei nº 8.666/93, com suas alterações.

11.5. A fiscalização de que trata este item não exclui nem reduz a responsabilidade da Contratada, inclusive perante terceiros, por qualquer irregularidade, ainda que resultante de

imperfeições técnicas ou vícios redibitórios, e, na ocorrência desta, não implica em corresponsabilidade da Administração ou de seus agentes e prepostos, de conformidade com o art. 70 da Lei nº 8.666, de 1993.

11.6. O representante da Administração anotará em registro próprio todas as ocorrências relacionadas com a execução do contrato, indicando dia, mês e ano, bem como o nome dos funcionários eventualmente envolvidos, determinando o que for necessário à regularização das falhas ou defeitos observados e encaminhando os apontamentos à autoridade competente para as providências cabíveis.

12. CLÁUSULA DÉCIMA SEGUNDA – DAS OBRIGAÇÕES DA CONTRATANTE E DA CONTRATADA

12.1. As obrigações da CONTRATANTE e da CONTRATADA são aquelas previstas no Termo de Referência.

13. CLÁUSULA DÉCIMA TERCEIRA – DAS SANÇÕES ADMINISTRATIVAS

13.1. As sanções referentes à execução do contrato são aquelas previstas no Termo de Referência.

14. CLÁUSULA DÉCIMA QUARTA - DA SUSPENSÃO

14.1. Caso a Anvisa suspenda a produção e o uso da vacina, automaticamente ficarão suspensas a execução e as obrigações previstas no presente instrumento.

15. CLÁUSULA DÉCIMA QUINTA – DA RESCISÃO

15.1. O presente Termo de Contrato poderá ser rescindido:

15.1.1. Por ato unilateral e escrito da Administração, nas situações previstas nos incisos I a XII e XVII do art. 78 da Lei nº 8.666, de 1993, e com as consequências indicadas no art. 80 da mesma Lei, sem prejuízo da aplicação das sanções previstas no Termo de Referência, anexo ao Edital;

15.1.2. Amigavelmente, nos termos do art. 79, inciso II, da Lei nº 8.666, de 1993;

15.1.3. Caso a Contratada não consiga a autorização para uso emergencial junto à Anvisa, nesta hipótese, sem qualquer ônus para a Contratante, não sendo devido, sequer, o pagamento pelas parcelas eventualmente entregues;

15.1.4. Caso, após a autorização para uso emergencial e antes da completa execução do contrato, a ANVISA não registre o produto e/ou revogue a autorização para uso emergencial, nessa hipótese, sem ônus para a Contratante em relação às doses ainda não entregues. Quanto às doses já entregues e não administradas, a Contratante será ressarcida pelo valor pago.

15.1.5. Por perda da autorização regulatória expedida pela ANVISA;

15.1.6. Pela falta de eficácia da vacina contra variantes que se tornem prevalentes em território nacional, em grau tal que impeça de atingir a efetiva imunidade de rebanho por vacinação na população brasileira

15.2. Os casos de rescisão contratual serão formalmente motivados, assegurando-se à

CONTRATADA o direito à prévia e ampla defesa.

15.3. A CONTRATADA reconhece os direitos da CONTRATANTE em caso de rescisão administrativa prevista no art. 77 da Lei nº 8.666, de 1993.

15.4. O termo de rescisão será precedido de Relatório indicativo dos seguintes aspectos, conforme o caso :

15.4.1. Balanço dos eventos contratuais já cumpridos ou parcialmente cumpridos;

15.4.2. Relação dos pagamentos já efetuados e ainda devidos;

15.4.3. Indenizações e multas.

16. CLÁUSULA DÉCIMA SEXTA – DAS VEDAÇÕES E PERMISSÕES

16.1. É vedado à CONTRATADA interromper a execução do contrato sob alegação de inadimplemento por parte da CONTRATANTE, salvo nos casos previstos em lei.

16.2. É permitido à CONTRATADA caucionar ou utilizar este Termo de Contrato para qualquer operação financeira, nos termos e de acordo com os procedimentos previstos na Instrução Normativa SEGES/ME nº 53, de 8 de julho de 2020.

16.3. A cessão de crédito, a ser feita mediante celebração de termo aditivo, dependerá de comprovação da regularidade fiscal e trabalhista da cessionária, bem como da certificação de que a cessionária não se encontra impedida de licitar e contratar com o Poder Público, conforme a legislação em vigor, nos termos do Parecer JL-01, de 18 de maio de 2020.

16.4. A crédito a ser pago à cessionária é exatamente aquele que seria destinado à cedente (contratada) pela execução do objeto contratual, com o desconto de eventuais multas, glosas e prejuízos causados à Administração, sem prejuízo da utilização de institutos tais como os da conta vinculada e do pagamento direto previstos na IN SEGES/ME nº 5, de 2017, caso aplicáveis.

17. CLÁUSULA DÉCIMA SÉTIMA – DOS CASOS OMISSOS

17.1. Os casos omissos serão decididos pela CONTRATANTE, segundo as disposições contidas na Medida Provisória nº 1.026 de 2021; na Lei nº 8.666 de 1993, na Lei nº 10.520 de 2002 e demais normas federais de licitações e contratos administrativos e, subsidiariamente, segundo as disposições contidas na Lei nº 8.078, de 1990 - Código de Defesa do Consumidor - e normas e princípios gerais dos contratos.

18. CLÁUSULA DÉCIMA OITAVA – DA APROVAÇÃO DA DISPENSA DE LICITAÇÃO

18.1. A lavratura do presente Contrato referente à **Dispensa de Licitação nº 10/2021**, com base no artigo 2º, inciso I, da Medida Provisória nº 1.026, de 6 de janeiro de 2021, foi publicada no Diário Oficial - Edição Extra em 19/02/2021, conforme determinado pelo caput do artigo 26 da Lei 8.666/93.

18.2. Incumbirá à CONTRATANTE, no prazo de cinco dias úteis contados da assinatura deste instrumento, providenciar a disponibilização, em sítio oficial específico na rede mundial de computadores (internet), do ato de autorização da contratação direta, bem como as disposições da Medida Provisória nº 1.026, de 6 de janeiro de 2021, observados, no que couber, os requisitos previstos

no § 3º do art. 8º da Lei nº 12.527, de 18 de novembro de 2011.

18.3. O presente Termo de Contrato se vincula ao Termo de Referência da Contratante e à proposta da Contratada.

19. CLÁUSULA DÉCIMA NONA – ALTERAÇÃO SUBJETIVA

19.1. É admissível a fusão, cisão ou incorporação da contratada com/em outra pessoa jurídica, desde que sejam observados pela nova pessoa jurídica todos os requisitos de habilitação exigidos na contratação; sejam mantidas as demais cláusulas e condições do contrato; não haja prejuízo à execução do objeto pactuado e haja a anuência expressa da Administração à continuidade do contrato.

20. CLÁUSULA VIGÉSIMA - DA SUBCONTRATAÇÃO

20.1. Não será admitida a subcontratação do objeto do Contrato.

21. CLÁUSULA VIGÉSIMA PRIMEIRA - DO FORO

21.1. É eleito o Foro da Judiciária do Distrito Federal - Justiça Federal para dirimir os litígios que decorrerem da execução deste Termo de Contrato que não possam ser compostos pela conciliação, conforme art. 55, §2º da Lei nº 8.666/93.

E, para firmeza e prova de assim haverem, entre si, ajustado e acordado, após ter sido lido juntamente com seu(s) anexo(s), o presente Contrato é assinado eletronicamente pelas partes.

22. TESTEMUNHAS

Marcelo Batista Costa

CPF: 052.126.897-40

Departamento de Logística em Saúde - DLOG/SE

Túlio Belchior Mano da Silveira

CPF: 189.185.558-14

Precisa Comercialização de Medicamentos Ltda.



Documento assinado eletronicamente por **TÚLIO BELCHIOR MANO DA SILVEIRA, Usuário Externo**, em 25/02/2021, às 14:28, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



Documento assinado eletronicamente por **Emanuela Batista de Souza Medrades, Usuário Externo**, em 25/02/2021, às 14:31, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



Documento assinado eletronicamente por **Roberto Ferreira Dias, Diretor(a) do Departamento de Logística**, em 25/02/2021, às 16:28, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



Documento assinado eletronicamente por **Marcelo Batista Costa, Coordenador(a)-Geral de Aquisições de Insumos Estratégicos para Saúde substituto(a)**, em 25/02/2021, às 16:22, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



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Referência: Processo nº 25000.175250/2020-85

SEI nº 0019155275

Divisão de Análise das Aquisições de Insumos Estratégicos para Saúde - DIVAN
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa, Brasília/DF, CEP 70058-900
Site - saude.gov.br



Ministério da Saúde
Secretaria Executiva
Departamento de Logística em Saúde

OFÍCIO Nº 62/2021/DLOG/SE/MS

Brasília, 22 de março de 2021.

Ao Senhor

ANTONIO BARRA TORRES

Diretor-Presidente da Agência Nacional de Vigilância Sanitária- GADIP

SIA, Trecho 5, Área Especial 57, Lote 200, Bloco A/B, 1º Andar

CEP.: 71205-050

Telefones: (61) 3462-4342

Email: gabinete.presidencia@anvisa.gov.br

Assunto: Solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN

Senhor Diretor Presidente,

1. Considerando Decreto Legislativo nº 06 de 20 de março de 2020 que ratifica o Reconhecimento, para os fins do art. 65 da Lei Complementar nº 101, de 4 de maio de 2000, a ocorrência do estado de calamidade pública, nos termos da solicitação do Presidente da República encaminhada por meio da Mensagem nº 93, de 18 de março de 2020;
2. Considerando trata-se de processo de aquisição celebrado entre este Ministério da Saúde (MS) e a empresa BHARAT BIOTECH LIMITED INTERNATIONAL, representada pela empresa PRECISA COMERCIALIZAÇÃO DE MEDICAMENTOS LTDA, CNPJ: 03.394.819/0005-00, com sede na Avenida Portugal nº 1100, Rua 5, Parte A-14-B, Itaquí, Itapevi/SP, CEP: 06.696-060, pelo instrumentado Contrato 29/2021 para aquisição de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN/BBV152 divididos em 05 (cinco) parcelas de 4.000.000 (quatro milhões) cada.
3. Considerando que o fabricante **BHARANT BIOTECH INTERNATIONAL LIMITED (BBIL)** localizado na **Genome Valley, Shameerpt, Hyderabad, Telangana, Índia**, não possui registro sanitário junto a Agência Nacional de Vigilância Sanitária (ANVISA);
4. Considerando o disposto nos Art. 4º e 5ª da Resolução da Diretoria Colegiada (RDC) nº 476, de 10 de março de 2021 que:

"Estabelece os procedimentos e requisitos para submissão de pedido de autorização excepcional e temporária para importação e distribuição de

medicamentos e vacinas contra Covid19 para o enfrentamento da emergência de saúde pública de importância nacional decorrente do surto do novo coronavírus (SARS-CoV-2), nos termos da Lei nº 14.124, de 10 de março de 2021". e

5. Considerando tratar-se de insumo essencial para o enfrentamento da Pandemia de SARS-COV-2, este Departamento de Logística (DLOG/SE-MS), vem por meio deste, *mui respeitosamente*, solicitar a Vossa Senhoria autorização para esta importação **EM CARÁTER EXCEPCIONAL das 20.000.000 (vinte milhões) de doses**, objeto do contrato em questão, afim de seja dada a devida continuidade deste processo.

6.

Atenciosamente,

ROBERTO FERREIRA DIAS

Diretor do Departamento de Logística em Saúde



Documento assinado eletronicamente por **Roberto Ferreira Dias, Diretor(a) do Departamento de Logística**, em 22/03/2021, às 15:07, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



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Referência: Processo nº 25000.043170/2021-42

SEI nº 0019668812

Departamento de Logística em Saúde - DLOG
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa, Brasília/DF, CEP 70058-900
Site - saude.gov.br

F. No. BIO/MA/20/000103
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FDA Bhawan, Kotla Road,
New Delhi- 110002

Dated: 11/3/2021

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500078.

Subject- Permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in Form CT-23 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940 - regarding.

Reference:

1. Permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021.
2. Your letter nos. BBIL/RA/21/173, 177, 187 dated 06.03.2021, 08.03.2021 & 10.03.2021 submitted to this office vide email dated 06.03.2021, 08.03.2021 & 10.03.2021.


Sir,

This is with reference to the permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021 to manufacture Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in public interest use in as an abundant precaution, in clinical trial mode with various conditions.

In this regard, the interim safety and efficacy data of phase III clinical trial of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) in the country submitted to this office was reviewed in consultation with SEC (COVID-19) committee on 08.03.2021 & 10.03.2021 respectively, wherein after detailed deliberation the committee recommended for omission of the condition of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation condition. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The firm should update the prescribing information and factsheet accordingly (under restricted use in emergency situation condition). All other conditions of the marketing authorisation shall continue to remain the same.

Accordingly, based on the recommendations of SEC, the condition "*This permission is for restricted use in emergency situation in public interest use in as an abundant precaution, in clinical trial mode*" as mentioned in the said permission is amended to read as "*This permission is for restricted use in emergency situation in public interest*". However, you are required to continue ongoing Phase III clinical trial as per approved clinical trial protocol & submit revised summary of product characteristics (SmPC), Prescribing Information (PI) and Factsheet.

Yours faithfully,


(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Drugs Controller Telangana, Directorate of Drug Control Administration, Drug Control Bhavan, Vengal Rao Nagar, Hyderabad-500 038, India.

New Delhi-110002
Date: 17/3/2021

Ms. Bharat Biotech International Ltd.,
Genome Valley, Shamshabad,
Hyderabad, India - 500078.

Subject: Permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in Form CT-33 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940 - regarding.

Reference:

1. Permission granted by the Directorate in Form CT-33 vide no. MF/BIC/1/00003 dated 03.01.2021.
2. Your letter no. BIL/BIA/21/177, dt. 08.03.2021, 08.03.2021 & 10.03.2021 submitted to this office vide email dated 08.03.2021, 08.03.2021 & 10.03.2021.

Sir,

This is with reference to the permission granted by the Directorate in Form CT-33 vide no. MF/BIC/1/00003 dated 03.01.2021 to manufacture Whole-virion inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in public interest use as an adjunct product in clinical trial mode with various conditions.

In this regard, the interim safety and efficacy data of phase III clinical trial of Whole Virion, Inactivated Coronavirus Vaccine (BBV152) in the country submitted to this office was reviewed in consultation with SEC (BIVD-18) committee on 08.03.2021 & 10.03.2021 respectively, wherein after detailed deliberation the committee recommended for omission of the restriction of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The trial should update the presiding information and label as per the restricted use in emergency situation condition. All other conditions of the marketing authorization shall continue to remain the same.

Accordingly, based on the recommendations of SEC, the condition "This permission is for restricted use in emergency situation in public interest use as an adjunct product, in clinical trial mode" as mentioned in the said permission is amended to read as "This permission is for restricted use in emergency situation in public interest. However, you are required to continue ongoing Phase III clinical trial as per approved clinical trial protocol & submit revised summary of product characteristics (SPC), Prescribing Information (PI) and Package Insert.

Yours faithfully,
/s/

(Dr. V. G. Srinivas)
Drugs Controller General (India)
Central Licensing Authority

File No: BIO/MA/20/000103
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FDA Bhawan, Kotla Road,
New Delhi- 110002.
Dated: 8/11/2021

To,

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500 078.

Subject: Request for amend the Form CT-23 for permission to manufacture Whole Virion, Inactivated Corona Virus Vaccine (BBV152) for sale and distribution – regarding.

References:

1. Your letter vide no. BBIL/RA/20/006 dated 05.01.2021 submitted to this office vide diary no. 120 dated 06.01.2021.
2. Permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021.

Sir/Madam,

With reference to the subject cited above and based on the submission of information/documents to this office, the name of product code of Whole Virion, Inactivated Corona Virus Vaccine mentioned in the cover letter and permission is hereby amended to read as "BBV152" instead of BBV152C or BBV152B respectively.

Further, as per the license issued in Form 28D, 2.5ml, 5ml & 10 ml vial presentations, are also permitted subject to condition mentioned in permission, license & communication in this regard including the provisions of New Drugs and & Clinical trials Rules, 2019 under Drugs and Cosmetics Act, 1940.

Yours faithfully,

V.G.S

(Dr. V. G. Somani)
Drugs Controller General (India)

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Director, CDL, Kasauli, HP



सत्यमेव जयते

File No. BIO/MA/20/000103

From:

**The Drugs Controller General, India
Directorate General of Health Services**

FDA Bhawan, Kotla Road,
New Delhi- 110002, India.
Dated: 03-JAN-2021

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500 078.

Subject: Application for permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152C) for restricted use in emergency situation in Form CT-23 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940- regarding.

Reference: SUGAM application no. BIO/CT21/FF/2020/22922 dated 07-Dec-2020.

Sir,

Please find enclosed herewith permission no. MF/BIO/21/000002 dated 03-Jan-2021 in Form CT-23 to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152C) for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode as per the provisions of New Drugs and Clinical Trial Rules, 2019 under Drugs & Cosmetics Act, 1940.

Yours faithfully,

VENUGOPAL
GIRDHARILAL
SOMANI

Digitally signed by VENUGOPAL
GIRDHARILAL SOMANI
DN: c=IN, o=MINISTRY OF HOME AFFAIRS,
ou=CDSCO DGHS, postalCode=431401,
serialNumber=25420=173403345df62d489632379a147
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7, cn=VENUGOPAL GIRDHARILAL SOMANI
Date: 2021.01.03 17:43:16 +05'30'

(Dr. V. G. Somani)

**Drugs Controller General (India)
Central Licensing Authority**

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Drugs Controller Telangana, Directorate of Drug Control Administration, Drug Control Bhavan, Vengal Rao Nagar, Hyderabad-500 038, India.

FORM CT-23

(See rules 81, 82, 83 and 84)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licensing Authority hereby grant permission to M/s Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com, Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com to manufacture for sale of pharmaceutical formulation manufactured by a manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this license:

| S. No | Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer). | Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site). | | | | | | |
|----------------|--|---|-----------|------------------------|----------------|----------------------------|--------------|----------------------------|
| 1. | Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com | Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com | | | | | | |
| | | <table border="1"> <thead> <tr> <th>Component</th> <th>Manufacturing facility</th> </tr> </thead> <tbody> <tr> <td>Drug substance</td> <td>• Facility PS2, Building S</td> </tr> <tr> <td>Drug Product</td> <td>• Building A, Facility PA1</td> </tr> </tbody> </table> | Component | Manufacturing facility | Drug substance | • Facility PS2, Building S | Drug Product | • Building A, Facility PA1 |
| Component | Manufacturing facility | | | | | | | |
| Drug substance | • Facility PS2, Building S | | | | | | | |
| Drug Product | • Building A, Facility PA1 | | | | | | | |

3. Details of pharmaceutical formulation:

| Name of the New drug to be manufactured: | Whole Virion Inactivated Corona Virus Vaccine, [BBV152B] | | | | | | | | | | | | | | |
|---|--|--------------------|----------|---|-------|----------------------|----------|---|---------|-----------------|--------|-----------------------------|--------|---------------------------|----------------|
| Dosage form: | Suspension for injection Presentation: single dose glass vial (0.5ml) Route of Administration: Intramuscular | | | | | | | | | | | | | | |
| Composition: | Each dose of 0.5ml contains: <table border="1"> <thead> <tr> <th>Active Ingredients</th> <th>Quantity</th> </tr> </thead> <tbody> <tr> <td>Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770)</td> <td>6 mcg</td> </tr> <tr> <th>Inactive Ingredients</th> <th>Quantity</th> </tr> <tr> <td>Aluminium Hydroxide gel equivalent to Al+++</td> <td>250 mcg</td> </tr> <tr> <td>TLR 7/8 Agonist</td> <td>15 mcg</td> </tr> <tr> <td>2-Phenoxyethanol (2PE) I.P.</td> <td>2.5 mg</td> </tr> <tr> <td>Phosphate Buffered Saline</td> <td>q.s. to 0.5 mL</td> </tr> </tbody> </table> * Produced in Vero cells. | Active Ingredients | Quantity | Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770) | 6 mcg | Inactive Ingredients | Quantity | Aluminium Hydroxide gel equivalent to Al+++ | 250 mcg | TLR 7/8 Agonist | 15 mcg | 2-Phenoxyethanol (2PE) I.P. | 2.5 mg | Phosphate Buffered Saline | q.s. to 0.5 mL |
| Active Ingredients | Quantity | | | | | | | | | | | | | | |
| Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770) | 6 mcg | | | | | | | | | | | | | | |
| Inactive Ingredients | Quantity | | | | | | | | | | | | | | |
| Aluminium Hydroxide gel equivalent to Al+++ | 250 mcg | | | | | | | | | | | | | | |
| TLR 7/8 Agonist | 15 mcg | | | | | | | | | | | | | | |
| 2-Phenoxyethanol (2PE) I.P. | 2.5 mg | | | | | | | | | | | | | | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | | | | | | | | | | | | | | |
| Indication: | For active immunization against Corona Virus Disease (COVID-19) for age ≥18 years when administered in two doses interval of day 0 & day 28. | | | | | | | | | | | | | | |
| Shelf life with storage condition: | 6 months when stored at 2 to 8 °C. | | | | | | | | | | | | | | |

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.
5. This permission is for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode.
6. The firm should provide the protocol for rolling out for the restricted use of the vaccine in emergency situation.
7. The firm should provide the updated prescribing information/ Package Insert and Summary of Product Characteristics (SmPC) for Whole Virion Inactivated Corona Virus Vaccine (BBV152B) and also disseminate the necessary information, instructions and educational materials through their website.
8. The firm should submit updated safety, efficacy & immunogenicity data from the ongoing Phase I, II & III clinical trials till the completion of trials as per requirement of New Drugs & Clinical Trials, 2019.
9. The firm should submit safety data including the data on AEFI and AESI, with due analysis, every 15 days for the first two months & monthly thereafter and also as per requirement of New Drugs & Clinical Trials, 2019.
10. The firm should submit Risk management plan.
11. The firm should submit ongoing stability of commercial scale batches (real time and accelerated) of drug substance & drug product.
12. The permission is subject to condition of satisfactory evaluation & lot release by CDL, Kasauli. Further, each batch/lot of Whole Virion Inactivated Corona Virus Vaccine, (BBV152B) shall be released from Central Drugs Laboratory, Kasauli.

Place: New Delhi
Date: 03-Jan-2021

VENUGOPAL
GIRDHARILA
L SOMANI

Digitally signed by VENUGOPAL GIRDHARILA SOMANI
DN: cn=VENUGOPAL GIRDHARILA SOMANI, o=MINISTRY OF HOME AFFAIRS,
ou=CDSCO DGHE, postalCode=110011,
serialNumber=254, c=IN
254, o=11769331588258991237914118F,
serialNumber=215467981247,
cn=VENUGOPAL GIRDHARILA SOMANI
Date: 2021.01.03 17:42:43 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

DECLARAÇÃO

Ateste de adoção das estratégias de monitoramento e cumprimento das diretrizes de Farmacovigilância nos termos da RDC/ANVISA 476, de 10 de março de 2021 artigo 12 inciso III e Anexo

A **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA.**, pessoa jurídica de direito privado, com endereço na Avenida Portugal, n.º 1100, Rua 5, parte A-14, Bairro Itaquí, Cidade de Itapevi, Estado de São Paulo, CEP 06696-060, CNPJ 03.394.819/0005-00, neste ato representada por **Emanuela Batista de Souza Medrades**, brasileira, farmacêutica, portador do RG 35.435.759-1- SSP-SP e CPF 330.976.208-42, considerando o disposto na Resolução de Diretoria Colegiada - RDC nº 476, de 10 de março de 2021, considerando o disposto na Resolução de Diretoria Colegiada - RDC nº 476, de 10 de março de 2021, o importador, na pessoa de **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA**, CPF/CNPJ 03.392.918/0005-00, **DECLARA** cumprir o disposto nas normas sanitárias vigentes para a importação e distribuição de medicamentos e vacinas para Covid-19. O importador declara que realiza todos os procedimentos necessários e possui capacidade técnica e administrativa para garantir a qualidade, segurança e eficácia do medicamento ou vacina para Covid-19 objeto da importação, bem como adotará as estratégias de monitoramento e cumprirá as diretrizes de farmacovigilância estabelecidas pela Anvisa. O importador, na pessoa de **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA**, se responsabiliza pela veracidade e fidedignidade das informações aqui prestadas e declara que está ciente de que é responsável pela qualidade, segurança e eficácia do medicamento ou vacina para Covid-19, bem como assegura que este está adequado aos fins a que se destina e cumpre os requisitos legais e sanitários. Declaro estar ciente que o descumprimento das disposições contidas nesta Resolução e nas demais vinculadas constitui infração sanitária, nos termos da Lei nº 6437, de 20 de agosto de 1977, sem prejuízo das responsabilidades civil, administrativa e penal cabíveis.

Por ser expressão da verdade, firmamos a presente para que surta os seus efeitos legais.

Brasília/DF, 17 de março de 2021.

EMANUELA BATISTA DE SOUZA MEDRADES

CPF 330.976.208-42

Representante Legal/Técnica

**COVID-19 WHOLE VIRION
INACTIVATED
CORONAVIRUS VACCINE
BBV152**

**INVESTIGATOR'S
BROCHURE FOR PHASE 3
CLINICAL TRIAL**

Version 4.0 Effective Date 08 Mar 2021

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DECLARATION BY RESPONSIBLE SPONSOR REPRESENTATIVE(S)

This Investigator Brochure version # 4.0 with effective from 08 Mar 2021 is authored by:



08.03.2021

Date

This Investigator Brochure was critically and scientifically reviewed, and has been approved by me.



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|--------|--|
| 2-PE | 2-Phenoxyethanol |
| AGMK | African Green Monkey Kidney |
| ATCC | American type culture Collection |
| BBIL | Bharat Biotech International Limited |
| BRM | Bacterial Reverse Mutation |
| BSC | Biosafety Cabinet |
| BP | British Pharmacopoeia |
| CoA | Certificate of Analysis |
| CPCSEA | Committee for the Purpose of Control and Supervision on Experimental Animals |
| CPE | Cytopathic Effect |
| CVS | Control Virus Sample |
| DCG(I) | Drugs Controller General(India) |
| DMSO | Dimethyl Sulphoxide |
| DNA | Deoxyribonucleic Acid |
| DMEM | Dulbecco's Modified Eagle's Medium |
| DSMB | Data Safety Monitoring Board |
| EDTA | Ethylenediamine Tetra Acetic Acid |
| ELISA | Enzyme Linked Immunosorbent Assay |
| EoPC | End of Production Culture |
| EP | European Pharmacopoeia |
| IHS | In-House Specification |
| IP | Indian Pharmacopoeia |
| FBS | Fetal Bovine Serum |
| GCP | Good Clinical Practices |
| GMP | Good Manufacturing Practices |
| HIV | Human Immunodeficiency Virus |
| HTLV | Human T-lymphotropic virus |
| IAEC | Institutional Animal Ethics Committee |
| IBSC | Institutional Biosafety Committee |
| ICH | International Council for Harmonization |
| IM | Intramuscular |
| IPA | Isopropyl Alcohol |
| IPQC | In-Process Quality Control |
| IRB | Institutional Review Board |
| LAF | Laminar Air Flow |
| MCB | Master Cell Bank |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MEM | Minimum Essential Medium,Eagle |
| MOI | Multiplicity of Infection |
| MTD | Mean Time to Death |
| MTD | Maximum Tolerated Dose |
| MVB | Master Virus Bank |
| NA | Not Applicable |
| NGS | Next Generation Sequencing |
| NLT | Not Less Than |
| NMT | Not More Than |
| NOAEL | No Observed Adverse Effect Level |
| NOC | No Objection Certificate |
| NRA | National Regulatory Authority |
| NSP | Non-Structural Protein |

| | |
|--------------------|--|
| OD | Optical Density |
| OECD | Organization for Economic Co-operation and Development |
| PBS | Phosphate Buffered Saline |
| PCR | Polymerase Chain Reaction |
| PERT | Product Enhanced Reverse Transcriptase |
| QA | Quality Assurance |
| QCD | Quality Control Department |
| QPERT | Quantitative Product Enhanced Reverse Transcriptase |
| R&D | Research and Development |
| RDT | Repeat Dose Toxicity |
| RNA | Ribonucleic Acid |
| RT-PCR | Reverse Transcription-Polymerase Chain Reaction |
| SHD | Single Human Dose |
| CCID ₅₀ | 50% Cell Culture Infectious Dose |
| TRS | Technical Report Series |
| USP | United States Pharmacopoeia |
| WCB | Working Cell Bank |
| WFI | Water for Injection |
| WHO | World Health Organization |
| WVB | Working Virus Bank |

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1 INTRODUCTION

1.1 CORONAVIRUS

In December 2019, a novel coronavirus (CoV) started causing illness and death in Wuhan province of China (1). The International Committee on Taxonomy of Viruses (ICTV) named the new virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of its phylogenetically close relationship with SARS-CoV and the disease was named Coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) (2,3). The WHO declared COVID-19 as global pandemic on March 11, 2020 as the number of confirmed cases increased outside China to 13-fold with increasing number of countries affected with the virus to three-fold(4). The number of confirmed cases and mortality keeps on increasing every day and at present (12th Sep 2020), there are about 30 million confirmed cases and 900,000 deaths reported worldwide (WHO) (5).

The first case of laboratory confirmed SARS-Cov-2 was detected on 1stDecember 2019 in Wuhan, China. The initial outbreak reported to occur in the Seafood market in Huanan involving about 41 people. An epidemiological alert was issued on 31st December 2019 to shut down the market on 1stJanuary 2020. The infection then spread many cities and provinces of China. The first exported case from china was detected in Thailand on 13thJanuary 2020 and simultaneously, the disease spread rapidly across many other countries involving 205 countries (6). As of 12th Sep 2020, about 30 million confirmed cases and 900,000 deaths have been reported worldwide involving 216 countries, territories or areas (5).The initial mortality rates for patients in the hospital were estimated to be 11%–15%, but more recent data were 2%–3%. The mortality rate also varies from country to country, co-morbid conditions, isolation practice of the country (6). As of March 08th 2021, the total number confirmed cases of COVID-19 cases and death in India are 11,229,398 and 157,853 deaths, respectively as per the Official data of Govt. of India official data and the first COVID-19 case in Brazil was reported on Feb 26, 2020, in the city of São Paulo, and as of 2 Feb 2021, approximately 224,504 deaths and 9,204,731 Cases have been reported (7).

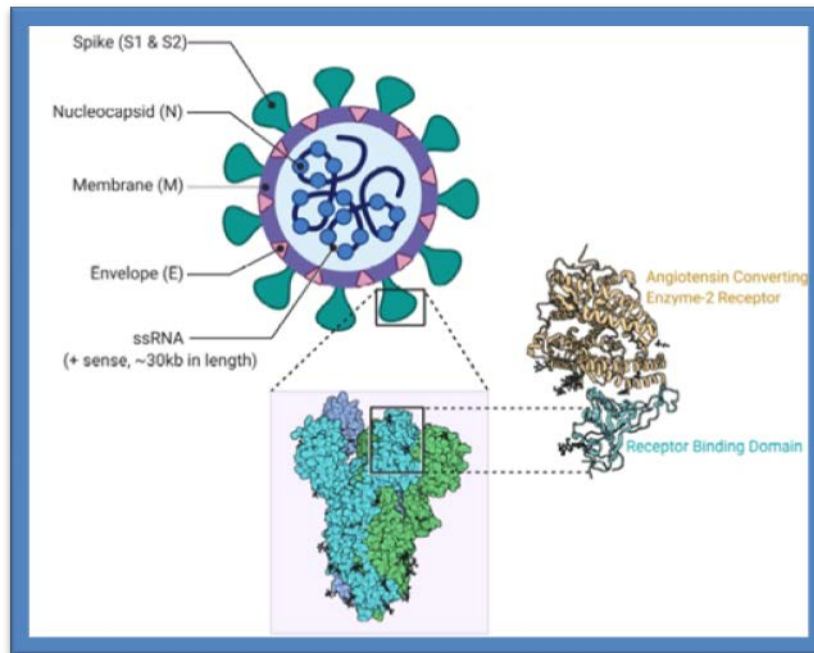
1.2 STRUCTURE

Coronavirus is a spherical or pleomorphic enveloped particle containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein projections. Some coronaviruses also contain a hem agglutinin-esterase protein (HE) [8].

Coronaviruses possess the largest genomes (26.4–31.7 kb) among all known RNA viruses, with G + C contents varying from 32% to 43%. Variable numbers of small ORFs are present between the various conserved genes (ORF1ab, spike, envelope, membrane and nucleocapsid) and, downstream to the nucleocapsid gene in different coronavirus lineages.

The viral genome contains distinctive features, including a unique N-terminal fragment within the spike protein. Genes for the major structural proteins in all coronaviruses occur in the 5'-3' order as S, E, M, and N [9].

The structure of SARS-CoV-2 consists of the following: a spike protein (S), hemagglutinin-esterase dimer (HE), a membrane glycoprotein (M), an envelope protein (E) a nucleocapsid protein (N) and RNA as seen in the figure below. [10]



SARS-CoV-2 STRUCTURE

Source: <https://www.ncbi.nlm.nih.gov/books/NBK554776/figure/article-52171.image.f3/>

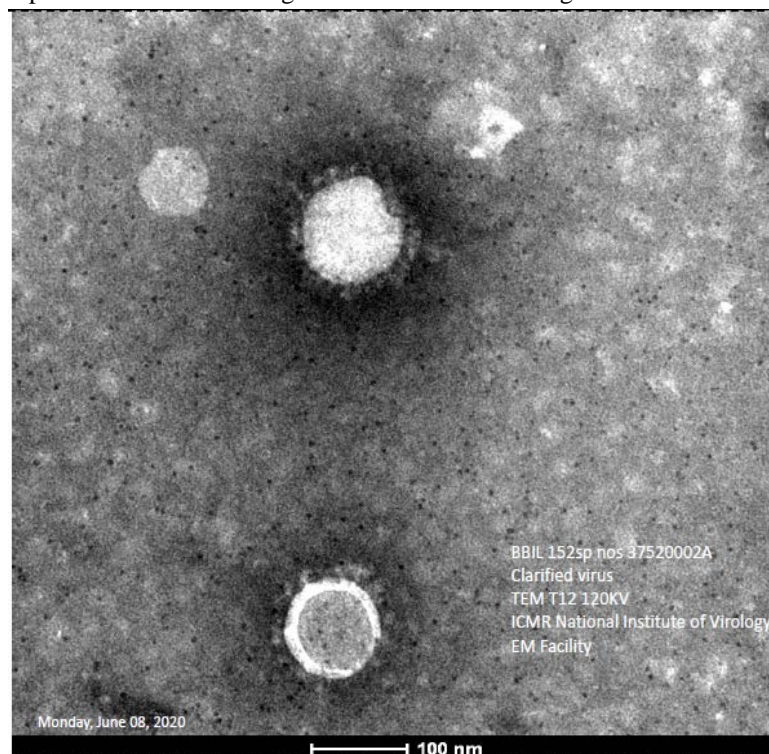


Figure 1: Electron Microscope image of SARS-CoV-2 Structure of BBIL Clarified virus from EM Facility, National Institute of Virology, Pune

Spike protein (S) is heavily glycosylated, utilizes an N-terminal signal sequence to gain access to the ER and mediate attachment to host receptors. It is the largest structure and makes the distinct spikes on the surface of the virus. S protein is cleaved by cellular furin-like protease [11] into two separate polypeptides S1 and S2.

Nucleocapsid protein (N) binds to RNA in vitro and is heavily phosphorylated. N proteins binds the viral genome in a bead on a string type conformation. This protein likely helps tether the viral genome to replicase-transcriptase complex (RTC), and subsequently package the encapsulated genome into viral particles.

Membrane protein (M) is the most abundant structural protein. It does not contain signal sequence and exists as a dimer in the virion. It may have two different conformations to enable it to promote membrane curvature as well as bind to nucleocapsid.

Envelope protein (E) is found in small quantities in within the virus. It is most likely a transmembrane protein and with ion channel activity. The protein facilitates assembly and release of the virus and has other functions such as ion channel activity. It is not necessary for viral replication but it is for pathogenesis.

RNA is the genome of the SARS-CoV-2 virus and contains positive-sense, single-stranded RNA.

Receptor-binding domain (RBD): Receptor recognition by coronaviruses is the first and essential step for infecting host cells. Coronavirus entry into host cells is mediated by the transmembrane S glycoprotein that forms homotrimers protruding from the viral surface [12]. S glycoprotein comprises two functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the receptor-binding domain (RBD) and contributes to stabilization of the prefusion state of the membrane-anchored S2 subunit that contains the fusion machinery [13]. The receptor binding motif (RBM) in RBD is responsible for direct binding to ACE2 and its binding affinity may directly affect the virus infectivity and transmissibility [14].

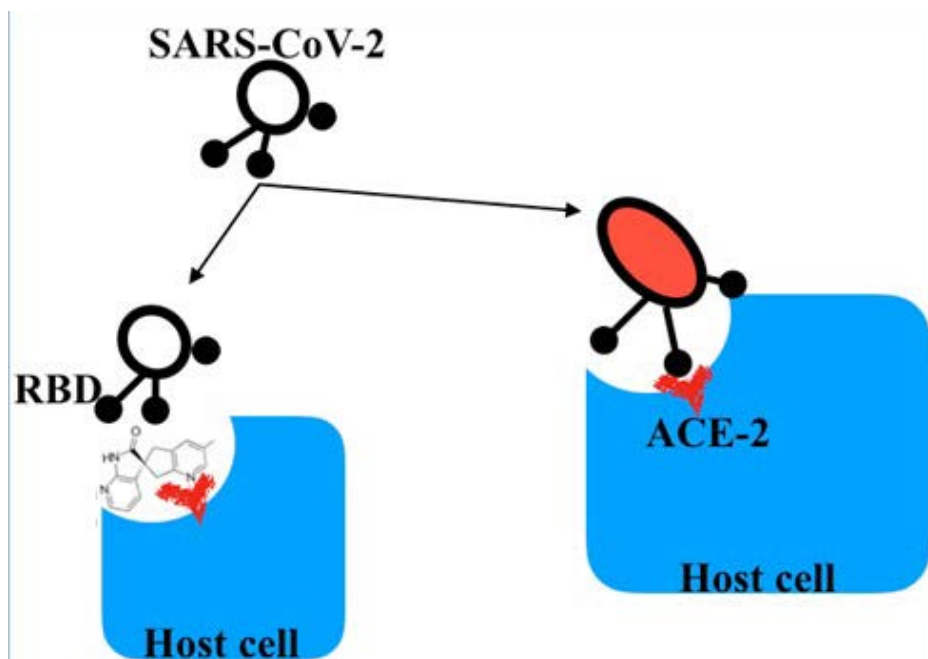


Figure 2: Receptor Binding Domain

[Source: Omotuyi, O.; Nash, O.; Ajiboye, B.; Metibemu, D.; Oyinloye, B.; Ojo, A.; Okaiyeto, K. The Disruption of SARS-CoV-2 RBD/ACE-2 Complex by Ubrogapant Is Mediated by Interface Hydration. Preprints 2020, 2020030466 (doi: 10.20944/preprints202003.0466.v1)[15].

Coronavirus entry into susceptible cells is a complex process that requires the concerted action of receptor-binding and proteolytic processing of the S protein to promote virus-cell fusion. As the coronavirus S glycoprotein is surface-exposed and mediates entry into host cells, it is the main target of neutralizing antibodies (Abs) upon infection and the focus of therapeutic and vaccine design.

1.3 GENETIC DIVERSITY

Nucleotide substitution has been proposed to be one of the most important mechanisms of viral evolution in nature. The rapid spread of SARS-CoV-2 raises intriguing questions such as whether its evolution is driven by mutations. To assess the genetic variation, Tung Phan reported that eighty-six complete or near-complete genomes of SARS-CoV-2 were collected from GISAID [<https://www.gisaid.org/>]. These SARS-CoV-2 strains were detected in infected patients from China (50), USA (11), Australia (5), Japan (5), France (4), Singapore (3), England (2), Taiwan (2), South Korea (1), Belgium (1), Germany (1), and Vietnam (1). The pair-wise nucleotide sequence alignment was performed by ClustalX2, and the sequence of the strain China/WHU01/2020/EPI_ISL_406716 was used as a reference genome. Like other beta-coronaviruses, the genome of SARS-CoV-2 has a long ORF1ab polyprotein at the 5' end, followed by four major structural proteins, including the spike surface glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein. The genetic analysis discovered three deletions in the genomes of SARS-CoV-2 from Japan (Aichi), USA

(Wisconsin), and Australia (Victoria). Two deletions (three nucleotides and twenty-four nucleotides) were in the ORF1ab polyprotein, and one deletion (ten nucleotides) was in the 3' end of the genome. The nucleotide sequence alignment also revealed ninety-three mutations over the entire genomes of SARS-CoV-2. Forty-two missense mutations were identified in all the major non-structural and structural proteins, except the envelope protein. Twenty-nine missense mutations were in the ORF1ab polyprotein, eight in the spike surface glycoprotein, one in the matrix protein, and four in the nucleocapsid protein. Of note, three mutations (D354, Y364, and F367) located in the spike surface glycoprotein receptor-binding domain. The spike surface glycoprotein plays an essential role in binding to receptors on the host cell and determines host tropism. It is also the major target of neutralizing antibodies. Mutations in the spike surface glycoprotein might induce its conformational changes, which probably led to the changing antigenicity. To date, a study on localization of amino acids involved in conformational changes of the SARS-CoV-2 spike surface glycoprotein structure is not available. The identification of these amino acids is of significance and should be investigated by further studies. [12].

2 CORONAVIRUS INFECTION

2.1 TRANSMISSION

The human-to-human transmissions occur via droplets and contact. The R_0 currently is estimated by the WHO as 1.4–2.5. R_0 describes about how many secondary cases that is expected to be produced from one primary infection in a susceptible population. For example, the median R_0 for seasonal flu is reported as 1.28 with interquartile range of 1.19–1.37), whereas for measles it is reported as 12–18. As R_0 value can be affected based on the local factors such as disease susceptibility, case detection rate and infection control measures, it should be calculated from population specific data taking local variability factors into consideration. Therefore, R_0 value of COVID-19 may be changed in future when additional information on the disease become available [13].

2.2 CLINICAL SYMPTOMS

Signs and symptoms of coronavirus disease 2019 (COVID-19) may appear two to 14 days after exposure. This time after exposure and before having symptoms is called the incubation period. Common signs and symptoms can include:

- Fever
- Cough
- Tiredness

Other symptoms can include:

- Shortness of breath or difficulty breathing
- Muscle aches
- Chills
- Sore throat

- Loss of taste or smell
- Headache
- Chest pain

This list is not all inclusive. Other less common symptoms have been reported, such as rash, nausea, vomiting and diarrhea. Children have similar symptoms to adults and generally have mild illness.

The severity of COVID-19 symptoms can range from very mild to severe. Some people may have only a few symptoms, and some people may have no symptoms at all. People who are older or who have existing chronic medical conditions, such as heart disease, lung disease, diabetes, severe obesity, chronic kidney or liver disease, or who have compromised immune systems may be at higher risk of serious illness. This is similar to what is seen with other respiratory illnesses, such as influenza.

Some people may experience worsened symptoms, such as worsened shortness of breath and pneumonia, about a week after symptoms start.

2.3 DISEASE BURDEN

In India, the first three SARS-CoV-2 cases were reported from Kerala during January 27-31, 2020. Later during March 2020, cases were also reported from a group of Italian tourists (n=15) and their contacts in New Delhi, India. Simultaneously, cases were reported in Agra, Uttar Pradesh, which was the outcome of close contact of an infected Delhi-based individual who returned from Italy. Subsequently, SARS-CoV-2 cases were reported from all over the country. As of Sep 12 2020, the total number confirmed cases of COVID-19 cases and death in India are ~ 5 million, and 77,000 deaths, respectively as per the Official data of Govt. of India official data [7].

2.4 DIAGNOSIS

2.4.1 MOLECULAR TEST

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. The samples require storage at four degrees celsius. In the laboratory, amplification of the genetic material extracted from the saliva or mucus sample is through a reverse polymerase chain reaction (RT-PCR), which involves the synthesis of a double-stranded DNA molecule from an RNA mold. Once the genetic material is sufficient, the search is for those portions of the genetic code of the CoV that are conserved. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org, and subsequent confirmatory evaluation by additional labs. If the test result is positive, it is recommended that the test is repeated for verification. In patients with

confirmed COVID-19 diagnosis, the laboratory evaluation should be repeated to evaluate for viral clearance prior to being released from observation. The availability of testing will vary based on which country a person lives in with increasing availability occurring nearly daily.

2.4.2 SEROLOGY

Despite the numerous antibody tests designed, to date serologic diagnosis has limitations in both specificity and sensitivity. Again, results from different tests vary. A CDC research on a test developed by the US Vaccine Research Center at the National Institutes of Health is ongoing. Of note, this test seems to have specificity higher than 99% with a sensitivity of 96%. Nevertheless, further research is needed for elucidating several aspects of the matter.

Inparticular:

- If IgG antibodies will provide immunity from future SARS-CoV-2 infection.
- On the protective titer of antibodies.
- On the duration of the protection.

Serologic, however, can have an important role in broad-based surveillance.

2.4.3 LABORATORY EXAMINATIONS

Concerning laboratory examinations:

- In the early stage of the disease, a normal or decreased total white blood cell count (WBC) and a decreased lymphocyte count can be demonstrated. Interestingly, lymphopenia appears to be a negative prognostic factor.
- Increased values of liver enzymes, lactate dehydrogenase (LDH), muscle enzymes, and C-reactive protein can be detected.
- Unless a bacterial overlap, a normal procalcitonin value is found.
- The elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) [neutrophil count divided by the result of WBC count minus neutrophil count], and platelet-to-lymphocyte ratio, can be the expression of the inflammatory storm.[23] The correction of these indices is an expression of a favourable trend.
- Increased D-dimer.
- In critical patients, D-dimer value is increased, blood lymphocytes decreased persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders, etc.) are found.

2.4.4 IMAGING

2.4.4.1 CHEST X-RAY EXAMINATION

Since the disease manifests itself as pneumonia, radiological imaging has a fundamental role in the diagnostic process, management, and follow-up. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes and in the initial stages of the disease. At this stage, it can be completely negative. In the more advanced stages of infection, the chest X-ray examination generally shows bilateral multifocal alveolar opacities, which tend to confluence up to the complete opacity of the lung. Pleural effusion can be associated.

2.4.4.2 CHEST COMPUTED TOMOGRAPHY

Given the high sensitivity of the method, chest computed tomography (CT), in particular high-resolution CT (HRCT), is the method of choice in the study of COVID-19 pneumonia, even in the initial stages. Several non-specific HRCT findings and patterns can be found. Most of these findings may also be observed in other lung infections, such as Influenza A (H1N1), CMV, SARS, MERS, streptococcus, and Chlamydia, Mycoplasma. The most common findings are multifocal bilateral "ground or ground glass" (GG) areas associated with consolidation areas with patchy distribution, mainly peripheral/subpleural and with greater involvement of the posterior regions and lower lobes. The "crazy paving" pattern can be also observed. This latter finding is characterized by the presence of GG areas with superimposed interlobular septal thickening and intralobular septal thickening. It is a non-specific finding that can be detected in different conditions. Other findings are the "reversed halo sign" which is a focal area of GG delimited by a peripheral ring with consolidation, and the finding of cavitations, calcifications, lymphadenopathies, and pleural effusion.

2.4.4.3 LUNG ULTRASOUND

Ultrasound approach can allow evaluating the evolution of the disease, from a focal interstitial pattern up to "white lung" with evidence often of sub-pleural consolidations. It should be performed within the first 24 hours in the suspect and every 24/48 hours and can be useful for patient follow-up, choice of the setting of mechanical ventilation, and for indication of prone positioning. The main sonographic features are:

- Pleural lines often thickened, irregular, and discontinuous until it almost appears discontinuous; subpleural lesions can be seen as small patchy consolidations or nodules.
- B lines. They are often motionless, coalescent, and cascade and can flow up to the square of "White lung".
- Thickenings. They are most evident in the posterior and bilateral fields especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.
- Perilesional pleural effusion

In summary, during the course of the disease, it is possible to identify the first phase with focal areas of fixed B lines, a phase of numerical increase of the lines B up to the white

lung with small subpleural thickenings, and further progress until evidence of posterior consolidations.

2.5 TREATMENT

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the first step for addressing respiratory impairment. Non-invasive and invasive mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy.

The clinical management of COVID-19 should be based on the stage and type of syndrome associated with disease at the time of presentation. Mild illness can be managed with conventional symptomatic treatment. Patients with severe illness may require immediate supplementary oxygen therapy. At present, there are no approved drugs with proven efficacy available for the treatment of COVID-19. Some of drugs approved for other diseases are currently used worldwide for the treatment of the patients. The drugs/therapy currently used are either re-purposed or tried as experimental therapy for the treatment of COVID-19 [13,16]. These are:

- 1) Anti-malarial drugs: Hydroxychloroquine, Chloroquine
- 2) Anti-retroviral drugs: Lopinavir/Ritonavir (Protease inhibitors)
- 3) Anti-viral drugs: Remdesivir (nucleoside analogue), Favipiravir
- 4) Corticosteroids: Methylprednisolone
- 5) Monoclonal antibodies: Tocilizumab
- 6) Intravenous immunoglobulin (IVIG)
- 7) Convalescent plasma transfusion

Remdesivir has been authorized in US under Emergency Use Authorization for the management of adult and pediatric patients for whom use of an IV agent is clinically appropriate and who are under the care or consultation of a licensed clinician skilled in the diagnosis and management of patients with potentially life-threatening illness. Favipiravir has been approved for restricted emergency use in India.

Although none of the vaccines are approved for the prevention of COVID-19, many vaccine candidates are under development throughout the world.

3 COVID 19 VACCINE DEVELOPMENT

3.1 RATIONALE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is accelerating globally leading to an increase in morbidity and mortality. The high-risk group includes the health care workers (HCW) (physicians and paramedical staff), working amid SARS-CoV-2 infected patients, all other people including household contacts of COVID-19 confirmed patients, people currently residing or working in COVID-19 hotspots/outbreak areas where there is a high risk of transmission of SARS-CoV-2 infection and especially the elderly people (age >60 Years). Though SARS-CoV-2 infection may cause mild symptoms in many, nearly 14% develop a severe disease that requires hospitalization and oxygen support, and

5% require admission to an intensive care unit. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome, sepsis, septic shock, and multiorgan failure with an estimated case fatality of 3.4%.

The COVID-19 pandemic is rapidly worsening in all parts of the world, overwhelming health systems. There is a serious threat to a densely populated country like India. Also, reports from all over the world demonstrate that the disease takes a severe course in elderly people and people with co-morbid conditions leading to higher mortality rates. Thus, there is an urgent need to ensure the safety and health of existing people living in COVID-19 affected areas where there is a high risk of disease transmission and find strategies to prevent the SARS-CoV-2 infection among such populations.

To date, no specific antiviral drug has been approved for COVID-19 although remdesivir has been given Emergency Use Authorization approval by USFDA, and Favipiravir has been used under restricted emergency use in India. Hence, there is a necessity to develop a vaccine to prevent SARS-CoV-2 infection. Various types of COVID-19 vaccines, such as DNA, RNA based formulations, recombinant subunit vaccines containing the viral protein (Spike) epitopes, vector-based formulations (eg: Adenovirus, Measles, Rabies,) and traditional inactivated vaccines are under development [10,11,12,13]. Two Chinese based vaccine manufacturing company (Sinovac Biotech Ltd., and China National Pharmaceutical Group Co., Ltd. (Sinopharm)) have developed inactivated vaccine formulation against the SARS-CoV-2 virus and proved its safety and immunogenicity in animals such as mice, rats, and non-primate mammal, rhesus macaque monkeys [17,18]. The phase 1/2 (Sinopharm) and Phase 2 (Sinovac Biotech Ltd.) results have been published and the inactivated vaccine have demonstrated safety and immunogenicity in healthy adults [19,20]. Currently, the phase 3 clinical trials for these two inactivated vaccines are ongoing.

3.2 HISTORY AND CURRENT STATUS

The potential vaccine target could be whole cell antigen (WCA), spike protein (S protein) (The Full-Length S Protein, RBD, NTD, S1 subunit, FP), nucleocapsid protein (N Protein), membrane protein (M Protein) or envelope protein (E protein). The potential vaccine candidates for covid-19 can be categorized into various types such as whole-cell killed and live-attenuated vaccines, subunit vaccines, mRNA vaccines, DNA vaccine, live vector vaccines, synthetic peptide or epitope vaccine.

As of 10th Aug 2020, about 139 vaccine candidates are in preclinical evaluation stage and 28 candidate vaccines in clinical evaluation stage. (The COVID-19 vaccine development landscape, WHO).

3.3 CHALLENGES IN NEW VACCINE DEVELOPMENT

New vaccine development is challenging as usually the reference reagents like antibodies,

reference vaccine for testing and virus strain suitable for vaccine development are not available. Hence fundamental work is required to qualify any virus strain to be used as a vaccine strain. Extensive validation is required to qualify primary in-house reference reagents. However, the most challenging aspect of a new vaccine development is the derivation and rationalization of vaccine doses for clinical testing. The use of different platform technologies renders comparison of protective correlates induced by the different candidate vaccines difficult to assess.

In the case of COVID19 vaccine development at Bharat Biotech there were additional challenges. The vaccine project was initiated at the time when very little or no information was available on virus pathogenesis, genetic diversity, transmission, diagnosis, serological correlates for protection or animal models to test the vaccine concepts. From vaccine point of view, there was no information on whether the virus can be cultured in vitro in cell substrates and if yes, which cell substrates are best suitable, mechanism of adaptation to cells, potential virus titers and the feasibility to manufacture the vaccine product for human administration, as the published information at that time pertained to passaging the virus in mouse brain which is not suitable for vaccine production. The extent of R&D work done on this vaccine has now led to the development of a very promising candidate vaccine being advanced into clinical development.

3.4 TARGET PRODUCT PROFILE

Table 1: Develop and license vaccine for reactive use in outbreak settings (Outbreak) and/or with long-term protection for administration to those at high ongoing risk of COVID-19 (LT)

| BBV 152 Vaccine characteristics | Preferred | Critical or Minimal |
|--|--|--|
| Indication for use | <u>Outbreak:</u> For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of infection of SARS-CoV-2; to be used in conjunction with other control measures to curtail or end an outbreak. <u>Long Term (LT):</u> For active immunization of at-risk persons to prevent COVID-19 | <u>Outbreak:</u> For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of COVID-19; to be used in conjunction with other control measures to curtail or end an outbreak <u>Long Term (LT):</u> For active immunization of at-risk persons to prevent COVID-19 |
| Contraindication | None | Some contraindications (e.g., immunocompromised) may |

| | | |
|---------------------------------|---|---|
| | | be acceptable |
| Target population | All ages ¹ . Suitable for administration to pregnant and lactating women. | Adults, including elderly |
| Safety/Reactogenicity | Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with only mild, transient adverse events related to vaccination and no serious AEs. | <u>Outbreak:</u> Safety and reactogenicity whereby vaccine benefits outweigh safety risks ² . <u>Long Term (LT):</u> Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with only mild, transient adverse events related to vaccination. |
| Measures of Efficacy | At least 70% efficacy (on population basis, with consistent results in the elderly ³ . Endpoint may be assessed vs. disease, severe disease, and/or shedding/transmission. <u>Outbreak:</u> Rapid onset of protection (less than 2 weeks). <u>Long Term (LT):</u> Rapid onset of protection is less important. | Clear demonstration of efficacy (on population basis) ideally with ~50% point estimate. Endpoint may be assessed vs. disease, severe disease, and/or shedding/transmission ⁴ . |
| Dose regimen | <u>Outbreak:</u> Two-dose primary series ⁵ . <u>Long Term (LT):</u> Lower frequency (yearly or less) of booster doses is preferred. | <u>Outbreak:</u> No more than two dose regimen ⁶ . <u>Long Term (LT):</u> Booster doses permitted |
| Durability of protection | Confers protection for at least 1 year. | Confers protection for at least 6 months ⁷ . |
| Route of Administration | <u>Outbreak:</u> Any route of administration is acceptable, if vaccine is safe and effective. | Any route of administration is acceptable, if vaccine is safe and effective |

| | | |
|--|--|---|
| | <u>Long Term (LT):</u> Any route of administration is acceptable. | |
| Product Stability and Storage | Higher storage temperatures and higher thermostability will greatly enhance vaccine distribution and availability, and are thus strongly preferred. | Outbreak: Storage at 2°C – 8°C or higher; <u>Long Term (LT):</u> Storage at 2°C – 8°C or higher; |
| Co-administration with other vaccines | <u>Outbreak:</u> Stand-alone product. <u>Long Term (LT):</u> potential for coadministration with other vaccines (e.g, flu, polio, measles, pneumococcal) preferred | Stand-alone product |
| Presentation | <u>Outbreak:</u> Multi-dose presentation is preferred for ease of use in campaigns. <u>Long Term (LT):</u> Mono-dose or multidose presentations are acceptable Maximum parenteral dose volume: 0.5 mL Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. | Multi- or mono- dose presentations are acceptable. Maximum parenteral dose volume: 1 mL Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy. |

1. Recognize that herd immunity (and transmission blocking) will depend on broad immunization, likely including children.

2 Benefit/risk may depend on age, other factors. Benefit/risk assessment should take potential for enhanced disease into account.

3 The lower confidence limit of the efficacy estimate could be lower

4 If regulatory authorization is provided with incomplete clinical efficacy data, effectiveness data are to be generated during use

5 Note strong preference for single-dose, but do not desire to discourage development of 2-dose vaccines if that is what is feasible

6 note cholera is 2 dose, and many 2 dose vaccines confer partial protection after a single dose. For two-dose vaccines, protection after single dose should be assessed

7 This might not be demonstrated in initial clinical studies, but could be supported by follow-on studies, animal data, etc

4 CORONAVIRUS VACCINE PRODUCT DEVELOPMENT AT BHARAT BIOTECH

4.1 SUMMARY

The aim was to manufacture a safe COVID-19 vaccine based on the whole-virion inactivated vaccine under BSL3 facility for human clinical trial. This vaccine was based on vero cell manufacturing platform, manufactured and characterized at Bioreliance USA. The safety is well established. This vaccine used the same platform used for vaccines, such as Rabies, Rotavirus, Chikungunya, Zika, Japanese Encephalitis, Inactivated Polio vaccines.

The coronavirus vaccine BBV152 is whole virion inactivated vaccine developed in collaboration with Indian Council of Medical Research and National Institute of Virology, Pune.

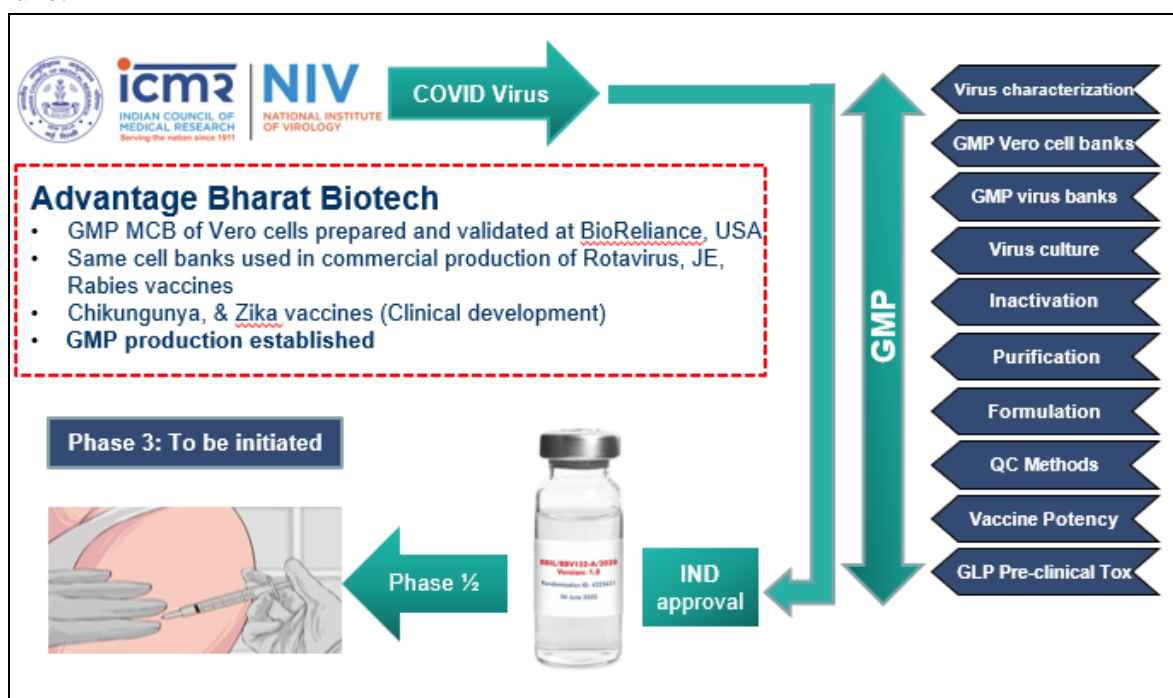


Figure 3: Summary of Vaccine product Development

4.2 VERO-CELL SUBSTRATE

4.2.1 MASTER CELL BANK (MCB) PREPARATION

Vero Cell MCB was prepared and characterized by BioReliance for BBIL. The preparation of MCB was initiated by BioReliance with 2 cryovials of Vero MCB (P/N: 5.41075L/N: 3006- 103388.) at passage #8 (equivalent to passage#130 of ATCC CCL-81). Vero Cells were seeded in 2 x 225 cm² flasks. Cells were serially passaged three more times up to the stage of 10⁵ x 225 cm² flasks. Cells were harvested from all the 10⁵ flasks and cryo preservation medium containing 90% FBS and 10% DMSO was added to the pooled cell suspension. The cell suspension was distributed in 1.0 mL aliquots into sterile cryo vials

labelled as under:

Vero MCB, P-11

P/N: BHAMC1.FP, L/N: 3006-104986

10/07/03 1 mL Vial #

BioReliance. Stored: Liq. N2

The running passage level of notional P#11 is P#133 as per the records of BioReliance. The Vero Cell MCB was completely characterized at BioReliance.

4.2.2 MASTER CELL BANK CHARACTERIZATION

- a) Sterility test in accordance with 21CFR, USP 26 AND EP. Result was satisfactory.
- b) Test for Bacteriostatic/Fungistatic activity of a test article using direct inoculation method. Result was satisfactory.
- c) Test for the presence of Agar cultivable and Non-Agar cultivable Mycoplasma. Results: Test was negative.
- d) Cell culture identification and characterization. Results: Isoenzyme analysis is consistent with cells of Cercopithecus monkey origin.
- e) Test for the presence of inapparent viruses in suckling mice, adult mice and embryonated hen's eggs. Results: No evidence of contamination with adventitious agents.
- f) In vitro assay for the presence of viral contaminants. Results: Adventitious viral contaminants were not detected.
- g) PCR assay for the detection of Simian Virus 40 in biological samples. Results: Negative for SV40 DNA
- h) PCR assay for the detection of Simian Retrovirus in biological samples. Results: Negative for SRV sequence
- i) Transmission electron microscopic evaluation of cultured cells. Results: Negative for virus like particles and other microbial agents.
- j) Product Enhanced Revert Transcriptase (PERT) assay for the detection of Retrovirus in biological samples. Results: Negative for RT activity.
- k) Cytogenetic analysis for the characterization of cell lines. Results: Identity confirmed as African Green Monkey Cells.

4.2.3 MANUFACTURER'S WORKING CELL BANK (MWCBC) PREPARATION

One cryovial was taken from the Vero MCB P/N: (BioReliance) P#133 and seeded into 1xT- 150 flask (P#134). At the time of revival, cell count of the re-suspended cells was found to be 5.6×10^6 cells and viability was found to be 56%. Cells were serially passaged further up to P#138 for expansion in order to obtain 144 x T-150 flasks. Cells were trypsinised, harvested and made into a cell suspension. To the cell suspension, cryopreservation medium (90% FBS+10% DMSO) was added. Cell suspension was

aliquoted in 1.2 mL aliquots into sterile cryovials.

4.2.4 MANUFACTURER'S WORKING CELL BANK CHARACTERIZATION

MWCB cryovials were tested for sterility and mycoplasma at BBIL. Samples were sent to BioReliance for characterization.

- a) Sterility test in accordance with 21 CFR, USP 27 AND EP for final product; Results: Satisfactory
- b) Test for the presence of Agar-cultivable and Non-Agar Cultivable Mycoplasmas in accordance with EP and USFDA; Results: Negative
- c) Cell culture identification and characterization; Results: Isoenzyme analysis consistent with cells of Cercopithecus monkey origin.
- d) Cytogenetic analysis for the characterization of cell lines; Results: Identified as African Green Monkey Kidney (AGMK) Cells

4.2.5 CHARACTERIZATION OF END OF PRODUCTION CELLS (EOPC)

- a) Evaluation of tumor formation in nude athymic mice following subcutaneous injection of cell suspension; Results: Non-tumorigenic.
- b) 28 Day in vitro assay for the detection of viral contaminants in 3 detector cell lines; Results: Negative for the presence of viral contaminants.

5 CORONAVIRUS VACCINE STRAIN

GENERAL DESCRIPTION AND HISTORY OF STARTING MATERIAL

5.1 CELL SUBSTRATE

The origin of Vero Cells is from ATCC. Vero Cell CCL-81(Lot No. F-11497) was procured by Bio Reliance Corporation (BRC) from ATCC and Master Cell Bank was prepared by (BRC). The part number of the Vero Cell batch is BHAMCI.FP and the Lot Number is 3006-104986.

5.2 SYSTEM OF SEED/MASTER/WORKING BANKS

5.2.1 MASTER CELL BANK ESTABLISHMENT AND CHARACTERIZATION:

Bharat Biotech engaged BioReliance Corporation, Rockville, MD, USA, in 2005 to prepare and characterize Vero Cell Master Cell Bank for the production of viral vaccines. The origin of Vero Cell line used by BioReliance Corporation, for the preparation of Vero Master Cell Bank for Bharat Biotech was Vero ATCC®.CCL-81™. Vero Cell line was developed in 1962 by Y. Yasumura and Y. Kawakita at the Chiba University in Chiba, Japan from the kidneys of a normal Cercopithecus aethiops monkey and was given to National Institutes of

Allergy and Infectious Diseases (NIAID) in the USA in 1964 and NIAID, in turn, provided the cell line to the American Type Culture Collection (ATCC) in 1966.

Bio Reliance received Vero Cells from ATCC with a passage number 122 and prepared MCB with a passage number at 133. It was numbered as Vero MCB P/N: BHAMC1.FP, L/N: 3006-104986. The MCB was fully characterized by BioReliance, the tests and results of which are given Table: 2.

Table – 2: Various tests performed for characterization of MCB and the results

| S. No | Test performed | Observation/Result |
|-------|---|---|
| 1. | Sterility Test in Accordance with 21CFR, USP 26 and/ or European Pharmacopeia (EP) for final product | Satisfactory |
| 2. | Test for Bacteriostatic / Fungistatic Activity of a test article using direct inoculation method | Satisfactory |
| 3. | Test for the presence of Agar cultivable and Non-Agar cultivable Mycoplasma | Negative |
| 4. | Cell culture identification and characterization | Isoenzyme analysis consistent with cells of Cercopithecus Monkey origin |
| 5. | Test for the Presence of inapparent viruses in suckling mice, adult mice and embryonated hen's eggs | No evidence of contamination with adventitious agents |
| 6. | In vitro assay for the presence of Viral contaminants | Adventitious viral contaminants were not detected |
| 7. | Polymerase chain Reaction assay for the detection of Simian Virus 40 (SV40) in Biological samples | Negative for SV40 DNA |
| 8. | Polymerase chain Reaction assay for the detection of Simian Retrovirus (SRV) in Biological samples | Negative for SRV Sequence |
| 9. | Transmission Electron Microscopic evaluation of cultured cells | Negative for Virus-Like Particles and other microbial agents |
| 10. | Product Enhanced Reverse Transcriptase (PERT) Assay for the detection of Retrovirus in Biological samples | Negative RT activity at a sensitivity of 2×10^7 RT Units/4.0 μ l of test article |
| 11. | Cytogenetic Analysis for the characterization of cell lines | Identified as African Green Monkey |

The tests done by BioReliance on End of Production Culture (EOPC), Vero-CCL81 EOPC P#159 is given in Table: 3

Table – 3: Tests performed and the results

| S. No | Test Performed | Results |
|-------|--|----------------------------------|
| 1 | Evaluation of Tumor formation in nude (NU/NU) athymic mice following subcutaneous injection of cell suspension | Not considered to be Tumorigenic |
| 2 | 28 Day In vitro Assay for the Detection of Viral Contaminants-3 Detector cell lines | Negative |

Each MCB cryovial contains approximately 10^7 cells/1.0mL. These cells are stored at -130°C or below in the cell bank storage area in Building 'C' and are controlled, monitored and issued by QA.

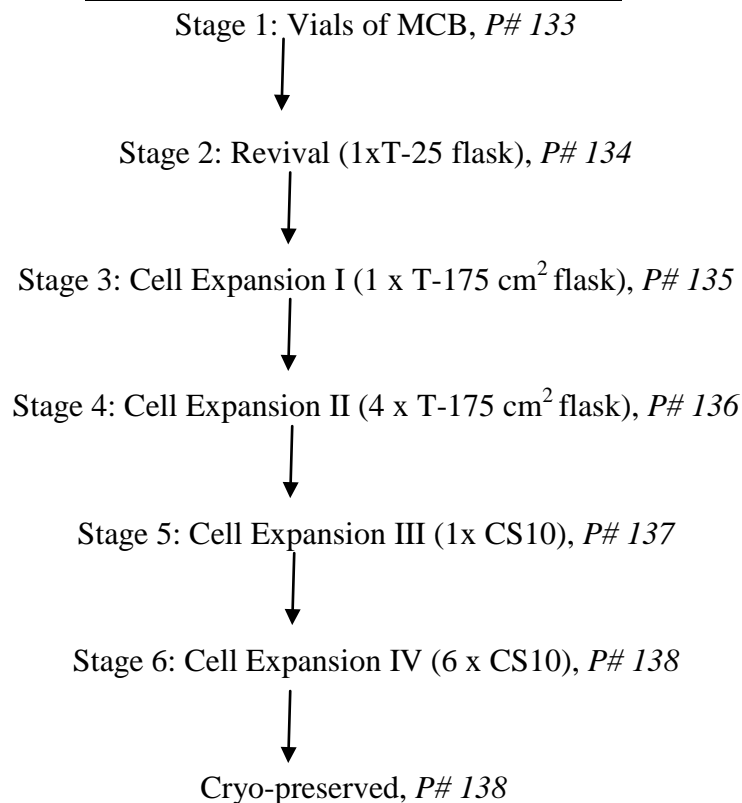
5.2.2 MANUFACTURER'S WORKING CELL BANK ESTABLISHMENT AND CHARACTERIZATION:

The MWCB was characterized by BBIL as per Specification no. SMS003

Table -4: Various tests performed for the characterization of MWCB and the results

| S.No | Test Performed | Specification | Results |
|------|--|---|------------------------------------|
| 1 | Identity | Should show 222 bp band after PCR amplification in Gel Analysis for AGMK species | 222 bp band observed |
| 2 | Sterility | No Growth should be observed | No Growth observed (Sterile) |
| 3 | Mycoplasma | Should be Negative for Mycoplasma | Negative for Mycoplasma species |
| 4 | Adventitious agents (in-vivo and in-vitro) | Should be Free from Adventitious Agents | Free from Adventitious Agents |
| 5 | Haemadsorption | Should be Free from Haemadsorbing viruses | Free from Haemadsorbing viruses |
| 6 | Growth characteristics | Cells should be healthy and growing | Cells are healthy and growing |
| 7 | Homogeneity test | 90% to 110% recovery should be observed from initial cell count in each cryovials | 98.94% |
| 8 | Cell Viability | NLT 80% | 98.7% |
| 9 | Cell count | NLT 5×10^6 cells/ cryovial | 5.21×10^6 cells/ cryovial |

Flow chart of Vero MWCB Preparation:



5.3 DESCRIPTION, HISTORY AND CHARACTERIZATION & SEED LOT SYSTEM FOR VERO CELLS

5.3.1 EMBRYONATED EGGS AND OTHER CELLS SUBSTRATES:

Not Applicable.

5.3.2 MASTER SEED AND WORKING SEED OF VIRUS BANKS

5.3.2.1 VIRUS STRAIN

A new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with human to human transmission and extreme human sickness has been as of late announced from the city of Wuhan in China. The nucleocapsid protein (N-protein) and spike protein (S-protein) are encoded by all coronaviruses, including the coronavirus (SARS-CoV-2, COVID-19) that was first detected in Wuhan City, China, in December 2019.

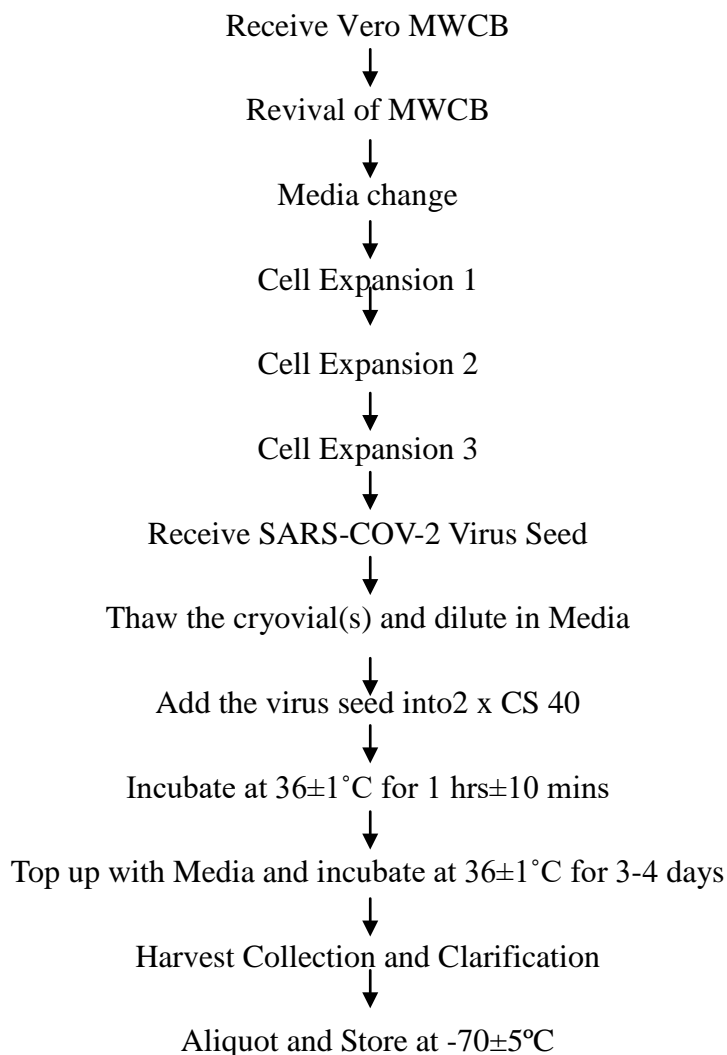
5.3.2.2 VIRUS SEED LOT SYSTEM

The seed virus (Strain NIV 2020-770) were transferred from ICMR –National Institute of Virology to Bharat Biotech. This strain was the first successful virus isolation from the nasal and throat swabs of person with a travel history from Italy. The seed virus received from the NIV was adapted and amplified to produce MASTER VIRUS BANK (MVB). WORKING

VIRUS BANK (WVB) was prepared from MVB and characterized. WVB is being used for the production.

5.4 PREPARATION OF MASTER VIRUS BANK (MVB)

SARS-COV-2 Master Virus Bank preparation flow chart



5.5 CHARACTERIZATION OF MVB

Characterization of MVB was done and the following QC tests certified the MVB for production of vaccine lots.

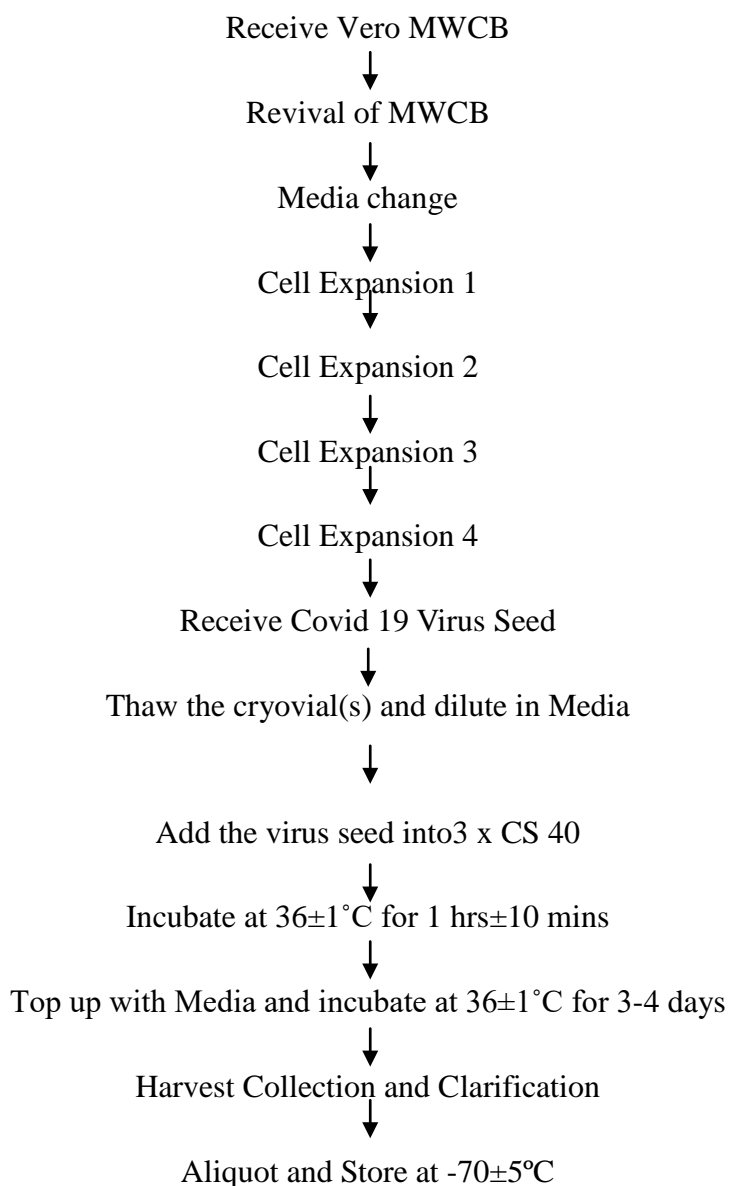
Table -5: Various tests performed for the characterization of MVB and the results

| S.No | TEST | SPECIFICATION |
|------|-------------------------------------|---|
| 1 | Identity (By In-vitro method) | Virus titration by qPCR serve as an identity test |
| 2 | Sterility | No Growth should be observed |
| 3 | Mycoplasma | Should be negative for mycoplasma |
| 4 | Virus titration (<i>in vitro</i>) | NLT 10 ^{6.00} CCID ₅₀ /mL |

| | | |
|---|--------------------------------|---|
| 5 | Virus Titration by qPCR | NLT $10^{6.00}$ Copies per mL |
| 6 | Adventitious agents (In-vitro) | Should be free from Adventitious agents |
| 7 | Haemadsorption | Should be free from Haemadsorption agents |
| 8 | Virus identity by NGS method | 95% sequence should match with published Sequence |

5.6 PREPARATION OF WORKING VIRUS BANK (WVB)

Working Virus Bank (WVB) was prepared from the well characterized MVB. The working virus banks were prepared as follows:



5.7 CHARACTERIZATION OF WORKING VIRUS BANK (WVB)

Characterization of WVB was done and the following QC tests certified the MVB for production of vaccine lots.

Table -6: Various test performed for the characterization of WVB with specification

| S.No | TEST | SPECIFICATION |
|------|-------------------------------------|---|
| 1 | Identity (By In-vitro method) | Virus titration by qPCR serve as an identity test |
| 2 | Sterility | No Growth should be observed |
| 3 | Mycoplasma | Should be negative for mycoplasma |
| 4 | Virus titration (<i>in vitro</i>) | NLT $10^{6.00}$ CCID ₅₀ /mL |
| 5 | Virus Titration by qPCR | NLT $10^{6.00}$ Copies per mL |
| 6 | Adventitious agents (In-vitro) | Should be free from Adventitious agents |
| 7 | Haemadsorption | Should be free from Haemadsorption agents |
| 8 | Virus identity by NGS method | 95% sequence should match with published sequence |

6 CORONAVIRUS BANKS

6.1 VIRUS SEED LOT SYSTEM

A virus seed lot system was established to provide traceability to the virus stocks used in the production of vaccine lots.

6.2 PREPARATION OF P3 MASTER SEED VIRUS

Coronavirus Seed Virus as described earlier was used for the preparation of P3 Master Seed. The seed virus was passaged twice in C6/36 Ae. albopictus cells and plaque purified twice from Vero cells to obtain 'Coronavirus Master Seed which was advanced into preparation of GMP Master Virus Banks. The virus titer in the P3 Master Seed is $10^{7.40}$ CCID₅₀ / mL.

6.3 CHARACTERIZATION OF P3 MASTER SEED VIRUS

The Corona P3 Master Seed Virus was extensively tested for mycoplasma, sterility, virus titer, whole genome sequencing by Next Generation Sequencing (NGS) platform before advancing to the preparation of GMP Master Virus Banks.

6.4 CHARACTERIZATION OF MVB

6.4.1.1 WHOLE GENOME SEQUENCING BY NGS PLATFORM

The genomic RNA isolated from the pre-seed was sequenced using NGS platform at Genotypic Technologies, Bangalore. The sequence confirmed the identity of the MR 766 strain of Coronavirus.

6.4.1.2 MVB CHARACTERIZATION AS PER WHO TRS963

Table 7: QC Specification No. SMS 034

| S.No. | Tests | Specifications | Results |
|-------|---|---|-------------------------|
| 1. | Virus identity by sequencing (NGS Method) | 95% Sequence should match with published sequence | Under Test |
| 2. | Virus identity by In-Vitro Method | Virus titration by qPCR serve as an Identity test | Complies |
| 3. | Sterility by direct inoculation method | No growth should be observed | Sterile |
| 4. | Mycoplasma by PCR method | Should be free from mycoplasma | Negative for mycoplasma |
| 5. | Virus titration (In-Vitro) | NLT 106.00 CCID50/ml | 106.25 CCID50/ml |
| 6. | Virus titration by qPCR | NLT 106.00 Copies per mL | 107.25 Copies per mL |
| 7. | Adventitious agents (In-vitro) | Should be free from adventitious agents | Under Test |
| 8. | Haemadsorption | Should be free from haemadsorbing viruses | Under Test |

6.5 PREPARATION OF WORKING VIRUS BANK (WVB)

Working Virus Bank (WVB) was prepared from the well characterized MVB under GMP conditions.

6.6 CHARACTERIZATION OF WVB

6.6.1 WHOLE GENOME SEQUENCING BY NGS PLATFORM

The genomic RNA isolated from the WVB was sequenced by NGS platform using Illumina NextSeq500. The nucleotide sequence confirmed the identity of coronavirus.

6.6.2 WVB CHARACTERIZATION AS PER TRS963

Table 8: QC Specification No. SMS 034

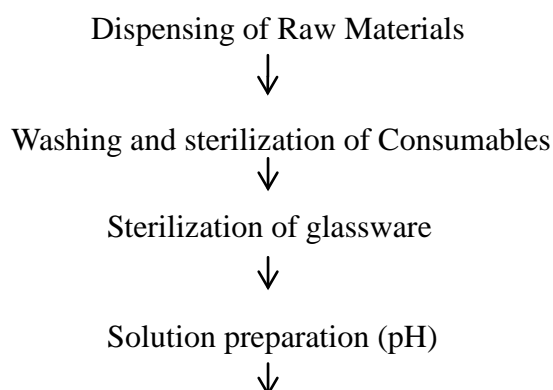
| S.No | Test | Specification | Results |
|------|---|---|-------------------------|
| 1 | Virus identity by sequencing (NGS Method) | 95% Sequence should match with | Under Test |
| 2. | Virus identity by In-Vitro Method | Virus titration by qPCR serve as an Identity test | Complies |
| 3 | Sterility by direct inoculation method | No growth should be observed | Sterile |
| 4 | Mycoplasma by PCR method | Should be free from mycoplasma | Negative for mycoplasma |
| 5 | Virus titration (In-Vitro) | NLT 106.00 CCID50/ml | 106.88 CCID50/ml |
| 6. | Virus titration by qPCR | NLT 106.00 Copies per mL | 107.44 Copies per mL |
| 7. | Adventitious agents (In-vitro) | Should be free from adventitious agents | Under Test |
| 8. | Haemadsorption | Should be free from haemadsorbing viruses | Under Test |

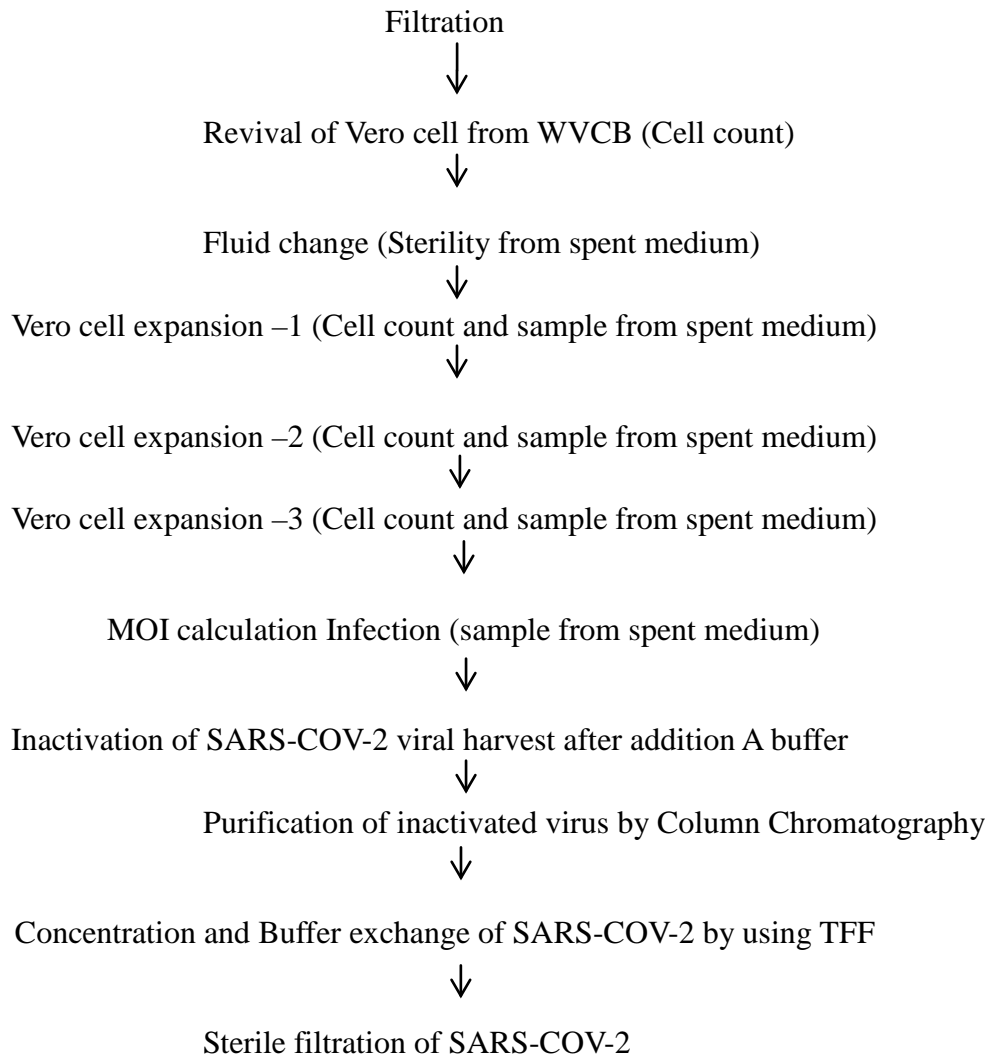
7 CORONAVIRUS VACCINE PRODUCTION

7.1 VACCINE BULK

GMP production of vaccine bulk was standardized at 80 L pilot scale. The flow chart below describes the steps involved in the bioprocess related to production of purified inactivated bulk of coronavirus vaccine. All the steps in production comply with the In-Process Quality Control (IPQC) parameters established for GMP production of vaccine bulk. In-process steps for quality checking of the vaccine bulk were developed at different stages of the bioprocess to ensure consistency and to prevent any inadvertent introduction of contamination from extraneous agents.

PROCESS FLOW CHART: drug substance





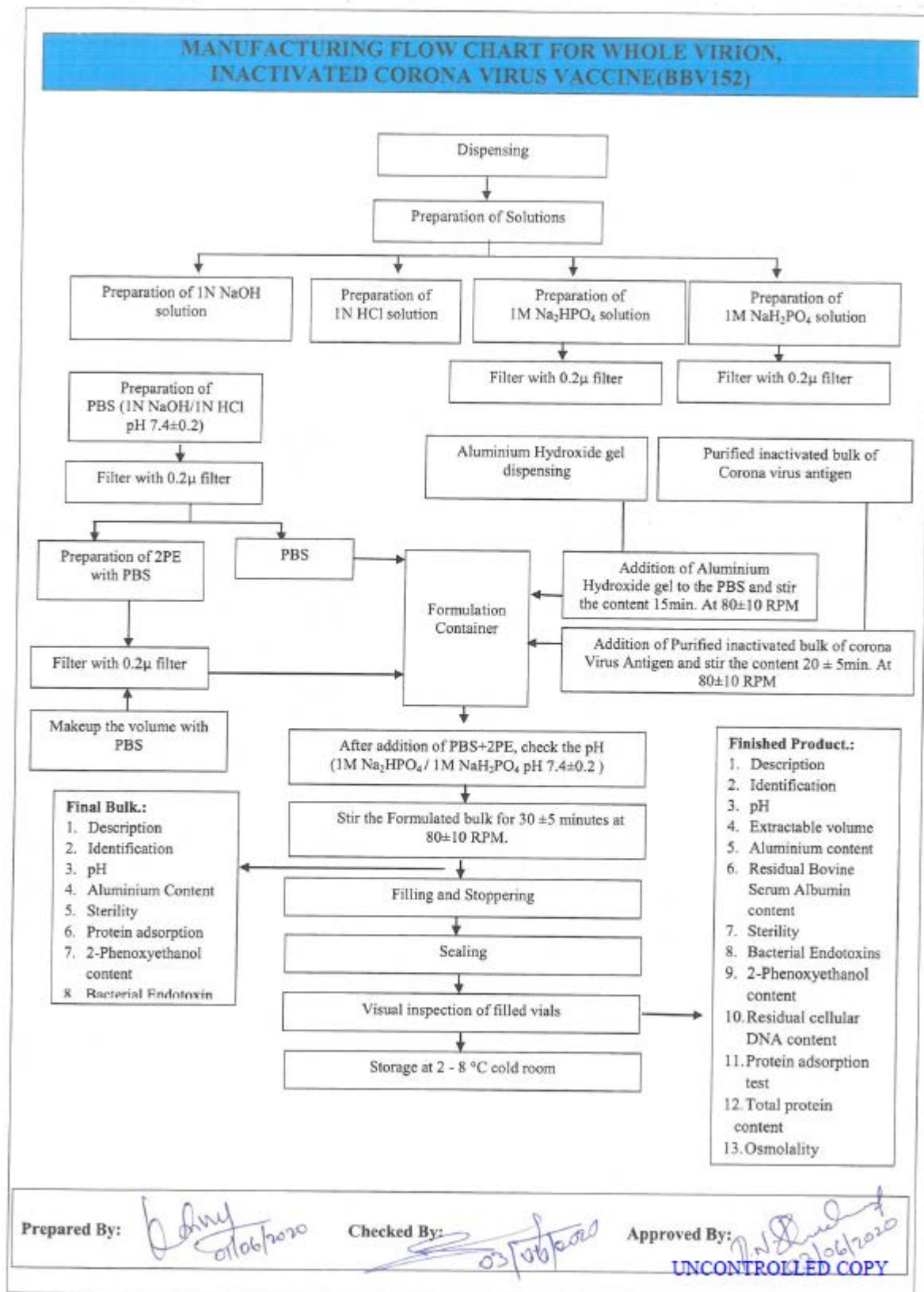


Figure 4: Manufacturing flow chart for Whole-virion Inactivated Coronavirus vaccine (BBV-152)

7.2 LOT RELEASE SPECIFICATIONS

The table lists the in-house specifications and the proposed limits of the constituents and extraneous matter in the Coronavirus vaccine product. The limits were defined after performing tests for consistency from R&D pilot scale batches of the vaccine. The GMP pilot scale batches of the product described in this document comply with the following specifications and the limits.

Table 9: Lot Release Specifications

| S.No | Tests Performed | Acceptance criteria |
|------------------|---------------------------------------|--|
| Final lot | | |
| 1. | Description | White, translucent liquid free from particulate matter |
| 2. | Identification | The ratio of OD of test sample to OD of negative control should not be less than 2 |
| 3. | pH | For Information Only |
| 4. | Extractable Volume | NLT 0.50 mL |
| 5. | Aluminium Content | NLT 0.19 mg/SHD and NMT 0.29 mg/SHD |
| 6. | Residual Bovine Serum Albumin content | NMT 50 ng per Single Human Dose |
| 7. | Sterility | No growth should be observed (Sterile) |
| 8. | Bacterial Endotoxins | Less than 25 international Units (IU) per single human dose (SHD) |
| 9. | 2-Phenoxyethanol content | NLT 85.0% and NMT 115.0% of the stated label claim |
| 10. | Residual Cellular DNA Content | NMT 10 ng per Single Human Dose |
| 11. | Protein adsorption Test | NLT 75% of the stated claim of total protein |

7.3 VACCINE STABILITY

7.3.1 BULK STABILITY

The stability testing of the bulk material that is stored after manufacture, but prior to formulation was studied. Stability testing has been planned for batches for which manufacture and storage are representative of the manufacturing scale of production. Hence, the qualities of the batches of vaccine bulk placed into the stability program are a representative of the quality of the material used in preclinical toxicology and to be used in clinical studies. During manufacture of the inactivated, purified Coronavirus bulk no specific intermediate

that can potentially alter the stability of the final purified bulk substance was identified. The protocols used for stability indicating profile of purified, inactivated Coronavirus bulk provides methods to detect changes in the purity and sterility of the product. Bulk substance batches for Phase I trial are planned to keep under stability programme at real time temperature. .

7.3.2 FINISHED PRODUCTSTABILITY

Stability testing has been done on batches of the formulated material that have been derived from the same vaccine bulk which was entered into the stability testing program. Stability testing specifications of the pilot scale batches and storage conditions can be considered as representative of the manufacturing scale of operations. Hence the quality of the batches of vaccine product placed into the stability program is a representative of the quality of the material used earlier in Pre-Clinical toxicology studies and of the quality of the material to be made at manufacturing scale. The samples will be stored at $5\pm 3^{\circ}\text{C}$ for real time stability and at $25\pm 2^{\circ}\text{C}$ for accelerated stability in an upright position and hence there was no interaction of the drug substance with the closure. The clinical batches manufactured under GMP will be kept for stability testing program and the studies are ongoing. At the accelerated storage condition of $25\pm 2^{\circ}\text{C}$ five time points, including the initial and final time points at 0, 1, 3 and 6 months would be carried out.

The stability of the vaccine product is planned to study under stress conditions with temperature stress of 37°C for 07 days. Good thermal stability of the product was observed up to 37°C during the above time period. This study helps us to understand the effect of minor or major excursions in temperature on the vaccine. From the results of the stability testing of the vaccine product from pilot scale batches, real time storage condition of $5\pm 3^{\circ}\text{C}$ will be confirmed with proposed shelf life of at least two years.

7.4 FORMULATION DEVELOPMENT

This product development report is limited for “Whole Virion, Inactivated Coronavirus Vaccine (BBV152)” for intended use to prevent the Coronavirus infection.

7.4.1 SCOPE:

The scope of this report is applicable to development of “Whole Virion, Inactivated Corona Virus Vaccine (BBV152)” which is intended for prevention of Coronavirus infection, wherein Algel is used as an adjuvant while the Whole Virion Inactivated Corona Virus protein is used as an antigen, based on extensive literature survey 2 concentration of antigens ie 3 and 6 mcg/single human dose in as 0.5mL presentation were used.

7.4.2 TYPE OF FORMULATIONS EXECUTED IS GIVEN BELOW:

1. 152A: 3µg of protein concentration /SHD with 0.25 mg/ml Algel2 (Al⁺⁺⁺) concentration
2. 152B: 6µg of protein concentration /SHD with 0.25 mg/ml Algel2 (Al⁺⁺⁺) concentration
3. 152C: 6µg of protein concentration /SHD with 0.25mg/ ml Algel1 (Al⁺⁺⁺) concentration

Three different formulations were carried out with varying concentration of the antigen as well as the Algel and in one formulation no Algel was added. In all the above formulations, 10mM PBS and 2Phenoxyethanol concentration 5mg/mL were common.

In brief the formulation was carried out using calculated quantity of sterile phosphate buffer, addition of the required quantity of the bulk protein, adjuvant, and 2-Phenoxyethanol 5mg/mL concentration and mixing for 60 minutes.

The formulations were tested for protein adsorption and it confirms that based on the above results it was concluded that the percentage of protein adsorption was meeting the criteria of over 75% binding of the protein to the gel.

8 ANALYTICAL METHODS ESTABLISHMENT

8.1 TESTS FOR VIRUS QUANTITATION

8.1.1 MEDIAN TISSUE CULTURE INFECTIOUS DOSE (CCID₅₀)

Tissue culture infectious dose is the amount of a virus which causes CPE in 50% of cell cultures and is expressed as CCID₅₀/ml. This assay is performed to determine the infectious titer of coronavirus that causes CPE over a period of 5 days while the cells in culture remain viable. Briefly, standardized numbers of Vero cells are seeded in growth medium 24 hrs before the assay in 96-well flat bottom tissue culture plates and the plates were incubated overnight in 37°C incubator with 5% CO₂. When the cells are 90-95% confluent, coronavirus vaccine was seeded at 10- fold serial dilutions (log dilutions) of the virus in serum free medium and incubated for 60 min at 37°C with 5% CO₂. Equal volume of growth medium was added in the control wells. After incubation, the virus containing medium was discarded and 200 µl of growth medium was added to each well and the plates were incubated in a 37°C incubator with 5% CO₂ for 5 days. Signs of CPE were monitored in each well using inverted microscope at the end of the incubation period. The number of CPE positive and negative wells was recorded and CCID₅₀ titer was calculated using Reed and Muench method.

Calculation:

$$\text{Proportionate Distance (PD)} = \frac{(\% \text{ CPE at dilution above } 50\%) - (50\%)}{(\% \text{ CPE at dilution above } 50\%) - (\% \text{ CPE at dilution below } 50\%)}$$

$$\begin{aligned} 50\% \text{ end point titer} &= 10^{\log \text{ total dilution above } 50\% - (\text{PD} \times \log \text{ DF})} \\ &= \text{CCID}_{50} / \text{ml} \end{aligned}$$

*DF = Dilution factor

8.1.2 SAFETY AND IMMUNOGENICITY TESTING OF THE CANDIDATE VACCINE

8.1.2.1 INSTITUTIONAL ANIMAL ETHICS COMMITTEE (IAEC) APPROVAL

All the animal studies were performed after obtaining permission from the Institutional Animal Ethics Committee (IAEC). The functioning of Bharat Biotech's IAEC is overseen by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). CPCSEA is a statutory body constituted under the Prevention of Cruelty to Animals Act, 1960, Govt. of India.

8.2 GLP PRE-CLINICAL TOXICITY STUDIES

8.2.1 8.2.1 GLP STATEMENT

The non-clinical (or pre-clinical) toxicity studies to assess the safety of the candidate Coronavirus vaccine 'BBV152' were performed in compliance with the norms of Good Laboratory Practice (GLP). The studies were carried out at RCC Laboratories India Pvt. Ltd Hyderabad, which is a OECD certified GLP laboratory. All the studies were conducted with the approval of the Institutional Biosafety Committee (IBSC) and the Institutional Animal Ethics Committee (IAEC) of the RCC Laboratories India Pvt. Ltd.

The pre-clinical studies complied with the following guidelines:

- Schedule Y (Amended version of 2005) of the Drugs and Cosmetics Act 1940 and Rules 1945 of the Government of India.
- ICH harmonized tripartite guidelines: Non-Clinical Safety studies for the conduct of Human Clinical Trials for Pharmaceuticals, 16 July 1997.
- WHO Guidelines on Nonclinical Evaluation of Vaccines, Adopted by the 64th meeting of the WHO Expert Committee on Biological Standardization, 21-25 November 2013.
- Annex 2 Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. WHO Expert Committee on Biological Standardization Sixty-fourth report, TRS 987 Annex 2.
- CPCSEA Guidelines for Laboratory Animal Facility, India Journal of Pharmacology, 2003; 35: 257-274.
- OECD Guidelines for the Testing of Chemicals, Section 4, Health Effects, 1998

8.2.2 ANIMAL MODELS

Human intended adjuvanted vaccine was tested for potency in 2 small animal models (Mice, and Rabbits) as per regulatory requirement. Animals were housed in Bharat Biotech, animal facility, after taking appropriate Institutional Animal Ethics Committee (IAEC) approvals. End point investigation (Histopathology, Biochemistry & Hematology) was carried out CRO (RCC Laboratories).

- a. **Mice:** Balb/C (inbred) mice were used for immunogenicity study. Swiss Albino (Outbred) mice were used for Repeated Dose toxicity.
- b. ***Rabbits:** New England White Rabbits were tested for Safety. However, we collected blood to evaluate the antigen specific antibody titer elicited by the Inactivated SARS-CoV-2 vaccine.
- c. ***Rats:** Wistar Rats were used to conduct repeated dose toxicity study for adjuvanted vaccine.
- d. **Hamster:** Syrian Hamster was conducted also be used to test protective efficacy and immunogenicity of inactivated vaccine at NIV, Pune.
- e. **Non-Human Primates:** Challenge studies were conducted to test protective efficacy and immunogenicity of BBV152 in Rhesus Macaques at NIV, Pune.

8.3 PRE-CLINICAL STUDIES:

8.3.1 SAFETY AND IMMUNOGENICITY IN MICE, RATS, AND RABBITS:

Study objective:

To evaluate the safety and immunogenicity of a whole-virion inactivated SARS-COV-2 vaccine (BBV152), adjuvanted with aluminium hydroxide gel (Algel), or anovel TLR7/8 agonist adsorbed Algel.

Study design:

We used a well-characterized SARS-CoV-2 strain and an established vero cell platform to produce large-scale GMP grade highly purified inactivated antigen, BBV152. Product development and manufacturing were carried out in a BSL-3 facility. Immunogenicity was determined at two antigen concentrations (3µg and 6µg), with two different adjuvants in mice, rats, and rabbits.

Three animal models were used to evaluate the immunogenicity and safety of the three inactivated whole virion vaccine formulations (BBV152 A, B & C).

- a) **Mice:** Balb/C or Swiss Albino mice (6-8week old) were vaccinated via an intraperitoneal or intramuscular route with either 1/10th or 1/20th of full human single

dose (BBV152 A, B or C) of inactivated vaccine with or without adjuvant on day 0, 7 & 14 days (n+1 (one extra dose compared to the intended human regimen doses). A formulation with 9µg was also tested.

- b) **Rats:** Wistar Rats (6-8weeks old) were vaccinated intramuscularly with 9µg of inactivated whole-virion vaccine with Algel-1 or Algel-2 on days 0, 7 & 14 days (n+1 doses).
- c) **Rabbits:** Zealand white rabbits (3-4 months old) were vaccinated via an intramuscular route with full Human intended single dose (BBV152 A, B or C; n+1 doses). The animals were observed up to 14 days, post third dose.

All studies were conducted with an equal number of males and females unless otherwise specified. The control group was injected with saline. Animals were bled from the retro-orbital plexus; 2hours before each immunization on 0, 7, 14 & 21 days, and serum was separated and stored at -20°C until further use.

Pooled and individual sera from vaccinated mice and rabbits were used to test the antigen-specific antibody binding titer and antibody isotyping profile by Enzyme-Linked Immunosorbent Assay (ELISA). Pooled or Individual sera from all vaccinated species (mice, rabbits & rats) were used to test neutralization antibody titer by Plaque Reduction Neutralization Test (PRNT90) or Micro Neutralization Test (MNT50).

BBV152 vaccine candidates were formulated with two alum adjuvants: Algel (aluminium hydroxide gel) and Algel-IMDG, an imidazoquinoline class molecule (TLR7/TLR8 agonist abbreviated as IMDG) adsorbed on aluminium hydroxide gel. The agonist molecule for Algel-IMDG was licensed from ViroVax LLC, USA. Three vaccine formulations were prepared with 3µg and 6µg with Algel-IMDG (BBV152A and BBV152B, respectively) and 6µg with Algel (BBV152C).

Results:

Both the adjuvanted vaccines (with Algel and Algel-IMDG), Antigen and Adjuvant alone did not reveal any treatment-related findings, except local reactions when administered through the human intended route (intramuscular) on days 0, 7, and 14 (n+1) with full Human single dose (HSD) or higher than HSD in rodents and non-rodents, thereby establishing the vaccine safety. All the three inactivated whole virion SARS-CoV-2 vaccine candidates showed 100% seroconversion with high titers of antigen binding and neutralizing antibody responses. The adjuvanted formulation, BBV152B, when immunized in Balb/C mice, showed 10 times higher dose sparing effect compared to antigen alone (Figure 5 & 6). These formulations also induced immunity that is biased towards Th1 mediated response, as demonstrated by the ratio between IgG2a and IgG1 (greater than 1) (Figure 7). Additionally, secretion of anti-viral cytokines such as IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, IFN-γ was observed on days 7 and 14 (7 days after the 1st & 2nd dose) of vaccination with Algel-IMDG adjuvanted formulations. A combination of high neutralizing antibody titers elicited against inactivated antigen alone

and the presence intact spike protein on the surface of the virus confirms that the antigen is in the right confirmation and can itself may act as a Th1 inducer with its surface glycoproteins, intracellular viral proteins. The study publication is available as pre-print at bioRxiv (doi: <https://doi.org/10.1101/2020.09.09.285445>) [21].

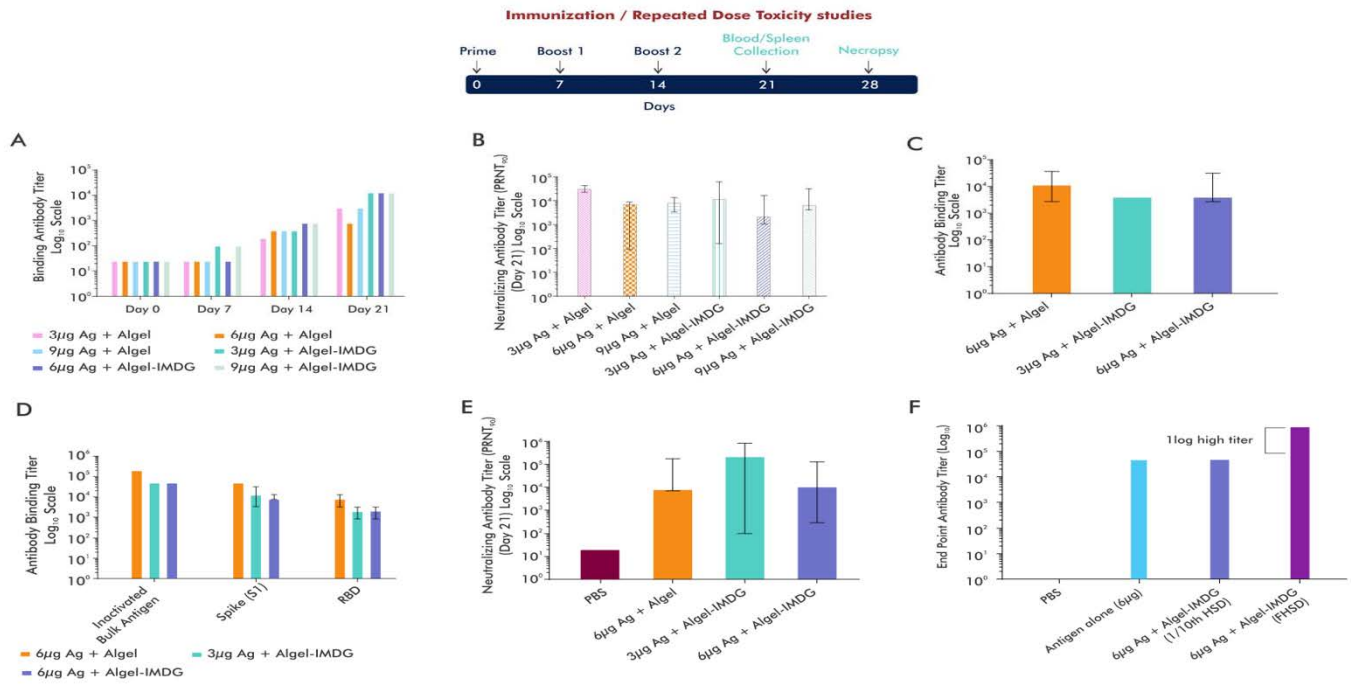


Figure 5: BBV152 Vaccines Induces High Virus-specific Antibody Response in Mice

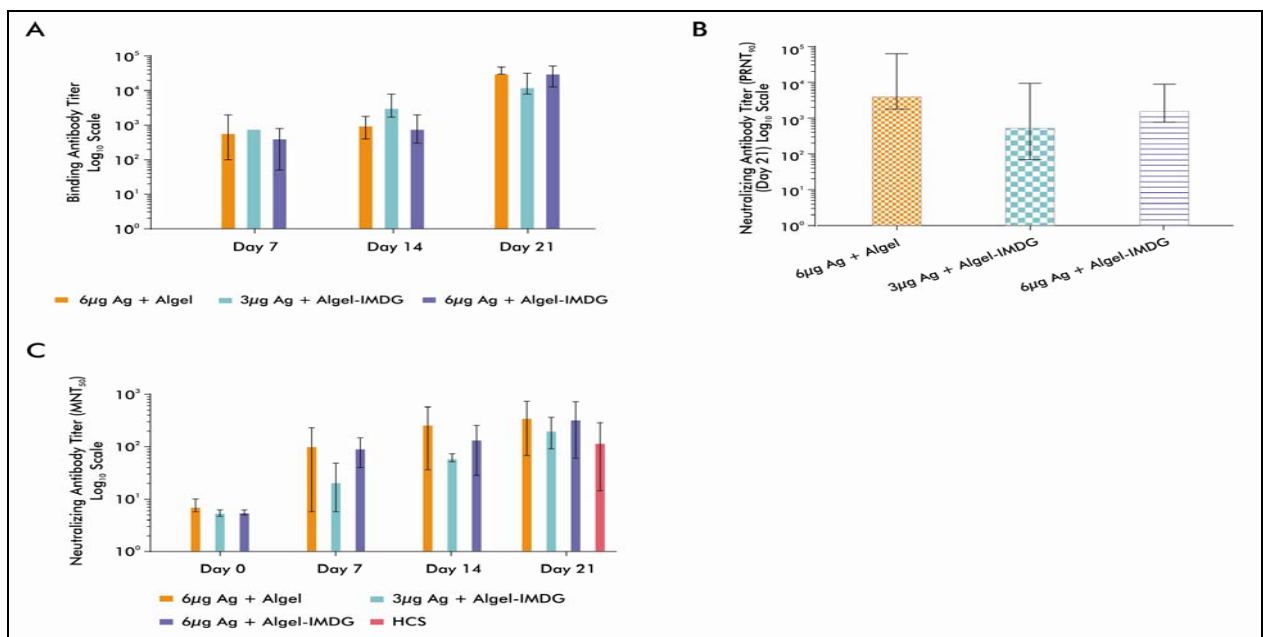


Figure 6: BBV152 Induces Robust Neutralizing Antibody Response in Rabbits

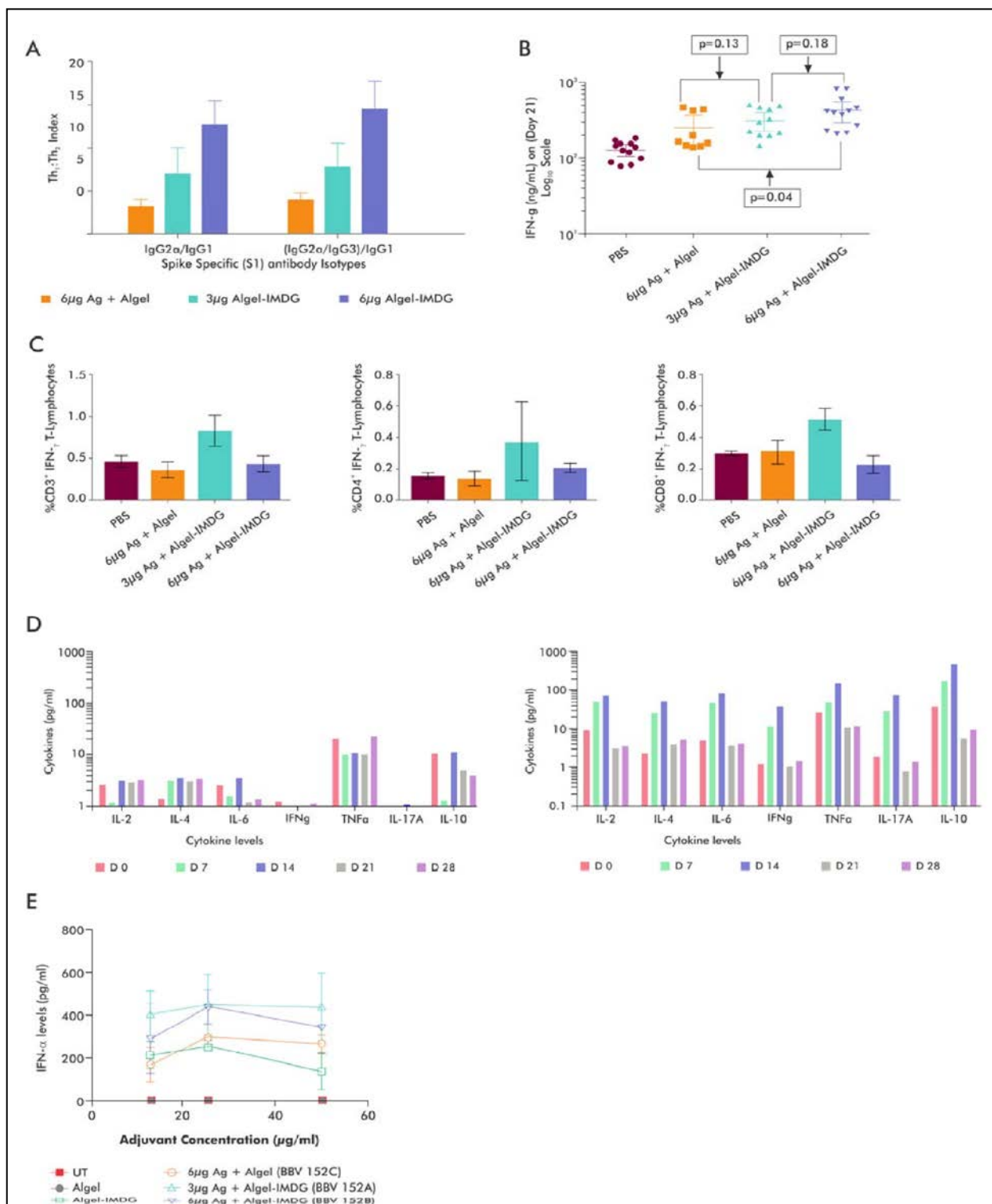


Figure 7: BBV152 Induces A Robust Virus-specific T Cell Response.

Conclusion:

BBV152 vaccine formulations generated significantly high antigen-binding and neutralizing antibody titers, at both concentrations, in all three species with excellent safety profiles. The inactivated vaccine formulation containing TLR7/8 agonist adjuvant-induced Th1 biased antibody responses with elevated IgG2a/IgG1 ratio and increased levels of SARS-CoV-2 specific IFN-γ + CD4 T lymphocyte response.

8.3.2 IMMUNOGENICITY AND PROTECTIVE EFFICACY IN THE SYRIAN HAMSTERS

Study objective:

To assess the immunogenicity and protective efficacy of an inactivated SARS-CoV-2 vaccine (BBV152) in hamsters.

Study design:

Two different antigen concentrations (3 µg and 6 µg) and 2 adjuvants namely Algel 1 (Alum) and Algel 2 (TLR 7/8 (imidazoquinoline) agonist adsorbed alum) in combinations were used for the study. The vaccine formulations evaluated in the study were 6 µg antigen with Algel1, 3 µg with Algel 2, and 6 µg with Algel 2. Accordingly, the animals were divided into 4 groups (9 animals/per groups):

1. Placebo –PBS
2. 6 µg antigen with Algel1
3. 3 µg with Algel 2
4. 6 µg with Algel 2

Immunization of hamsters

Animals of each group were immunized with 0.1 ml of PBS/vaccine formulations intramuscularly in the left hind leg under isoflurane anaesthesia 0, 14, and 35 days. Post immunization hamsters were observed daily for clinical signs and injection site reaction. Rectal temperature was monitored every 24 hours for 3 days post-immunization and weekly thereafter. Body weight was measured every alternate day for the first week and weekly thereafter. The hamsters were bled on day 12, 21, and 48 post-immunization to check for antibody response.

Challenge study in hamsters

For optimization, of the intranasal virus challenge dose, SARS-CoV-2 dilutions ranging from $10^{1.5}$ TCID₅₀ /0.1ml to $10^{5.5}$ TCID₅₀ /ml were inoculated in 5 groups of 6 Syrian hamsters each in containment facility.

The immunized hamsters were challenged with 0.1 ml of $10^{5.5}$ TCID₅₀ SARS-CoV-2 virus intranasally on the eighth-week post-immunization (day 50) in the containment facility of ICMR-National Institute of Virology, Pune under isoflurane anaesthesia.

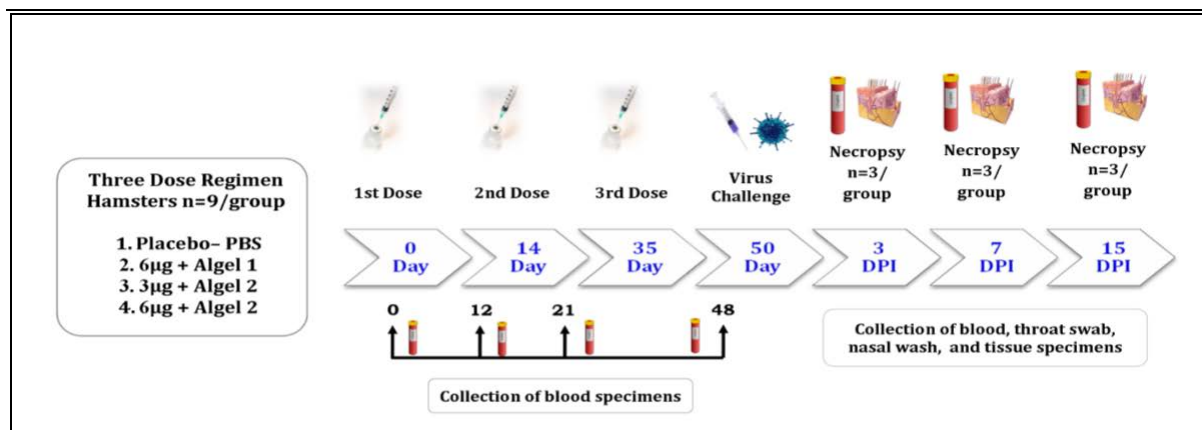


Figure 8: Experiment summary of the workflow Syrian Hamster study

Results

Three dose vaccination regimes with three formulations of BBV152 induced significant titres of SARS-CoV-2 specific IgG and neutralizing antibodies (Figure 9). The formulation with imidazoquinoline adsorbed on alum adjuvant remarkably generated a quick and robust immune response. Th1 biased immune response was demonstrated by the detection of IgG2 antibodies. Post-SARS-CoV-2 infection, vaccinated hamsters did not show any histopathological changes in the lungs. The protection of the hamsters was evident by the rapid clearance of the virus from lower respiratory tract, reduced virus load in upper respiratory tract, absence of lung pathology and robust humoral immune response. The study publication is available as pre-print at Research Square (DOI:10.21203/rs.3.rs-76768/v1) [22].

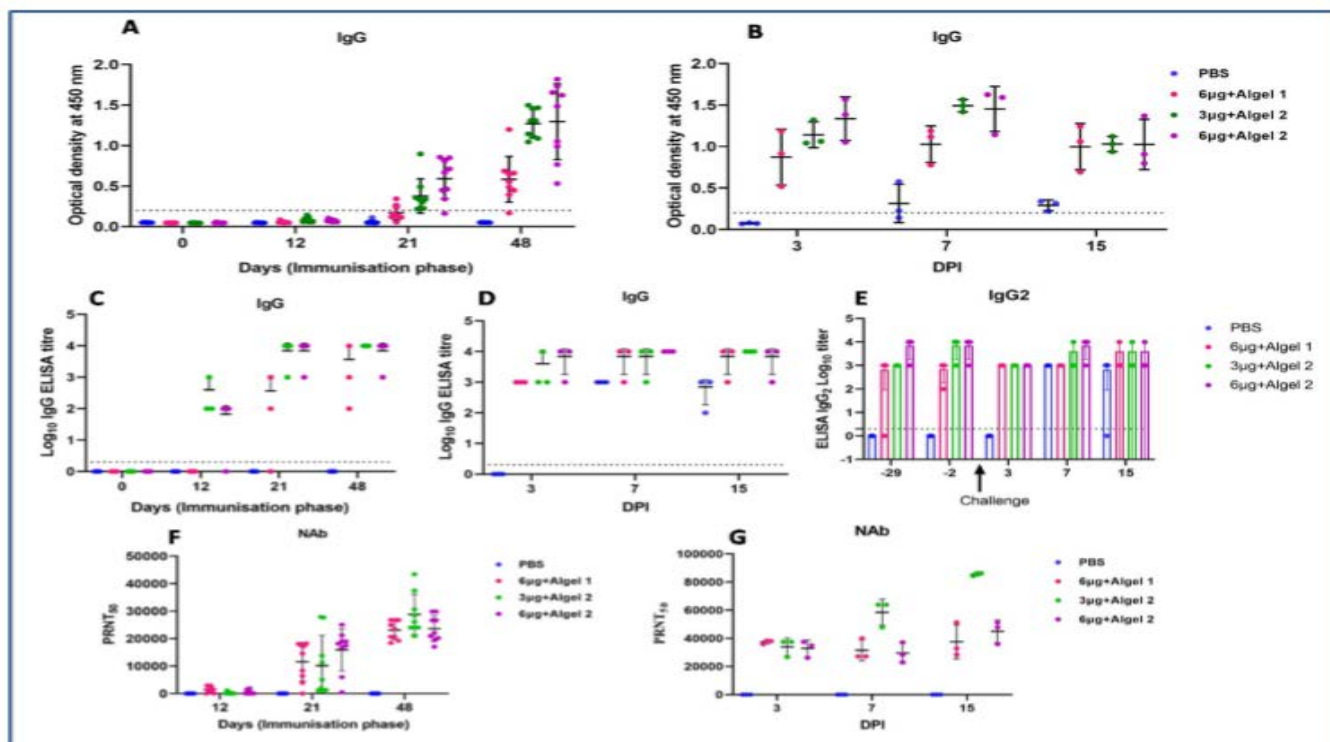


Figure 9: Humoral response in vaccinated animals

Conclusion: These findings confirm the immunogenic potential of BBV152 and further protection of hamsters challenged with SARS-CoV-2.

8.3.3 IMMUNOGENICITY AND PROTECTIVE EFFICACY IN RHESUS MACAQUES

Study objective:

To assess the immunogenicity and protective efficacy of an inactivated SARS-CoV-2 vaccine (BBV152) in rhesus macaques.

Study design:

Twenty macaques were divided into four groups of five animals each. One group was administered a placebo while three groups were immunized with three different vaccine candidates at 0 and 14 days. The groups were:

1. Group I: Placebo –PBS
2. Group II: 6 µg + Adjuvant A
3. Group III: 3 µg + Adjuvant B
4. Group IV: 6 µg + Adjuvant B

All the macaques were challenged with SARS-CoV-2 fourteen days after the second dose.

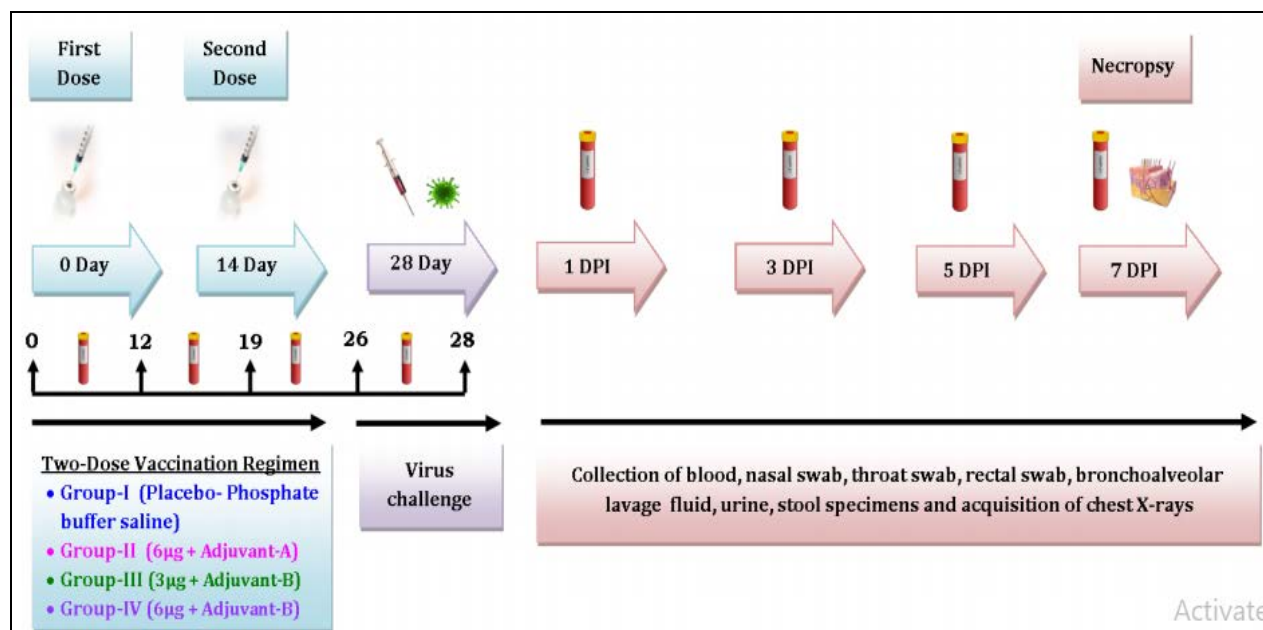


Figure 10: Experiment summary of the workflow of NHP study

Results

The protective response was observed with increasing SARS-CoV-2 specific IgG and neutralizing antibody titers from 3rd-week post-immunization. Weight loss, pyrexia and worsening of SpO₂ at room air, lethargy, reduced food and water intake, reduced self-grooming was observed in placebo group and persisted till 7 DPI whereas these features resolved in the other group II and IV. Viral clearance was observed from bronchoalveolar

lavage fluid, nasal swab, throat swab, and lung tissues at 7 days post-infection in the vaccinated groups. No evidence of pneumonia was observed by histopathological examination in vaccinated groups, unlike the placebo group which showed features of interstitial pneumonia and localization of viral antigen in the alveolar epithelium and macrophages by immunohistochemistry. The study publication is available as pre-print at Research Square (DOI:10.21203/rs.3.rs-65715/v1) [23].

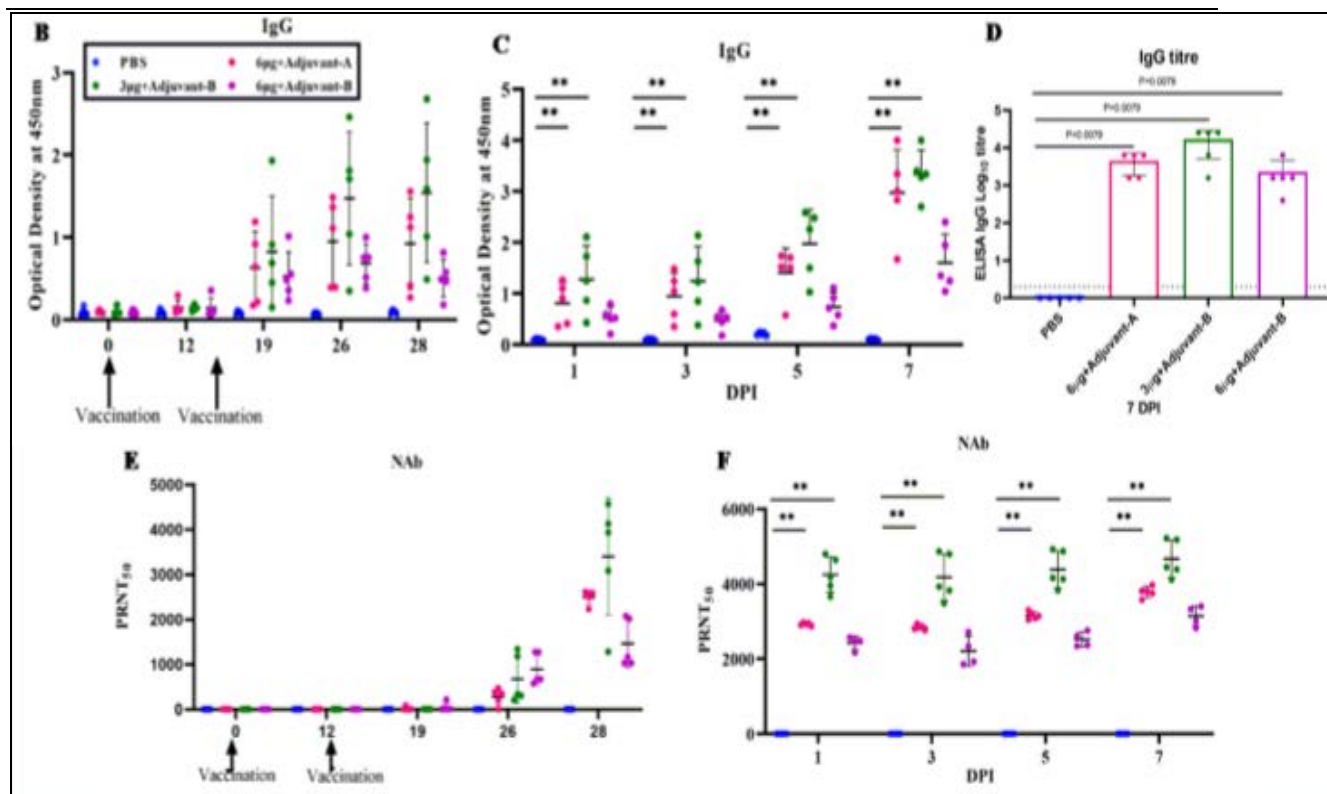


Figure 11: Humoral response in vaccinated animal

Conclusion:

The study demonstrates that a two-dose vaccination regimen induced a significant immune response and provided effective protection in animals challenged with SARS-CoV-2.

Table 10: Overview of the pre-clinical studies:

| Study Type | Test System | Test Item | Route of Administration | Dosing Regimen | Unit dose | Key Test Item result |
|---|---------------------------------|---|-------------------------|----------------|---|---|
| Repeated dose toxicity studies | Wistar Rats | Antigen, Adjuvante vaccines, Adjuvants | Intramuscular | Day 0, 7 & 14 | 1/10 th or 1/20 th of human equivalent dose. (3µg and 6µg with Algel-IMDG(BBV152A and BBV152B, respectively), and 6µg with Algel (BBV152C)) | All the Test Items have been demonstrated to be safe from a Toxicology perspective. |
| | Swiss Albino Mice | Adjuvanted vaccines & Adjuvants | Intramuscular | | | |
| | BALB/c Mice | Antigen, Adjuvanted vaccines, & Adjuvants | Intraperitoneal | | | |
| | New Zealand White Rabbits | Adjuvanted Vaccines | Intramuscular | | | |
| Mutagenicity assay (Bacterial Reverse Mutation) | Salmonella typhimurium | Algel-IMDG | - | - | - | |
| Maximum Tolerated Dose studies | Swiss albino mice & Wistar Rats | Algel-IMDG | Intramuscular | Day 0 | 200µg Algel and 20µg IMDG | |
| Immunogenicity and protective efficacy | Syrian hamsters | BBV-152A, B, C, and placebo | Intramuscular | Day 0 & 14 | 3µg and 6µg with Algel-IMDG (BBV152A and BBV152B, respectively), and 6µg with Algel (BBV152C)) | BBV152, an inactivated vaccine induced potent humoral immune response in hamsters. Th1 biased immune response was elicited by BBV152. BBV152 protected Syrian hamsters from SARS-CoV-2 pneumonia. |
| Immunogenicity and protective efficacy | Rhesus macaques | BBV-152A, B, C, and placebo | Intramuscular | Day 0 & 14 | 3µg and 6µg with Algel-IMDG (BBV152A and BBV152B, respectively), and 6µg with Algel (BBV152C) | A two-dose vaccination regimen using 3µg dose of the vaccine candidate with adjuvant B induce a significant immune response and provide effective protection in animals challenged with SARS-CoV-2. |

8.3.4 OVERALL CONCLUSION OF THE PRECLINICAL STUDIES:

Based on the above pre-clinical study results, it was concluded that all formulations shown to be safe, immunogenic, in both mice, rats & rabbits. The vaccine candidates showed good immune response and protective efficacy in Syrian hamsters and Rhesus macaques. Hence, it can be concluded that the vaccine candidate manufactured was safe and effective.

9 CLINICAL DEVELOPMENT PATHWAY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are accelerating globally leading to an increase in morbidity and mortality. In view of the prevailing covid-19 pandemic, the clinical trial has been designed in a seamless manner (phase1/2) compared to conventional approach. The sample size has been deliberately kept large to assess the immune responses from the vaccine ensuring a high degree of power.

The Clinical study was designed as a adaptive, Seamless Phase 1, Followed by Phase 2. The safety, reactogenicity, tolerability, and immunogenicity was evaluated through Four arms (BBV152-A, BBV152-B, BBV152-C and Placebo) in Phase I and Based on the Phase1 results two arms (BBV152-A and BBV152-B) were selected for Phase II.

WholeVirion, Inactivated SARS-CoV-2 Vaccine (BBV152) has proven to be safe and well-tolerated in the Phase II study. The vaccine containing 6 µg of whole virion plus adjuvant was selected for Phase 3.

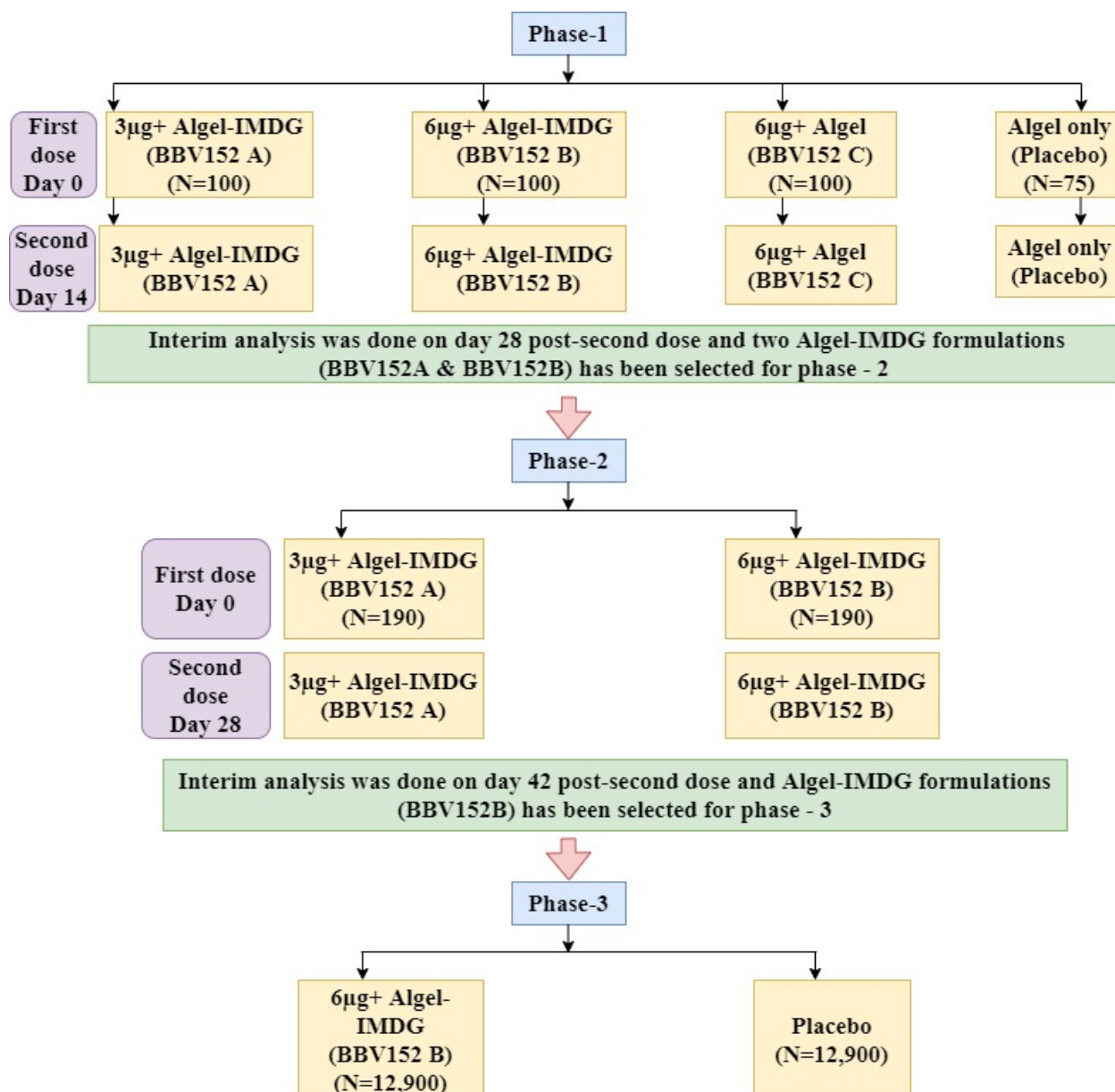


Figure 12: COVAXIN Clinical Trial Pathway

Preliminary Report of the Phase 1 Clinical Trial

We conducted a double-blind, multicentre, randomized, controlled phase 1 trial to evaluate the safety, reactogenicity, tolerability, and immunogenicity of three different formulations of BBV-152 (BBV-152A, BBV-152B, and BBV-152C) in healthy male and nonpregnant female volunteers.

9.1 STUDY DESIGN AND PARTICIPANTS

Healthy individuals aged 18-55 years were taken into study. All the individuals were screened for eligibility based on the health status, including medical history, laboratory findings, vital signs, and physical examination and enrolled after getting signed and dated

written informed consent (audio/video consent for vulnerable participants). Participants who tested positive for Covid-19 at the screening by either nucleic acid test or serology were excluded from the trial. Details of inclusion and exclusion criteria can be found on www.clinicaltrials.gov: NCT04471519.

Participants were assigned a computer-generated randomization number (IWRS). After meeting eligibility, participants were randomized equally to receive three vaccine groups (BBV 152A, BBV 152B, BBV 152C) and a control group of aluminum hydroxide (alum) adjuvant only. A two-dose intramuscular regimen was adopted, 14 days apart at dose strength.

The trial was conducted across 11 sites in India. The trial was approved by the Central Licensing Authority (India), respective Ethics Committees, and was conducted in compliance with all International and local Ethical guidelines.

9.1.1 STUDY VACCINE

BBV152 (manufactured by Bharat Biotech) is a whole virion β -propiolactone-inactivated SARS-COV-2 vaccine. The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7/TLR8 agonist abbreviated as IMDG) adsorbed onto Algel. The agonist molecule for Algel-IMDG was licensed from ViroVax LLC, USA. Three vaccine formulations were prepared with 3 μ g and 6 μ g with Algel-IMDG (BBV152A and BBV152B, respectively) and 6 μ g with Algel (BBV152C). The placebo group contained only sterile phosphate-buffered solution and Algel adjuvant. The vaccine was provided as a sterile liquid for injection through the intramuscular route at a volume of 0.5mL/dose, as a two-dose regimen, 14 days apart.

9.1.2 STUDY PROCEDURES

Two doses of BBV 152 vaccine were administered at a volume of 0.5mL/dose injection intramuscularly (deltoid muscle) at days 0 and 14. The follow-up visits were scheduled on days 7, 28, 42, 104, and 194 days. The study was performed in a dose-escalation manner wherein after completing vaccination in the first 50 participants with BBV 152A (the lowest antigen concentration) and placebo, the participants were followed up for seven days and safety was assessed by an independent Data Safety Monitoring Board (DSMB). Based on the DSMB recommendation, the trial was allowed to continue by the remaining participants' enrollment across all groups.

9.1.3 BLINDING

The appearance, color, viscosity across all treatment, and control formulations were identical. Treatment groups were blinded against participants, investigators, study coordinators, study-related personnel, and the sponsor (excluding an unblinded CRO, tasked with the dispatch of vaccine vials and generation of master randomization code). Blinding was maintained using the randomization code.

9.1.4 SAFETY ASSESSMENTS

The primary safety outcome was the number and percentage of participants with solicited local and systemic reactogenicity within -two hours, -7 days, -14 days, and 28 days after vaccination. Participants recorded local and systemic reactions using a diary card for seven days after each vaccination. No formal instructions on the use of analgesics were given to participants before or after vaccination. Laboratory values (serum chemistry and hematology) were compared between the pre-vaccination (day 0) and the post-vaccination (day 28) visits.

9.1.5 IMMUNOGENICITY ASSESSMENTS

Binding antibody (IgG) responses against RBD, S, and N proteins of SARS-CoV-2, were assessed by enzyme-linked immunosorbent assay (ELISA) and expressed as Geometric Mean Titers (GMTs). Neutralizing antibody titers (NAb) were assessed by wild type virus neutralization assays: micro-neutralization assay (MNT₅₀) across the entire cohort. Seroconversion (SCR) rates were defined as titers remaining ≥ 4 -fold above baseline. All serum samples were analyzed in a blinded manner at Bharat Biotech and NIV.

9.2 RESULTS

Among the 555 screened between July 13th and July 29th, 2020, 375 participants were randomized. Among the three treatment arms, 100 each were randomized into the BBV152-A, -B, and C groups, respectively, and 75 were randomized into the control arm.

9.2.1 SAFETY

After the first and second vaccination, all AEs were mild or moderate in severity and resolved transiently. Pain at the injection site was the most common local adverse event reported. The other adverse events reported were fever, headache, fatigue, body pain, cold, cough, nausea, vomiting, and dizziness. The distribution of local and systemic AEs was equal amongst all groups, and is mentioned in the below table. A total of 7 AEs was reported within 2 hours after Dose 1 (3 μ g with Algel-IMDG: 0; 6 μ g with Algel-IMDG: 2, 6 μ g with Algel: 1, Control arm: 4) The AEs were pain at injection site, swelling of arm, headache, giddiness, feeling hungry. No immediate AEs were reported after Dose 2.

One serious adverse event was reported in the BBV152 C arm. The participant was found positive for SARS-CoV-2 (by RT-PCR) 9 days after screening and 5 days following the administration of vaccine. The participant was hospitalized, and recovered after treatment. Based on the causality assessment, the serious adverse event was not related to the vaccine.

Table 11: Adverse events reported in Phase 1 study

| Adverse Events | 3 μ g with Algel-IMDG N=100 | 6 μ g with Algel-IMDG N=100 | 6 μ g with Algel N=100 | Control Arm N=75 |
|-------------------------------|------------------------------------|------------------------------------|-------------------------------|---------------------|
| 0-7 Days | | | | |
| Local reactions | | | | |
| Pain at injection site | | | | |

| Mild | 4(4%; 1.1 – 9.9) | 4(4%; 1.1 – 9.9) | 1 (1%; 0.0-5.5) | 2(3%; 0.3-9.3) |
|-------------------------------|-------------------------|-------------------------|------------------------|-----------------------|
| Moderate | 1(1%; 0.0-5.5) | 1(1%; 0.0-5.5) | 0 | 0 |
| Swelling | | | | |
| Mild | 0 | 0 | 0 | 1(1%; 0.0-7.2) |
| Moderate | 0 | 0 | 0 | 0 |
| Systemic reactions | | | | |
| Fever | | | | |
| Mild | 0 | 1(1%; 0.0-5.5) | 1(1%; 0.0-5.5) | 0 |
| Moderate | 0 | 1(1%; 0.0-5.5) | 2 (2%; 0.2-7.0) | 0 |
| Body ache | | | | |
| Fatigue | | | | |
| Mild | 1(1%; 0.0-5.4) | 0 | 0 | 0 |
| Moderate | 2(2%; 0.2- 7.0) | 3(3%; 0.6-8.5) | 0 | 0 |
| Headache | | | | |
| Mild | 1(1%; 0.03-5.5) | 2(2%; 0.2-7.0) | 0 | 5(7%; 2.2-14.9) |
| Moderate | 0 | 3(3%; 0.6-8.5) | 2(2%; 0.2-7.0) | 0 |
| Nausea or vomiting | | | | |
| Mild | 1(1%; 0.03-5.5) | 2(2%; 0.2-7.0) | 2(2%; 0.2-7.0) | 2(3%; 0.3-9.3) |
| Moderate | 0 | 0 | 0 | 0 |
| 0-14 Days | | | | |
| Local reactions | | | | |
| Pain at injection site | | | | |
| Mild | 2(2%; 0.2-7.0) | 1(1%; 0.03-5.5) | 1(1%; 0.0-5.5) | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Swelling | | | | |
| Mild | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Systemic reactions | | | | |
| Fever | | | | |
| Mild | 2 | 1 | 1 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Body ache | | | | |
| Mild | 0 | 0 | 0 | 0 |
| Moderate | 1(1%; 0.0-5.5) | 0 | 0 | 0 |
| Fatigue | | | | |
| Mild | 1(1%; 0.03-5.4) | 0 | 3(3%;0.6-8.5) | 0 |
| Moderate | 1 | 0 | 0 | 0 |
| Headache | | | | |
| Mild | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Nausea or vomiting | | | | |
| Mild | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |

Data are n (%; 95% CI). The safety set includes all participants who received one dose of the vaccine (n=375). Dose 1 events are from days 0–7 and dose 2 events are days 14–21. The grading scale for most adverse events was based on the US Food and Drug Administration

(FDA) guidance document for toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. For adverse events where grading was not mentioned in the FDA guidance document, we have used the common terminology criteria for adverse events grading. There were no severe adverse events.

9.2.2 IMMUNE RESPONSES

Neutralizing Antibody Titers

Since all recruited participants were screened for IgM and IgG antibodies to SARS-CoV-2, no participants had detectable NAbs at baseline (analyzed by MNT₅₀). The proportion of participants that demonstrated seroconversion (after Day 28) was 87.88%, 91.92%, and 82.8% in the BBV152 -A, -B, and -C, groups, respectively. Post second dose GMTs (Day 28) among the three vaccine arms were 61.7, 66.4, and 48 in the BBV152 -A, -B, and -C groups, respectively. Responses in BBV152 -A and -B were noticeably higher than BBV152C, albeit not statistically significant. Anti-spike glycoprotein IgG antibodies secretion was seen on day 104 post vaccination, which shows the long-lasting T-cell memory response generated by BBV152. Similar results of long-term immunity were reported in convalescent patients who previously had COVID-19. Presently, memory B-cell responses from BBV152 are currently being evaluated [24, 25].

Table 12: Neutralizing titers and Seroconversion rates in different treatment groups

| Groups | Day 0 | Day 14 | | Day 28 | |
|-----------------------|----------------------|------------------------|-------------------------------|-------------------------|-------------------------------------|
| | GMT (95% CI) | GMT (95% CI) | n (SC%) (95% CI) | GMT (95% CI) | n (SC%) (95% CI) |
| Treatment A N=99 | 6.21 (5.92,6.52) | 9.14 (8.05, 10.40) | 10 (10.1%) (4.16, 16.04) | 61.70 (49.50, 76.90) | 87 (87.88%) (81.45, 94.31) |
| Treatment B N=99 | 6.01 (5.81, 6.23) | 11.20 (9.56, 13.00) | 21 (21.21%) (13.16, 29.27) | 66.4 (53.40, 82.40) | 91 (91.92%) (86.55, 97.29) |
| Treatment C (N=93) | 5.95 (5.80, 6.10) | 9.45 (8.20, 10.90) | 7 (7.53%) (2.16, 12.89) | 48.00 (37.70, 61.10) | 77 (82.8%) (75.12, 90.47) |
| Treatment D (N=73) | 6.13 (5.84, 6.43) | 6.07 (5.86, 6.28) | -- | 7.20 (6.39, 8.11) | 6 (8.22%) (1.92, 14.52) |

9.3 CONCLUSION:

Based on the interim results of the Phase 1 clinical trial, the BBV-152 B formulation (6µg + adjuvant B (Alum + imidazoquinoline)) produced better immune response compared to BBV-152A and C although the difference was not statistically different.

In conclusion, Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) has been proven to be safe and well tolerated, and immunogenic in the Phase 1 study.

COVAXIN Phase I clinical study publication and Supplementary data is enclosed as **Annexure 1**

10 PRELIMINARY REPORT OF THE PHASE 2 CLINICAL TRIAL

We conducted a double-blind, randomized, multicentre phase 2 trial to evaluate the immunogenicity and safety of BBV-152 in healthy adults and adolescents.

10.1 STUDY DESIGN AND PARTICIPANTS

Healthy individuals aged 12-65 years were taken into study. All the individuals were screened for eligibility based on the health status, including medical history, laboratory findings, vital signs, and physical examination and enrolled after getting signed and dated written informed consent (audio/video consent for vulnerable participants). Participants who tested positive for Covid-19 at the screening by either nucleic acid test or serology were excluded from the trial. Details of inclusion and exclusion criteria can be found on www.clinicaltrials.gov: NCT04471519.

Participants were assigned a computer-generated randomization number (IWRS). After meeting eligibility, participants were randomized equally to receive two groups BBV152 and a control group of aluminum hydroxide (alum) adjuvant only. A two-dose intramuscular regimen was adopted, 28 days apart.

The trial was conducted across 9 sites in India. The trial was approved by the Central Licensing Authority (India), respective Ethics Committees, and was conducted in compliance with all International and local Ethical guidelines.

10.2 STUDY VACCINE

BBV152 (manufactured by Bharat Biotech) is a whole virion β -propiolactone-inactivated SARS-COV-2 vaccine. The vaccine candidate is formulated with Algel-IMDG, an imidazoquinoline class molecule (TLR7/TLR8 agonist abbreviated as IMDG) adsorbed onto Algel. The agonist molecule for Algel-IMDG was licensed from ViroVax LLC, USA. The vaccine was provided as a sterile liquid for injection through the intramuscular route at a volume of 0.5mL/dose, as a two-dose regimen, 28 days apart.

10.3 STUDY PROCEDURES

Two doses of BBV 152 vaccine were administered at a volume of 0.5mL/dose injection intramuscularly (deltoid muscle) at days 0 and 28. The follow-up visits were scheduled on days 42, 56, 118, and 208 days.

10.4 BLINDING

The appearance, color, viscosity across all treatment, and control formulations were identical. Treatment groups were blinded against participants, investigators, study coordinators, study-related personnel, and the sponsor (excluding an unblinded CRO, tasked with the dispatch of vaccine vials and generation of master randomization code). Blinding was maintained using the randomization code.

10.5 SAFETY ASSESSMENTS

The primary safety outcome was the number and percentage of participants with solicited local and systemic reactogenicity within -two hours, 7 days (days 0-7 and days 28-35) post vaccination. All the events are to be recorded in a memory aid containing fields for symptom onset, severity, time to resolution, and concomitant medications, and participants were instructed to complete the form daily. The form was collected during the next visit to the site. Routine telephone calls were scheduled following the first 7 days after each vaccination. Laboratory values (serum chemistry and hematology) were compared between the pre-vaccination (day 0) and the post-vaccination (day 28) visits.

10.6 IMMUNOGENICITY ASSESSMENTS

Anti-IgG responses against the spike (S1) glycoprotein, receptor-binding domain (RBD), and nucleocapsid protein of SARS-CoV-2 were assessed by ELISA (Syngene, Bangalore, India), and are expressed as geometric mean titres (GMTs). Wild-type virus neutralising antibody titres in serum samples were analysed with a microneutralisation assay (MNT50) and a plaque-reduction neutralisation test (PRNT50) at Bharat Biotech in a masked manner. MNT50 and PRNT50 were developed in-house. Seroconversion was defined as a post-vaccination titre at least four-fold higher than the pre-vaccination titre. To ensure the validity of our assay, an arbitrary number of serum samples (n=40) were selected at random and tested by PRNT50 at National Institute of Virology.

10.7 RESULTS

Among the 921 screened between September 7th and September 11th, 2020, 380 participants were randomized. Among the two treatment arms, 190 each were randomized into the BBV152-A, and B groups, respectively.

10.8 SAFETY

After the first and second vaccination, all AEs were mild or moderate in severity and resolved transiently. Pain at the injection site, followed by headache, fatigue and fever were the most common adverse event reported. No severe or life-threatening solicited adverse events were reported. No significant difference in safety was observed between these two groups. No serious adverse events were reported in this study.

Table 13: Adverse events reported in Phase 2

| Adverse Events | Dose 1 | | Dose 2 | |
|----------------|----------------------|----------------------|----------------------|----------------------|
| | 3 µg with Algel-IMDG | 6 µg with Algel-IMDG | 3 µg with Algel-IMDG | 6 µg with Algel-IMDG |

| | N=190 | N=190 | N=190 | N=190 |
|----------------------------------|--------|--------|--------|--------|
| Local reactions | | | | |
| Pain at injection site | | | | |
| Mild | 5(3%) | 6(3%) | 7(4%) | 4(2%) |
| Moderate | 1 (1%) | 0 | 0 | 1 (1%) |
| Redness at injection site | | | | |
| Mild | 1(1%) | 1(1%) | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Itching | | | | |
| Mild | 1(1%) | 1(1%) | 0 | 2(1%) |
| Moderate | 0 | 0 | 0 | 0 |
| Stiffness in upper arm | | | | |
| Mild | 1(1%) | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Weakness injection arm | | | | |
| Mild | 0 | 0 | 1(1%) | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Systemic reactions | | | | |
| Body ache | | | | |
| Mild | 0 | 2(1%) | 1(1%) | 2 (1%) |
| Moderate | 0 | 1(1%) | 0 | 0 |
| Fever | | | | |
| Mild | 2 (1%) | 5(3%) | 5(3%) | 4 (2%) |
| Moderate | 1(1%) | 3(2%) | 0 | 0 |
| Headache | | | | |
| Mild | 2(1%) | 1 (1%) | 1 (1%) | 2 (1%) |
| Moderate | 0 | 0 | 0 | 1 (1%) |
| Malaise | | | | |
| Mild | 4 (2%) | 1 (1%) | 3 (2%) | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Weakness | | | | |
| Mild | 0 | 0 | 1 (1%) | 2 (1%) |
| Moderate | 0 | 1 (1%) | 0 | 0 |
| Rashes | | | | |
| Mild | 0 | 0 | 1 (1%) | 0 |
| Moderate | 0 | 0 | 0 | 0 |

Data are n (%). The safety analysis set includes all participants who received one dose of the vaccine (n=380). The number of participants who had a solicited adverse event after receiving dose 1 (days 0–7) and dose 2 (days 28–35) is shown.

10.9 IMMUNE RESPONSES

Neutralizing Antibody Titers

Since all recruited participants were screened for IgM and IgG antibodies to SARS-CoV-2, no participants had detectable NABs at baseline (analyzed by MNT₅₀). Seroconversion based on PRNT₅₀ at day 56 was reported in 170 (92.9% [95% CI 88.2–96.2]) of 184 participants in the 3 µg with Algel-IMDG group and 174 (98.3% [95.1–99.6]) of 177 participants in the 6 µg with Algel-IMDG group. GMTs (MNT₅₀) at day 56 were 92.5 (95% CI 77.7–110.2) in the 3 µg with Algel-IMDG group and 160.1 (135.8–188.8) in the 6 µg with Algel-IMDG group. Seroconversion based on MNT₅₀ at day 56 was reported in 161 (88.0% [95% CI 82.4–92.3]) of 184 participants in the 3 µg with Algel-IMDG group and 171 (96.6% [92.8–98.8]) of 177 participants in the 6 µg with Algel-IMDG group. The 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations elicited T-cell responses that were biased to a Th1 phenotype at day 42. No significant difference in the proportion of participants who had a solicited local and systemic adverse reaction in the 3 µg with Algel-IMDG group (37 [9.7%; 95% CI 6.9–13.2] of 380) and the 6 µg with Algel-IMDG group (39 [10.3%; 7.4–13.8] of 380) was observed between days 0–7 and days 28–35; no serious adverse events were reported in the study. From the phase 1 trial, 3-month post-second-dose GMTs (MNT₅₀) were 39.9 (95% CI 32.0–49.9) in the 3µg with Algel-IMDG group, 69.5 (53.7–89.9) in the 6 µg with Algel-IMDG group, 53.3 (40.1–71.0) in the 6 µg with Algel group, and 20.7 (14.5–29.5) in the Algel alone group.

10.10 CONCLUSION:

Based on the interim results of the Phase 2 clinical trial, the BBV-152 B formulation produced better immune response compared to BBV-152A.

In conclusion, Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152) has been proven to be safe and well tolerated, and immunogenic in the Phase 2 study.

COVAXIN Phase II clinical study publication and supplementary data is enclosed as **Annexure 2**

11 INVESTIGATIONAL VACCINE (INV)

11.1 RATIONALE FOR PHASE 3 DOSE SELECTION:

- Two antigen concentrations (3µg and 6µg) with two different adjuvants were studied in different animal models such as mice, rats, rabbits, Syrian hamsters, and *Rhesus macaques*.
- All BBV152 vaccine formulations generated significantly high antigen-binding and neutralizing antibody titers, at both concentrations, in the three-animal species (mice, rats, and rabbits) with excellent safety profiles.
- Likewise, three dose vaccination regimens with three formulations of BBV152 induced significant titres of SARS-CoV-2 specific IgG and neutralizing antibodies in the Syrian Hamster challenge study. The formulation with imidazoquinoline adsorbed on alum adjuvant (BBV-152 A

and B) remarkably generated a quick and robust immune response.

- In the *Rhesus macaques* challenge study, the protective response was observed with increasing SARS-CoV-2 specific IgG and neutralizing antibody titers from 3rd-week post-immunization. Based on the antibody titres, viral loads in nasal, throat, and bronchoalveolar lavage swab, respiratory tract, lungs, and extra-pulmonary organs, clinic-radiological analyses, histopathological examinations, and immunohistochemistry findings, the study demonstrated that a two-dose vaccination regimen adjuvant B (Alum + imidazoquinoline) induced a significant immune response and provided effective protection in animals challenged with SARS-CoV-2.
- Based on the interim results of the Phase 1 clinical trial, the BBV-152B formulation (6µg + adjuvant B (Alum + imidazoquinoline)) produced better immune response compared to BBV-152 A and C.

- Based on the results of the mice, rat, and rabbit study, Syrian hamster and rhesus macaques challenge study, and interim results of the Phase 1 clinical trial, the BBV-152 B formulation (6µg + adjuvant B (Alum + imidazoquinoline)) was selected for the Phase 3 Efficacy Study.

11.2 COMPOSITION OF STUDY VACCINE

Whole Virion Inactivated SARS-CoV-2 vaccine (BBV152-B) will be administered as an intramuscular injection.

| Active Ingredient | Quantity |
|--|----------------|
| Whole Virion, Inactivated Corona Virus Antigen (Strain: NIV-2020-770) | BBV152B |
| | 6µg |
| Inactive Ingredients | |
| Aluminium Hydroxide Gel equivalent to Al ⁺⁺⁺ | 250 mcg |
| TLR7/8 Agonist | 15 mcg |
| 2-Phenoxyethanol (2PE) I.P. | 2.5 mg |
| Phosphate Buffered Saline | q.s. to 0.5 mL |

11.3 PLACEBO COMPOSITION

The vaccine composition of the placebo per single human dose (SHD) of 0.5 ml is as follows:

| Ingredient | Quantity |
|------------|----------|
|------------|----------|

| | |
|---|----------------|
| Aluminium Hydroxide Gel equivalent to Al ⁺⁺⁺ | 250 mcg |
| 2-Phenoxyethanol (2PE) I.P. | 2.5 mg |
| Phosphate Buffered Saline | q.s. to 0.5 mL |

11.4 DOSAGE FORM AND ROUTE OF ADMINISTRATION

COVID-19 Vaccine (BBV152-B) is a liquid 0.5 mL Vero cell-derived inactivated vaccine containing NLT 6µg and administered as a two-dose regimen intramuscularly (IM) 4 weeks apart (Day 0 and Day 28).

11.5 VACCINE STORAGE

Inactivated Whole-virion inactivated vaccine 'BBV152 B' and the placebo vaccine should be stored refrigerated at +2 to +8°C. The vaccine consignment will be shipped with a temperature logger. Any excursion in the temperature during storage below +2°C or above +8°C for more than 24 hours should be notified to the Sponsor, and should wait for Sponsor instructions for further action.

11.6 HANDLING OF STUDY VACCINE AND PLACEBO

The study vaccine and placebo will be stored at +2°C to +8°C at the study site. The required number of test articles and placebo vials will be transported from the Sponsor's manufacturing site in insulated vaccine vial containers containing cool packs. The vaccine vial should be taken from the refrigerator only minutes before injection and the used vial with remaining contents if any, should be immediately discarded.

11.7 STUDY DESIGN AND SUBJECT SELECTION

The study is conducted as Event-Driven, Phase3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥18 Years of Age.

11.8 BLINDING

The control is identical to the vaccine. Sufficient measures will be taken to assure that blinding of participants and evaluation staff is maintained. Study product assignments will be accessible to the data coordinating center staff and others who are required to know this information to ensure proper trial conduct. The DSMB members may also be unblinded to treatment assignment as required to review vaccine safety and efficacy. Emergency unblinding decisions are expected to be rare and justified only when that information is needed for the future clinical management of that participant.

If in the opinion of the investigator, the event the health and safety of the participant will benefit from knowing the treatment code, efforts will be made to contact the medical monitor as long as patient safety is not at imminent risk. If the subject is at imminent risk, the investigator should have the ability to unblind although should notify the Medical Monitor (MM) and Sponsor as soon as possible thereafter.

11.9 METHOD OF ADMINISTRATION

The vials are taken from the refrigerator just before use and brought to ambient temperature. The contents of the vials are mixed well before drawing with a needle. Sterile, disposable, single use syringe and needle are to be used for injection. The vaccine is administered into the deltoid muscle above arm pit and below acromion.

11.10 PRECAUTIONS FOR HANDLING VACCINE SUPPLIES

A vaccine inventory log shall be maintained at the site of storage. Vaccine shall be stored in a refrigerator at +2°C to +8°C. The temperature should be monitored and recorded at regular intervals. A temperature log shall be posted on the refrigerator. An effective power back up shall be maintained to counter any power failures.

11.11 WARNING

- Do NOT allow access to any unauthorized person to the vaccine storage area. If possible, keep the refrigerator locked.
- Do NOT store food or any eatables, chemicals, drugs or any material other than the test articles in the refrigerator
- Once taken out of the refrigerator, the vaccine should be administered immediately or discarded.

11.12 EFFICACY ASSESSMENT

Success will be defined by a two-sided 95% CI for vaccine efficacy (adjusted as necessary for interim monitoring) with a lower bound $\geq 30\%$. The International Coalition of Medicines Regulatory Authorities noted that “a specific numeric value to be used for the lower bound and vaccine efficacy point estimate was not agreed upon at this stage”. It was also reflected that efficacy estimates crossing a certain pre-specified lower bound for efficacy, due to factors such as epidemiological evolution of the pandemic, would not preclude the possibility of a positive benefit-risk conclusion if there also were other data supportive of efficacy.

It is anticipated that the 6-month COVID-19 attack rate in the control arm will be approximately 1 percent. The trial is endpoint driven; the primary efficacy analysis is triggered by the accrual of 130 primary endpoint events across the two arms, at which point the results will be analyzed and reported. In the event overwhelming efficacy is detected during the interim analysis, placebo participants may be provided with closeout vaccinations.

11.13 SAFETY

There are 25,800 participants were recruited in the study. It is decided to consider all AEs reported till 11 am (IST) March 1, 2021 for first 8000 enrolled participants. All the participants were followed up telephonically for 7 days after each dose of vaccination and reported all the solicited AEs. Unsolicited AEs from all the participants were reported throughout follow-up period (Till Day 42). A total of 655 adverse events were reported and equally distributed in both vaccine and placebo groups. Among these 655 AEs 605 were mild, 34 were moderate and 16 were severe and the severity of the AEs is similar in both the groups. All the AEs except 20 were resolved without sequelae. Detailed AEs list is summarized in the Table 14.

TABLE 14 : Adverse events reported in Phase III (Interim Analysis)

| Description | Treatment Arm | | Total (N=7,865) n (%) |
|---|------------------------------|-------------------------------|-----------------------------|
| | BBV152 (N=4,061) n (%) | Placebo (N=3,804) n (%) | |
| No of Subject with at least one Adverse Event | 335 (8.25) | 300 (7.89) | 635 (8.07) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 99 (2.44) | 94 (2.47) | 193 (2.45) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 55 (1.35) | 39 (1.03) | 94 (1.20) |
| No of Subjects with at least one Systemic Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 94 (2.31) | 55 (1.45) | 149 (1.89) |
| No of subjects with at least one Systemic Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 30 (0.74) | 23 (0.60) | 53 (No 0.67) |
| No of subjects with at least one Unsolicited Adverse Events | 50(1.23) | 67(1.76) | 117 (1.49) |
| All Ongoing Adverse Events | 9 (0.22) | 11 (0.29) | 20 (0.25) |
| Severity | | | |
| Mild | 317 (7.81) | 288 (7.57) | 605 (7.69) |
| Moderate | 17 (0.42) | 17 (0.45) | 34 (0.43) |
| Severe | 9 (0.22) | 7 (0.18) | 16 (0.20) |

11.13.1 SERIOUS ADVERSE EVENTS

All the participants (25800) were followed up for serious adverse events (SAEs) and 43 SAEs were reported till date and among those cases 33 were resolved, 3 cases are ongoing and 7 deaths were reported. All the SAEs were not related to the vaccine and distributed equally among the two treatment groups. Detailed description of the SAEs is given in the Table 15.

TABLE 15: SAEs Line Listing of Phase III (Interim Analysis)

| S. No | Study site (Screening Number) | Date of administration | Date of occurrence of SAE | Seriousness Criteria | Diagnosis of the Event | Causality Assessment by PI | Causality Assessment by Sponsor | Outcome of the Event |
|-------|---|--|---------------------------|----------------------|--|----------------------------|---------------------------------|---|
| 1 | NIMS, Hyderabad (32000107) | 19-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 20-11-2020 | Hospitalization | Road traffic accident (RTA)- Crush Injury left foot and Fracture neck of 2 nd 3 rd and 4 th metatarsal. | Unrelated | Unrelated | Recovered and discharged from hospital on 23 rd Nov 2020. |
| 2 | NIMS, Hyderabad (32000073) | 18-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 29-11-2020 | Hospitalization | Uncontrolled Type-2 Diabetes mellitus with Diabetic ketoacidosis and dyselectrolytemia. | Unlikely | Unrelated | Recovered and discharged from hospital on 12 th Dec 2020 |
| 3 | PGIMS, Rohtak (32100001) | 20-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from hospital 30 th Dec 2020 in stable condition |
| 4 | NIMS, Hyderabad (32000428) | 28-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | Shortness of breath, pedal edema and fever (3 days). | Unlikely | Unrelated | Recovered and discharged from hospital 6 th Dec 2020 in stable condition |
| 5 | NIMS, Hyderabad (32000272) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 11 th Dec 2020 in stable condition |
| 6 | NIMS, Hyderabad (32000242) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 10-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 15 th Dec 2020 in stable condition |
| 7 | Grant Medical College & JJ Hospital, Mumbai (31600192) | 08-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 12-12-2020 | Hospitalization | Homocysteine | Unrelated | Unrelated | Recovered and discharged from hospital in stable condition on 26 th Dec 2020 |
| 8 | SRM Medical College & Hospital, Chennai (32500018) | 07-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 15-12-2020 | Hospitalization | Clinical enteric fever with dehydration. | Unrelated | Unrelated | Recovered and discharged from hospital on 17 th Dec 2020 |
| 9 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900546) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 17-12-2020 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from hospital on 18 th Dec 2020 with advice to follow up for further treatment plan |

| | | | | | | | | |
|----|---|--|---|-----------------|---|-----------|-----------|--|
| 10 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900809) | 12-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 21-12-2020 | Death | Death | Unrelated | Unrelated | Fatal |
| 11 | MGMCRI-SBV, Puducherry (30800390) | 26-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 01-01-2020 | Hospitalization | "Hollow viscus perforation with Acute Kidney Injury -? Cause" | Unrelated | Unrelated | Recovered |
| 12 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900578) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 06-01-2021 | Hospitalization | Liver abscess | Unrelated | Unrelated | Recovered and discharged from hospital on 15 th Jan 2021 |
| 13 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore. (31100060) | 09-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-12-2020 (Date of awareness of SAE:06-01-2021) | Hospitalization | Left lung opacity-LRTI | Unrelated | Unrelated | Recovered and discharged from Hospital on 23 rd December 2020 |
| 14 | People's College of medical research center, Bhopal, Madhya Pradesh (30900546) | 10/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-01-2021 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from Hospital on 21 st Jan 2021. |
| 15 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901496) | 18-12-2020 (1 st Dose) (Vaccine/Placebo; blinded) 2 nd dose was not administered | 08-01-2021 | Hospitalization | Injury in both the lower limbs (ankle) | Unrelated | Unrelated | Recovered and discharged from Hospital on 19 th Feb 2021. |
| 16 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901257) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 30-12-2020 (Date of awareness of SAE:13/01/2021) | Hospitalization | Mature cataract | Unrelated | Unrelated | Recovered and discharged from hospital on 1 st Jan 2021. |
| 17 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901279) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 03/01/2021 (Date of awareness of SAE: 13/01/2021) | Hospitalization | CAD with hypertension with B/L Pneumonitis /ACS/TVD. She was also positive with COVID-19. | Unrelated | Unrelated | Recovered and discharged from hospital on 6 th Jan 2021. |

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|----|---|--|--|-----------------|---|-----------|-----------|--|
| 18 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901436) | 17/12/2020 (1 st Dose) 14/01/2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 15/01/2021 | Hospitalization | Acute cholecystitis and cholelithiasis. | Unrelated | Unrelated | Recovered and discharged from the hospital on 22-01-2021 |
| 19 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901004) | 14-12-2020 (1 st Dose) 11-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 18-01-2021 | Hospitalization | Renal Calculi with Hepatomegaly. | Unrelated | Unrelated | Recovered and discharged from the hospital on 19-01-2021 |
| 20 | NIMS, Hyderabad (32001145) | 21-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-01-2021 (Date of awareness of the SAE: 21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 21 | Jawaharlal Nehru Medical college and Hospital, AMU, Aligarh (31300207) | 25-11-2020 (1 st Dose) 24-12-2020 (2 nd dose) (Vaccine/Placebo; Blinded) | 10-01-2021 (Date of awareness of the SAE: 21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 22 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100290) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 11-01-2021 (Date of awareness of the SAE: 14-01-2021) | Hospitalization | Atypical viral pneumonia | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-01-2021 |
| 23 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901512) | 18-12-2020 (1 st Dose) 20-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 21-01-2021 | Hospitalization | Generalised body pain | Unrelated | Unrelated | Recovered and discharged from the hospital on 25-01-2021 |
| 24 | AIIMS, New Delhi (30100090) | 5-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 22-01-2021 (Date of SAE Awareness: 24-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 25 | GMERS Medical College and Civil Hospital, Sola, Ahmedabad (31500928) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 08-01-2021 (Date of awareness of SAE: 27-01-2021) | Death | Death | Unlikely | Unlikely | Fatal |
| 26 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900901) | 13-12-2020 (1 st Dose) 10-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-02-2021 | Hospitalization | Right eye mature cataract and left eye pseudophakia | Unrelated | Unrelated | Recovered and discharged from Hospital on 12 th Feb 2021. |

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|----|---|--|--|-----------------|----------------------------------|---------------------------------------|------------------|--|
| 27 | SRM Medical College Hospital & Research Centre, Kanchipuram, Tamil Nadu (32500447) | 28-12-2020 (1 st Dose) 25-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 31-01-2021 (Date of awareness by Sponsor: 01-02-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 28 | SRM Medical College Hospital & Research Centre Kanchipuram, Tamil Nadu (32500303) | 23-12-2021 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 27-01-2021 (Date of awareness-02-02-2021) | Hospitalization | Viral pneumonia due to COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 9 th Feb 2021 in stable condition |
| 29 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900770) | 12-12-2020 (1 st Dose) 09-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Chronic Otitis media | Unrelated | Unrelated | Recovered and discharged from the hospital on 18-02-2021 |
| 30 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Bronchial asthma | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-02-2021 |
| 31 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700845) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |
| 32 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700848) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |
| 33 | AIIMS, New Delhi (30100013) | 27-11-2020 (1 st Dose) 26-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-02-2021 (Date of awareness-06-02-2021) | Hospitalization | Immune Thrombocytopenia Purpura. | Could be associated with the vaccine. | Under Evaluation | Recovered and discharged from the hospital on 08-02-2021 |
| 34 | Director of Public Health & Medicine study site, Chennai (31200001) | 09-12-2020 (1 st Dose) 06-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 16-02-2021 |
| 35 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900391) | 07-12-2020 (1 st Dose) 05-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | Chronic otitis media | Unrelated | Un related | Recovered and discharged from the hospital on 22-02-2021 |
| 36 | Prakash Institute of Medical Science & Research, Sangli, | 30-12-2020 (1 st Dose) 26-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 13-02-2021 | Hospitalization | Fever, headache, and cough | Unrelated | Unrelated | Recovered and discharged from the hospital on 14-02-2021 |

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|----|---|--|--|-----------------|----------------------------|------------------|------------------|---|
| | Maharashtra (32900012) | | | | | | | |
| 37 | AIIMS, New Delhi (30100044) | 02-12-2020 (1 st Dose) 30-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 19-02-2021 | Hospitalization | Myocardial infarction (MI) | Unlikely | Unrelated | Recovered and discharged from the hospital on 01-03-2021 |
| 38 | NIMS, Hyderabad (32001185) | 22-12-2020 (1 st Dose) 19-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | COVID-19 | Unlikely | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 39 | Sir Ganga Ram Hospital Marg, Rajinder Nagar, New Delhi (32300066) | 19-12-2020 (1 st Dose) 20-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | Fever and body ache | Under Evaluation | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 40 | Aligarh Muslim University, Aligarh (31300560) | 30-11-2020 (1 st Dose) 31-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 27-02-2021) | Hospitalization | Epistaxis | Unrelated | Under Evaluation | Recovered and discharged from the hospital on 27-02-2021 |
| 41 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 03-03-2021) | Hospitalization | Acute exacerbation of COPD | Unrelated | Under Evaluation | Ongoing |
| 42 | AIIMS, New Delhi (30100314) | 26-12-2020 (1 st Dose) 23-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 05-03-2021) | Hospitalization | Cholecystitis | Unlikely | Under Evaluation | Recovered and discharged from the hospital on 02-03-2021 |
| 43 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100476) | 06-01-2021 (1 st Dose) 03-02-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-03-2021 (Date of Awareness: 05-03-2021) | Death | Death | Under Evaluation | Under Evaluation | Fatal |

11.14 INTERIM PHASE 3 RESULTS:

The Phase 3 study enrolled 25,800 participants between 18-98 years of age, including 2,433 over the age of 60 and 4,500 with comorbidities. The primary endpoint of Phase 3 clinical trial is based on the first occurrence of PCR-confirmed symptomatic (mild, moderate, or severe) COVID-19 with onset at least 14 days after the second study vaccination in serologically negative (to SARS-CoV-2) adult participants at baseline.

The first interim analysis is based on 43 cases, of which 36 cases of COVID-19 were observed in the placebo group versus 7 cases observed in the BBV152 (COVAXIN[®]) group, resulting in a point estimate of vaccine efficacy of 80.6%.

The interim analysis included a preliminary review of the safety database, which showed that severe, serious, and medically attended adverse events occurred at low levels and were balanced between vaccine and placebo groups. The trial's conduct and monitoring are as per Good Clinical Practice guidelines and have been outsourced to IQVIA.

Analysis from the National Institute of Virology indicates that vaccine-induced antibodies can neutralize the UK variant strains and other heterologous strains, which has been published in bioRxiv. <https://doi.org/10.1101/2021.01.26.426986>

Phase III efficacy interim report is enclosed as **Annexure 3**

12 RESTRICTED USE OF COVAXIN UNDER CLINICAL TRIAL MODE

Bharat Biotech International Limited (BBIL) in collaboration with Indian Council of Medical Research (ICMR) has developed an inactivated whole virion COVID-19 vaccine, COVAXIN®. The COVAXIN® has been evaluated for safety, reactogenicity and immunogenicity in phase 1 and 2 clinical trials and the trial reports were submitted to the Central Drugs Standard Control Organization (CDSCO) India. COVAXIN® has been approved under emergency use authorization with permission number MF/BIO/21/000002, dated 03.01.2021, F. No: BIO/MA/20/000103. This permission is given for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, where COVAXIN® vaccine will be administered to the vaccine recipients and they will be followed up for safety. COVAXIN® (prepared under Good manufacturing practices, as required under the Drugs and Cosmetics Act, 1940 and the NCDT Rules 2019) has been approved by CDSCO for Restricted Use in Emergency situation in Public Interest as an abundant precaution in Clinical Trial Mode, in India on 3rd January 2021.

12.1 IMPLEMENTATION PLAN – PROCEDURES

Bharat Biotech along with ICMR has taken approval for the Implementation Plan from the Central Ethic Committee of ICMR and SEC committee of CDSCO. Subsequently, BBIL has sent lakhs of hard copies of Fact Sheets, Informed Consent forms and Information Leaflets to each designated vaccination sites across the country.

1. The Fact sheet in regional language was provided to the vaccine recipient before vaccination and vaccine recipients were given time to read (in case of inability to read – it was read out to him/her by vaccination staff) to understand it. Opportunity was given to the vaccine recipients to ask clarifying questions to the vaccinator. Vaccinator has used the information leaflet to answer the queries raised by the vaccine recipient. Following questions and clarifications, the fact sheet was returned by the vaccine recipients to the vaccinator.

2. If the vaccine recipient agrees to be vaccinated with COVAXIN®, he/she has to sign an informed consent form (ICF) (in case of inability to write, he/she has put a left thumb impression on the ICF). Only after signing the informed consent, the vaccine recipients were vaccinated with COVAXIN®.
3. The informed consent is required at the time of first dose only. The separate consent is not required for subsequent dose.

12.1.1 VACCINATION PROCEDURE:

Vaccine recipients were provided information in local language pertaining to the vaccine administration with the help of a Fact Sheet containing details about COVAXIN®. On day 01 (Visit 1) and day 28 (Visit 2) recipients were administered with the doses of the COVAXIN® via the intramuscular route. After Day 1 and Day 28 vaccination, Vaccine recipients were given Adverse Event Form to record the adverse events and they were made to remain for at least 30 minutes after vaccination for observation to record any adverse event.

12.1.2 ADVERSE EVENTS AND SAEs COLLECTION PROCEDURE:

1. The designated staff has collated the consent forms obtained on the previous day for record keeping. These were files with date of vaccination, session site specifications and planning unit mentioned on it. A team, consisting of about 150 BBIL sales and marketing employees and ICMR employees, was set-up at the regional level to telephonically contact and enquire about the adverse events based on grouping of vaccine recipients as follows:
 - Day 7 after dose 1 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 28 after dose 1 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 7 after dose 2 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 28 after dose 2, including symptoms related to Covid-19 and positive RTPCR test (if any)
2. The list of the vaccine recipients was generated on a daily basis with contact numbers.
3. Adverse events and serious adverse events following immunization (AEFI) informed during the aforementioned contacts were recorded application against the respective personnel identified of a vaccine recipient.
4. Grouping of the vaccine recipients in minor, severe and serious adverse event (as the case may be) was done by District Immunization Officer (DIO) on a daily basis. For all

serious and severe cases, the Case Report Form (CRF) has been raised for further investigation by District AEFI Committee.

5. In case of any serious adverse events linked to the COVAXIN™ immunization program, the details of the serious adverse events were recorded by the designated Immunization officers or Health care workers of the vaccination site. BBIL has coordinated through email/telephone/other means to coordinate with the Immunization officers/Health care workers to get the required details of SAE. Upon receipt of these details, submitted SAE report to DSMB, ICMR Central Ethics Committee CDSCO/DCGI.
7. Drug regulators (Drugs Controller General of India, DCGI) has been provided with the collated data for review and assessment on vaccine safety, on a monthly basis.
8. The end point and the final outcome of the aforementioned AEFI monitoring related to COVAXIN was based on the recommendations made by the regulatory authority (DCGI).

A toll-free number and an email, the details of which are in the fact sheet, were assigned at BBIL to answer the queries of vaccine beneficiaries. Numerous queries via telephone and emails were addressed on a daily basis. Causality of all SAEs was assessed by the Immunization officer, BBIL, ICMR Central Ethics Committee.

12.1.3 CONCLUSIONS

The Restricted use of COVAXIN® under clinical trial mode was initiated on 16th Jan 2021. Under this program, a total of more than 13 lakh beneficiaries have been vaccinated with COVAXIN®. Despite numerous attempts by BBIL and ICMR, data was not shared in a timely manner by the site immunization officers. A total of 8149 beneficiaries have reported adverse events following immunization. No death cases were reported in the restricted use of COVAXIN® under clinical trial mode. In conclusion, the COVAXIN® can be considered as a safe vaccine.

Restricted Use of COVAXIN® under clinical trial mode report is as **Annexure-4**.

13 NEUTRALIZATION OF UK-VARIANT VUI-202012/01 WITH COVAXIN VACCINATED HUMAN SERUM

National Institute of Virology (NIV), India was successfully isolated and characterized the hCoV-19/India/20203522 SARS-CoV-2 (VOC) 202012/01 from UK returnees in India with all signature mutations of the UK-variant.

The plaque reduction neutralization test (PRNT₅₀) using sera collected from the 26 recipients of BBV152/COVAXIN™ against hCoV-19/India/20203522 (UK-variant) and hCoV27 19/India/2020Q111 (heterologous strain). A comparable neutralization activity

of the vaccinated individuals sera showed against UK-variant and the heterologous strain with similar efficiency, dispel the uncertainty of possible neutralization escape.

Neutralization of UK-variant VUI-202012/01 with COVAXIN vaccinated human serum
Publication is enclosed as **Annexure 5**

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ANNEXURE-1

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial



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Summary

Background To mitigate the effects of COVID-19, a vaccine is urgently needed. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel).

Methods We did a double-blind, multicentre, randomised, controlled phase 1 trial to assess the safety and immunogenicity of BBV152 at 11 hospitals across India. Healthy adults aged 18–55 years who were deemed healthy by the investigator were eligible. Individuals with positive SARS-CoV-2 nucleic acid and/or serology tests were excluded. Participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group. Block randomisation was done with a web response platform. Participants and investigators were masked to treatment group allocation. Two intramuscular doses of vaccines were administered on day 0 (the day of randomisation) and day 14. Primary outcomes were solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. Secondary outcome was seroconversion (at least four-fold increase from baseline) based on wild-type virus neutralisation. Cell-mediated responses were evaluated by intracellular staining and ELISpot. The trial is registered at ClinicalTrials.gov (NCT04471519).

Findings Between July 13 and 30, 2020, 827 participants were screened, of whom 375 were enrolled. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10·5–26·1) participants in the 3 µg with Algel-IMDG group, 21 (21%; 13·8–30·5) in the 6 µg with Algel-IMDG group, 14 (14%; 8·1–22·7) in the 6 µg with Algel group, and ten (10%; 6·9–23·6) in the Algel-only group. The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven [2%]). All solicited adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose. One serious adverse event of viral pneumonitis was reported in the 6 µg with Algel group, unrelated to the vaccine. Seroconversion rates (%) were 87·9, 91·9, and 82·8 in the 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, and 6 µg with Algel groups, respectively. CD4⁺ and CD8⁺ T-cell responses were detected in a subset of 16 participants from both Algel-IMDG groups.

Interpretation BBV152 led to tolerable safety outcomes and enhanced immune responses. Both Algel-IMDG formulations were selected for phase 2 immunogenicity trials. Further efficacy trials are warranted.

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Introduction

Spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has led to a global COVID-19 pandemic. Vaccines from multiple manufacturers will be needed to address the global need for SARS-CoV-2 vaccines and thus far, 194 vaccine candidates are in development.¹

A desirable characteristic for any COVID-19 vaccine candidate is the ability to induce T-helper-1 cell (Th1) responses.² Whole-virion inactivated vaccines are usually formulated with Alum, which does not have the ability to induce cell-mediated responses.^{3,4} An imidazoquinoline

molecule, which is a toll-like receptor (TLR) 7/8 agonist, has been used to stimulate cell-mediated responses.^{5,6} Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]) has been designed to traffic vaccine antigen directly to draining lymph nodes without diffusing into the systemic circulation. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG.

Preclinical studies in mice, rats, and rabbits showed appropriate safety profiles and humoral and cell-mediated responses.⁷ Two live viral challenge protective efficacy studies in hamsters and non-human primates were done.

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For the WHO COVID-19 dashboard see <https://covid19.who.int/>

Research in context

Evidence before this study

We searched PubMed on Jan 15, 2020, for published research articles using the search terms “SARS-CoV-2”, “COVID-19”, “vaccine”, and “clinical trial”, with no language or date restrictions. We found several publications on COVID-19 vaccine clinical trials from mRNA, adenovirus, protein subunit, and inactivated vaccines.

As of Jan 15, 2020, nine vaccines have received emergency use authorisation to be administered to prevent COVID-19. Inactivated vaccines have been approved for decades with well established safety profiles. Immune responses from two other inactivated vaccines have been reported; however, with few results on cell-mediated responses. Bharat Biotech has developed a vero cell-based whole-virion inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (BBV152) formulated with alum and a TLR7/8 agonist producing a T-helper-1 cell skewed response. This vaccine candidate reported protection in two live viral non-human primate and hamster challenge models.

Added value of this study

We report the preliminary analyses for the safety and immunogenicity of the vaccine candidate BBV152 in 375 vaccinated adults. All vaccine groups had similar reactogenicity and serological outcomes to the control group. BBV152 led to enhanced immune responses; the 3- μ g and 6- μ g Algel-IMDG vaccines induced T-cell responses that were biased to T-helper-1 cells.

Implications of all the available evidence

Findings from other inactivated SARS-CoV-2 vaccine candidates are corroborating. However, to the best of our knowledge, ours is the only reported inactivated COVID-19 vaccine candidate inducing cell-mediated responses and humoral neutralising responses. Both Algel-IMDG formulations will be assessed in a phase 2 immunogenicity trial.

In both studies, protection was evident by rapid clearance of virus in the lower and upper respiratory tract, and absence of lung pathology (after viral challenge).^{8,9} Here, we report the interim findings from the randomised, controlled, double-blind phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 and one control group containing Algel (without antigen). This phase 1 trial was done with the intention of selecting two formulations for progression to the phase 2 trial.

Methods

Study design and participants

This is a randomised, double-blind, multicentre, phase 1 trial to assess the safety, reactogenicity, tolerability, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine (BBV152) in healthy adult volunteers, at 11 hospitals across nine states of India (appendix pp 5, 13). Participants were aged 18–55 years and deemed healthy by the investigator at the time of enrolment. At the screening visit, participants were tested with both SARS-CoV-2 nucleic acid (TRUPCR SARS-CoV-2 RT-PCR; 3B BlackBio Biotech, Bhopal, India) and serology (chemiluminescence immunoassay; LIAISON SARS-CoV-2 S1/S2 IgG; DiaSorin, Saluggia, Italy) tests (conducted at Dr Dangs Lab [New Delhi, India] using commercially available assays; appendix p 3). If found positive for any one test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 4 days (range 3–6). Other key exclusion criteria were an axillary temperature of more than 37.0°C and known allergy to any vaccine component. Participants were screened for eligibility on the basis of their health status, including their medical history, laboratory findings (haematology, biochemistry, and urine tests), vital signs, and physical examination

results, and were enrolled after providing signed and dated informed consent forms. Full inclusion and exclusion criteria are in the protocol.

The trial was approved by the National Regulatory Authority (India) and the respective ethics committees and was conducted in compliance with all International Council for Harmonization Good Clinical Practice guidelines.

Randomisation and masking

The master randomisation list was uploaded on the interactive web response system, which contained the randomisation number and intended allocation. The depot manager uploaded the kit code list and assigned the kits to the sites that had the kit codes and the allocation groups. At the site level, the system would set the randomisation number and the allotment of the kit without displaying the true group allocation, and the system would allocate the same treatment group for the second visit. For the first 50 participants, a block size of five with ten blocks was generated for the 3 μ g with Algel-IMDG and control groups at a ratio of 4:1. In the remaining participants, the number of blocks was 20. For the first 15 blocks, a block size of 16 was used to randomly assign participants (3:5:5:3) to 3 μ g with Algel-IMDG, 6 μ g with Algel-IMDG, 6 μ g with Algel, or Algel-only control. The next five blocks were size 17, and used to randomly assign participants (3:5:5:4) to 3 μ g with Algel-IMDG, 6 μ g with Algel-IMDG, 6 μ g with Algel, or Algel-only control. An unmasked contract research organisation, Sclin Soft Technologies, generated the randomisation list for the study.

Participants, investigators, study coordinators, study-related personnel, and the funder were masked to treatment group allocation (excluding an unmasked member of the contract research organisation, who was

See Online for appendix

tasked with the dispatch and labelling of vaccine vials and the generation of the master randomisation code). Participants were assigned a computer-generated randomisation code that maintained masking. The masked study nurse was responsible for vaccine preparation and administration. Each vial contained a unique code that ensured appropriate masking. The appearance, colour, and viscosity were identical across all vaccine and control formulations.

Procedures

The virus strain (NIV-2020-770) containing the Asp614Gly mutation, isolated from a COVID-19 patient and sequenced at the Indian Council of Medical Research National Institute of Virology, was provided to Bharat Biotech.¹⁰ Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform (with proven safety in other licensed live and inactivated vaccines) were used for the rapid development of BBV152.^{11–16}

BBV152 (manufactured by Bharat Biotech) is a whole-virion β -propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by aspartic acid to glycine shift at the amino acid position 614 of the spike protein.¹⁰

The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7 and TLR8 agonist) adsorbed onto Algel. After their eligibility was established, participants were assigned to the four groups. The control group contained only a sterile phosphate-buffered solution and Algel. Both the vaccine and control were stored at 2–8°C.

The vaccine (BBV152) and the control were provided as a sterile liquid that was injected intramuscularly (deltoid muscle) at a volume of 0.5 mL/dose in a two-dose regimen on day 0 (day of randomisation) and day 14. This accelerated schedule was chosen given the context of the ongoing pandemic. No onsite dose preparation was required. Each glass vial contained a single dose of either vaccine or control formulation that required no additional dilution steps. No prophylactic medication (ibuprofen or acetaminophen) was prescribed either before or after vaccination.

The follow-up visits were scheduled on days 7, 28, 42, 104, and 194 after vaccination. The study was done in a dose-escalation manner after completing vaccination in the first 50 participants with 3 μ g with Algel-IMDG (the lowest antigen concentration) and the control; these participants were monitored for 7 days for safety. The independent data safety monitoring board reviewed masked safety data and decided whether the trial was allowed to continue with enrolment of the remaining participants into all groups.

Outcomes

The primary outcome was the number and proportion of participants with solicited local and systemic reactogenicity

events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. The secondary outcomes were immunogenicity, in terms of geometric mean titres (GMTs) and four-fold seroconversion rate of neutralising antibodies, from baseline to days 14, 28, 42, 104, and 194.

Safety assessments

The unsolicited adverse events were recorded for 28 days after vaccination. Laboratory values (serum chemistry, haematology, and urine) were compared before vaccination (day 0) and after vaccination (day 28).

Participants were observed for 2 h after vaccination to assess reactogenicity. They were instructed to record local and systemic reactions within 7 days (days 0–7 and days 14–21) after vaccination using a diary card. The diary card contained fields for symptom onset, severity, time to resolution, concomitant medication, and was collected during the next visit to the site. Routine telephone calls were scheduled after the first 7 days after each vaccination.

Solicited local adverse events were pain at the injection site and swelling, and systemic adverse events, including fever, fatigue or malaise, myalgia, body aches, headaches, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. Adverse events were graded according to the severity score (mild, moderate, or severe) and whether they were related or not related to the investigational vaccine, as detailed in the protocol (appendix p 6).

Immunogenicity assessments

IgG responses against the spike (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 were assessed by an in-house-developed ELISA and are expressed as GMTs. Neutralising antibody titres were assessed by wild-type virus neutralisation assays: a microneutralisation assay (MNT₅₀) and a plaque-reduction neutralisation test (PRNT₅₀), at Bharat Biotech. These assays were based on the Asp614Gly strain (appendix p 4). To establish interlaboratory comparability, a subset of randomly selected serum samples (n=50) was analysed by MNT₅₀ at the National Institute of Virology. Additionally, three laboratory strains were used in vitro for PRNT₅₀ at the National Institute of Virology: the BBV152 strain NIV-2020-770 homologous, and two heterologous strains from the O clade (nCoV-Q111 and nCoV-Q100). Genomic analyses of strains were reported by Potdar and colleagues.¹⁷ Only the NIV-2020-770 strain contained the Asp614Gly mutation.¹⁰

To compare vaccine-induced responses to natural SARS-CoV-2 infections, 41 convalescent serum samples (collected within 1–3 months after nucleic acid test-based diagnosis) were tested by MNT₅₀. These serum samples were collected from both self-reported symptomatic (n=25) and asymptomatic (n=16) patients with COVID-19 at Nizam's Institute of Medical Sciences (NIMS;

Hyderabad, India). The age of these participants was 23–62 years. For symptomatic patients, ascertainment of severity grading and requirement of supplemental oxygen was not obtainable. A participant who achieved seroconversion was defined as having a post-vaccination titre at least four-fold greater than their respective pre-vaccination titre. Serum samples were analysed in a masked manner at Bharat Biotech and the National Institute of Virology.

Cell-mediated responses were assessed in a subset of participants at one site (NIMS). The contract research organisation generated a random code containing randomisation numbers, which was provided to the staff to identify participants. Blood (3–5 mL) was collected from those participants who consented to the additional volume on days 0 and 28. Peripheral blood mononuclear cells were collected to assess IFN- γ by ELISpot (13 in vaccinated groups and six in the control group). Intracellular cytokine staining was used to assess T-cell responses in the remaining samples that contained an adequate number of cells. To ensure equal distribution, eight samples in each vaccine group were selected. These assays were done at Indoor Biotechnologies (Bangalore, India) and Bharat Biotech. All samples were analysed in

a masked manner. The details of all assay methods are in the appendix (p 5).

Statistical analysis

Using a two-sided 5% significance level, power was calculated for several levels of the absolute difference between seroconversion rates for vaccine formulations, and we decided on the power to find a statistically significant difference between rates if the true underlying absolute difference was at least 20%. The allocation ratio was 1:1:1 for three vaccine formulations and 4:1 for the vaccine (all formulations combined) to placebo. The placebo group was not included in the sample size calculations. For a sample size of 90 for each formulation, the power to find a statistically significant absolute difference for a true underlying difference of 20% was at least 80% if the lower seroconversion rate for two formulations was at least 52%, which is lower than the seroconversion rate we expected for an effective vaccine. The sample size chosen was 100 per vaccine formulation, to allow for loss of data because of withdrawals or loss to follow-up. We did not incorporate an adjustment for multiple comparisons, because this phase 1 study was not a pivotal study for licensure, and we planned to

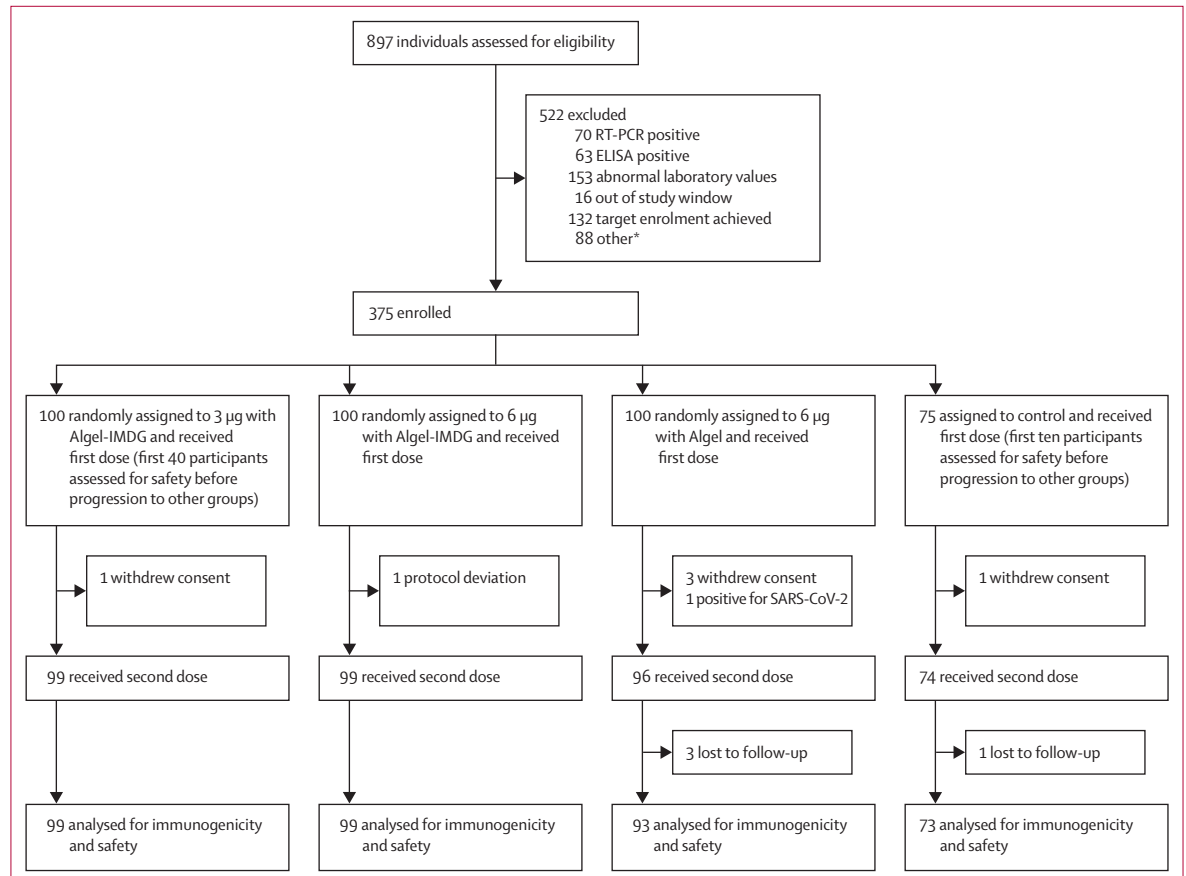


Figure 1: Trial profile

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Unable to contact the participant for vaccination or withdrawal of consent.

choose two vaccine formulations from the phase 1 study for further assessment. Sample size estimation was done using PASS 13 software, version 13.0.17.

Safety endpoints are described as frequencies (%). GMTs with 95% CI are used for immunological endpoints. For continuous variables (<20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. The Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the \log_{10} (titre) and the assumption that the \log_{10} (titre) was normally distributed. A comparison of GMTs was done with *t* tests on the means of the \log_{10} (titre). Significance was set at $p < 0.05$ (two-sided). This preliminary report contains results regarding immunogenicity (days 0–28) and safety outcomes (days 0–42). Descriptive and inferential statistics were assessed using SAS, version 9.2. The trial was registered at ClinicalTrials.gov (NCT04471519).

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report, but was involved in study design. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 13 and 30, 2020, 897 individuals were screened and 375 were enrolled. Of the 522 initially screened individuals who were excluded, 133 participants were excluded because they were positive for SARS-CoV-2 by nucleic acid test or serology and 153 were excluded because of abnormal laboratory values (figure 1). The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). Demographic characteristics of the participants were similar across groups (table 1).

After dose 1, solicited local adverse reactions were reported by five (5%; 95% CI 1.9–11.8) participants in the 3 μg with Algel-IMDG group, five (5%; 1.9–11.8) in the 6 μg with Algel-IMDG group, one (1%; 0.05–6.2) in the 6 μg with Algel group, and three (3%; 1.04–12.03), in the Algel-only control group. Solicited systemic adverse reactions were reported by five (5%; 1.9–11.8) participants in the 3 μg with Algel-IMDG group, 14 (14%; 8.1–22.7) in the 6 μg with Algel-IMDG group, eight (8%; 3.8–15.6) in the 6 μg with Algel group, and seven (7%; 4.2–18.9) in the Algel-only group (table 2; appendix p 14). The most common solicited adverse events were injection site pain (17 [5%] of 375 participants), headache (13 [3%]), fatigue (11 [3%]), fever (nine [2%]), and nausea or vomiting (seven

[2%]). All adverse events were mild or moderate in severity and resolved within 24 h of onset. After both doses, solicited local and systemic adverse reactions were reported by 17 (17%; 95% CI 10.5–26.1) participants in the 3 μg with Algel-IMDG group, 21 (21%; 13.8–30.5) in the 6 μg with Algel-IMDG group, 14 (14%; 8.1–22.7) in the 6 μg with Algel group, and ten (10%; 6.9–23.6) in the Algel-only group. All adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose than the second. No significant differences were observed between the vaccinated and control groups.

44 unsolicited adverse events were reported by 24 (6%) of 375 participants (appendix p 6). Biochemical, haematological, and urine parameters outside of the normal

| | BBV152 3 μg with Algel- IMDG (n=100) | BBV152 6 μg with Algel- IMDG (n=100) | BBV152 6 μg with Algel (n=100) | Algel only (n=75) |
|---|--|--|---|----------------------|
| Age, years | | | | |
| Median (IQR) | 32.5 (25.0–40.0) | 35.0 (25.0–40.0) | 32.0 (25.0–40.0) | 29.0 (24.0–38.0) |
| ≥ 18 to ≤ 25 | 29 (29%) | 28 (28%) | 31 (31%) | 22 (29%) |
| ≥ 26 to ≤ 40 | 47 (47%) | 47 (47%) | 45 (45%) | 37 (49%) |
| > 40 to ≤ 55 | 24 (24%) | 25 (25%) | 24 (24%) | 16 (21%) |
| Sex | | | | |
| Men | 78 (78%) | 82 (82%) | 76 (76%) | 61 (81%) |
| Women | 22 (22%) | 18 (18%) | 24 (24%) | 14 (19%) |
| Body-mass index*, kg/m ² | 24.8 (3.5) | 25.8 (4.2) | 24.9 (3.7) | 24.6 (3.5) |
| Vital signs | | | | |
| Systolic blood pressure, mm Hg | 122.9 (8.5) | 123.5 (7.9) | 121.6 (8.3) | 123.6 (8.5) |
| Diastolic blood pressure, mm Hg | 79.4 (5.9) | 79.3 (6.5) | 79.2 (5.3) | 79.4 (6.4) |
| Pulse rate, beats per min | 77.4 (7.3) | 78.1 (8.2) | 78.0 (5.9) | 78.3 (7.6) |
| Respiratory rate, breaths per min | 16.9 (2.3) | 16.7 (2.6) | 17.1 (2.6) | 16.9 (2.2) |
| Temperature, °C | 36.6 (0.4) | 36.5 (0.6) | 36.5 (0.4) | 36.6 (0.4) |
| Sites | | | | |
| All India Institute of Medical Sciences, New Delhi | 3 (3%) | 6 (6%) | 3 (3%) | 4 (5%) |
| All India Institute of Medical Sciences, Patna | 25 (25%) | 9 (9%) | 6 (6%) | 7 (9%) |
| Gillukar Multispeciality Hospital | 10 (10%) | 14 (14%) | 19 (19%) | 12 (16%) |
| Institute of Medical Sciences and SUM Hospital | 4 (4%) | 5 (5%) | 9 (9%) | 5 (7%) |
| Jeevan Rekha Hospital | 1 (1%) | 1 (1%) | 2 (2%) | 0 |
| Nizam's Institute of Medical Sciences | 11 (11%) | 14 (14%) | 15 (15%) | 7 (9%) |
| Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences | 22 (22%) | 10 (10%) | 15 (15%) | 16 (21%) |
| Prakhar Hospital | 8 (8%) | 10 (10%) | 11 (11%) | 10 (13%) |
| Rana Hospital and Trauma Centre | 1 (1%) | 3 (3%) | 2 (2%) | 2 (3%) |
| Redkar Hospital | 7 (7%) | 14 (14%) | 13 (13%) | 9 (12%) |
| SRM Hospital and Research Center | 8 (8%) | 14 (14%) | 5 (5%) | 3 (4%) |

Data are n (%) or mean (SD) unless otherwise stated. The intention-to-treat population included all participants who received at least one dose. *Calculation was based on the bodyweight and height measured at the time of screening. No data on race were collected; all participants were south Asian.

Table 1: Demographic characteristics of the participants in the intention-to-treat population

| | Dose 1 | | | | Dose 2 | | | |
|---------------------------|------------------------------|------------------------------|-------------------------|-------------------|------------------------------|------------------------------|-------------------------|-------------------|
| | 3 µg with Algel-IMDG (n=100) | 6 µg with Algel-IMDG (n=100) | 6 µg with Algel (n=100) | Algel only (n=75) | 3 µg with Algel-IMDG (n=100) | 6 µg with Algel-IMDG (n=100) | 6 µg with Algel (n=100) | Algel only (n=75) |
| Local reactions | | | | | | | | |
| Pain at injection site | | | | | | | | |
| Mild | 4 (4%; 1.1–9.9) | 4 (4%; 1.1–9.9) | 1 (1%; 0.0–5.5) | 2 (3%; 0.3–9.3) | 2 (2%; 0.2–7.0) | 1 (1%; 0.03–5.5) | 1 (1%; 0.0–5.5) | 0 |
| Moderate | 1 (1%; 0.0–5.5) | 1 (1%; 0.0–5.5) | 0 | 0 | 0 | 0 | 0 | 0 |
| Swelling | | | | | | | | |
| Mild | 0 | 0 | 0 | 1 (1%; 0.0–7.2) | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Systemic reactions | | | | | | | | |
| Fever | | | | | | | | |
| Mild | 0 | 1 (1%; 0.0–5.5) | 1 (1%; 0.0–5.5) | 0 | 2 (2%; 0.2–7.0) | 1 (1%; 0.0–5.5) | 1 (1%; 0.0–5.5) | 0 |
| Moderate | 0 | 1 (1%; 0.0–5.5) | 2 (2%; 0.2–7.0) | 0 | 0 | 0 | 0 | 0 |
| Body ache | | | | | | | | |
| Mild | 0 | 1 (1%; 0.03–5.5) | 0 | 0 | 0 | 0 | 0 | 0 |
| Moderate | 0 | 1 (1%; 0.0–5.5) | 1 (1%; 0.0–5.5) | 0 | 1 (1%; 0.0–5.5) | 0 | 0 | 0 |
| Fatigue | | | | | | | | |
| Mild | 1 (1%; 0.0–5.4) | 0 | 0 | 0 | 1 (1%; 0.03–5.4) | 0 | 3 (3%; 0.6–8.5) | 0 |
| Moderate | 2 (2%; 0.2–7.0) | 3 (3%; 0.6–8.5) | 0 | 0 | 1 (1%; 0.0–5.5) | 0 | 0 | 0 |
| Headache | | | | | | | | |
| Mild | 1 (1%; 0.03–5.5) | 2 (2%; 0.2–7.0) | 0 | 5 (7%; 2.2–14.9) | 0 | 0 | 0 | 0 |
| Moderate | 0 | 3 (3%; 0.6–8.5) | 2 (2%; 0.2–7.0) | 0 | 0 | 0 | 0 | 0 |
| Nausea or vomiting | | | | | | | | |
| Mild | 1 (1%; 0.03–5.5) | 2 (2%; 0.2–7.0) | 2 (2%; 0.2–7.0) | 2 (3%; 0.3–9.3) | 0 | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Data are n (%; 95% CI). The safety set includes all participants who received one dose of the vaccine (n=375). Dose 1 events are from days 0–7 and dose 2 events are days 14–21. The grading scale for most adverse events was based on the US Food and Drug Administration (FDA) guidance document for toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. For adverse events where grading was not mentioned in the FDA guidance document, we have used the common terminology criteria for adverse events grading. There were no severe adverse events.

Table 2: Solicited adverse events in the safety set

ranges had no corroborating clinical manifestations (appendix pp 7–9).

One serious adverse event was reported in the 6 µg with Algel group. The participant was screened on July 25 and vaccinated on July 30. 5 days later, the participant reported fever and headache (initially reported as a solicited adverse event), and on Aug 8 tested positive for SARS-CoV-2 (by a nucleic acid test). The symptoms were initially mild in nature, with the onset of relapsing fever requiring admission to hospital on Aug 15. The participant had stable vital signs (except body temperature) during their hospital stay and did not require supplemental oxygen. The participant was discharged on Aug 22 after a negative nucleic acid test result. The event was not causally associated with the vaccine. No other symptomatic SARS-CoV-2 infections were reported between days 0 and 75. However, follow-up of routine SARS-CoV-2 nucleic acid testing was not done on any scheduled or illness visit.

IgG titres (GMTs) to all epitopes (spike protein, receptor-binding domain, and nucleocapsid protein) increased rapidly after the administration of both doses

(figure 2A–C; appendix pp 3–4). Both 3 µg and 6 µg with Algel-IMDG groups reported similar anti-spike, anti-receptor binding, and anti-nucleoprotein IgG titres (GMTs), adding to the dose-sparing effect of the adjuvant. Binding antibody titres to the whole-virion inactivated antigen are shown in the appendix (p 15). The mean isotyping ratios (IgG1/IgG4) were greater than 1 for all vaccinated groups, which was indicative of a Th1 bias (figure 2D).

Seroconversion rates (after the second dose), based on MNT₅₀ were 87.9% (95% CI 79.8–94.3) in the 3 µg with Algel-IMDG group, 91.9% (84.6–96.0) in the 6 µg with Algel-IMDG group, and 82.8% (73.7–89.2) in the 6 µg with Algel group (figure 3A). Seroconversion (at day 28) in the control group was reported in six (8% [3.6–17.2]) of 75 participants, suggestive of asymptomatic infection. The post-second-dose GMTs (MNT₅₀) were 61.7 (49.5–76.9) in the 3 µg with Algel-IMDG group, 66.4 (53.4–82.4) in the 6 µg with Algel-IMDG group, and 48.0 (37.7–61.1) in the 6 µg with Algel group. Responses in the Algel-IMDG groups were not significantly different to the response in the 6 µg with Algel group. The vaccine-induced responses were similar to those observed in the convalescent

serum collected from 41 patients who had recovered from COVID-19 (figure 3B). On these 41 patients, the median titre of symptomatic patients ($n=25$; median 142·2 [IQR 56·6–350]) was significantly higher than that of the asymptomatic patients ($n=16$; 22·6 [9·0–56·5]; appendix p 16). Seroconversion rates analysed by PRNT₅₀ (after the second dose) were 93·4% (95% CI 83·7–97·8) in the 3 µg with Algel-IMDG group, 86·4% (75·1–93·2) in the 6 µg with Algel-IMDG group, and 86·6% (74·3–93·6) in the 6 µg with Algel group (figure 3C).

MNT₅₀ wild-type neutralising antibody responses for a subset of paired serum samples ($n=50$) were analysed at the National Institute of Virology and Bharat Biotech (on day 28, 2 weeks after the second vaccination in all groups). Additionally, neutralising antibodies were analysed by PRNT₅₀ at Bharat Biotech and the National Institute of Virology. Similar results were obtained for MNT₅₀ and PRNT₅₀ assays at both laboratories (appendix p 17). Randomly selected serum samples from day 28 were analysed by PRNT₅₀ at the National Institute of Virology with homologous and heterologous strain assessments. Neutralisation responses, regardless of the challenge strain, were observed (figure 3D).

In a subset of randomly selected blood samples at one site, IFN-γ ELISpot responses against SARS-CoV-2 peptides peaked at about 100–120 spot-forming cells per million peripheral blood mononuclear cells in all vaccinated groups on day 28. Both the Algel-IMDG groups elicited CD3⁺, CD4⁺, and CD8⁺ T-cell responses that were reflected in the IFN-γ production, albeit in a small number of samples. However, there was a minimal detection of less than 0·5% of CD3⁺, CD4⁺, and CD8⁺ T-cell responses in the 6 µg with Algel group and the Algel only group (appendix p 16).

Discussion

We report the interim findings from the phase 1 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The vaccine was well tolerated in all dose groups with no vaccine-related serious adverse events. Both humoral and cell-mediated responses were observed in the recipients of the Algel-IMDG-based vaccines.

The most common adverse event was pain at the injection site, followed by headache, fatigue, and fever. The overall incidence of solicited local and systemic adverse events in this study was 14–21% in all vaccine-treated groups, which is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates^{18–23} and similar to the rates for other inactivated SARS-CoV-2 vaccine candidates^{24,25}. One serious adverse event (positive for SARS-CoV-2 by a nucleic acid test) in an individual in the 6 µg with Algel group was not related to vaccination. Because the event occurred in the 5 days after vaccination, the development of a protective immune response was not likely.

BBV152 induced binding and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.^{24,25} Titres

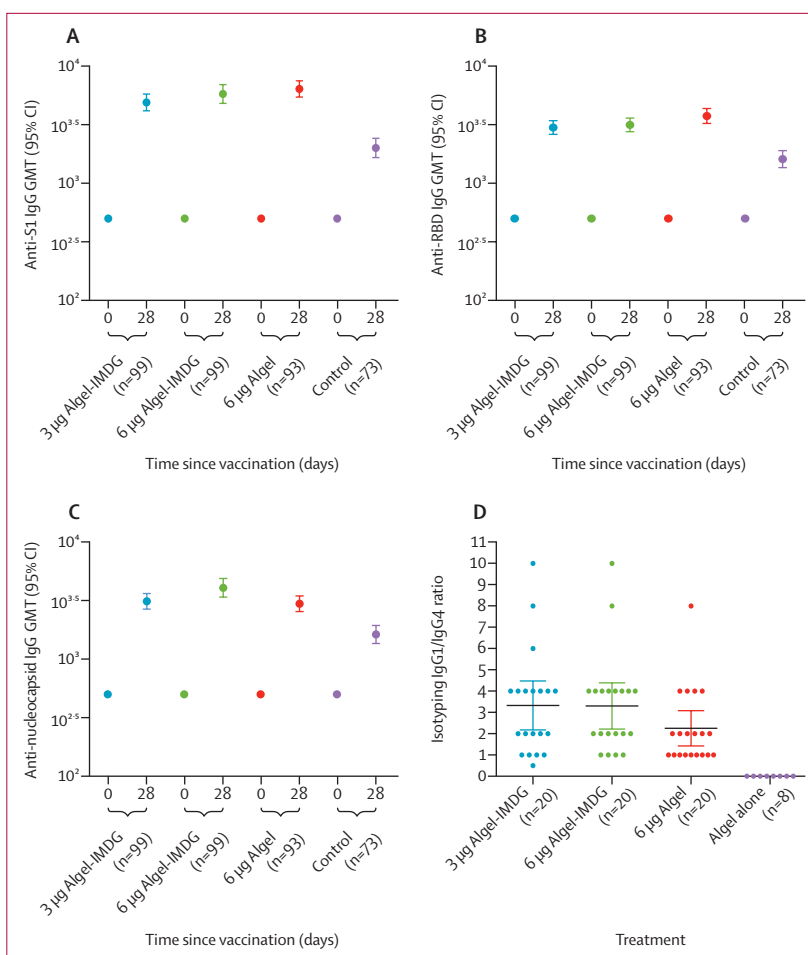


Figure 2: SARS-CoV-2 IgG titres against anti-spike protein (A), receptor-binding domain (B), and nucleocapsid IgG (C) and anti-spike protein IgG1/IgG4 ratio (D)
ELISA results at baseline (day 0) and 2 weeks after the second vaccination (day 28). In A–C, error bars show 95% CIs. The cutoff for detectable antibodies was 1/500. Some samples were positive for SARS-CoV-2 in the control group, as evident by the antibody titres on day 28. Endpoint titre dilution for day 28 sera samples was established with baseline (day 0), interpolated from the absorbance of the corresponding day 0 sample. Cutoff (mean \pm 3 SD) for day 0 was calculated considering the absorbance of all sera dilutions (1/500 to 1/32000) tested, except the lowest dilution (1/500). ELISA titres (endpoint titres) on day 14 were not analysed. In D, the isotyping ratio was calculated (in a randomly selected subset) as IgG1/IgG4; dots show the individual datapoints and horizontal bars show means with error bars for 95% CIs. Endpoint titre=the highest sera dilution at which the absorbance was above the cutoff. GMT=geometric mean titre. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

from the Anti-spike IgG ELISA assay correlated positively with live virus microneutralisation assay titres ($R^2=0\cdot51$). We assessed an accelerated schedule (vaccination 2 weeks apart) and did not include a routine schedule (vaccination 4 weeks apart). It has been reported that a routine schedule for another SARS-CoV-2 vaccine candidate offers better immune responses, as is to be expected.²⁶ The 4-week schedule for BBV152 3 µg and 6 µg with Algel-IMDG is being assessed in a phase 2 trial in 380 volunteers (NCT04471519). Here, we showed that all vaccine formulations were Th1 skewed with IgG1/IgG4 ratios greater than 1. Furthermore, the Algel-IMDG formulations were associated with an increase in the frequency of CD4⁺ INF-γ⁺ T cells compared with the 6 µg

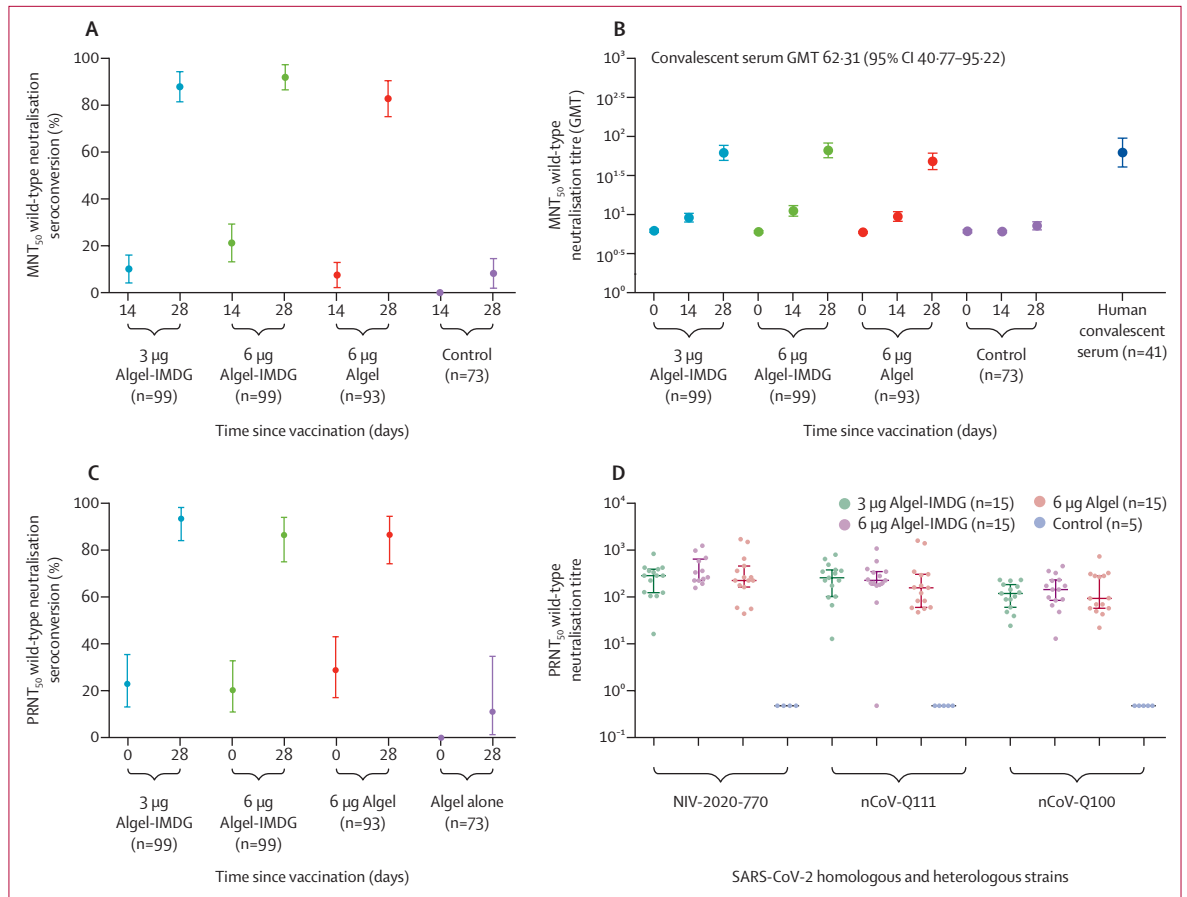


Figure 3: SARS-CoV-2 wild-type MNT₅₀ seroconversion rates (A) and GMT (B) and PRNT₅₀ seroconversion rates (C) and medians (D). Results at baseline (day 0), 2 weeks after the first vaccination (day 14), and 2 weeks after the second vaccination in the immunogenicity cohort. Seroconversion rates were defined by the proportion of titres achieving at least four-fold greater than baseline. In A–C, error bars show 95% CIs. In B, the human convalescent serum panel included specimens from participants with PCR-confirmed symptomatic or asymptomatic COVID-19, obtained at least 30 days after diagnosis (41 samples for MNT₅₀). In D, randomly selected serum samples from day 28 were analysed by PRNT₅₀ at the National Institute of Virology for homologous (NIV-2020-770) and heterologous (nCoV-Q11 and nCoV-Q100) assessments; dots show individual datapoints and horizontal bars show medians with error bars for IQRs. GMT=geometric mean titre. MNT₅₀=microneutralisation assay. PRNT₅₀=plaque-reduction neutralisation test. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

with Algel formulation, which is indicative of a Th1 bias. Additionally, cell-mediated responses from other SARS-CoV-2 inactivated vaccine candidates have not been reported thus far.

A few animal studies of SARS-CoV and Middle East respiratory syndrome-CoV inactivated or vectored vaccines adjuvanted with alum have shown Th2 responses resulting in eosinophilic infiltration in the lungs.^{27–29} Adverse events might be associated with the induction of weakly neutralising or non-neutralising antibodies that lead to antibody-dependent enhancement or enhanced respiratory disease, thus prompting the attempt to develop SARS-CoV-2 vaccines that induce a CD4⁺ Th1 response with a minimal Th2 response.^{2,30–32} Whole-virion inactivated vaccines are mostly developed with Algel (alum) as the adjuvant. The response generated by alum is primarily Th2 biased, with the induction of strong humoral responses by neutralising antibodies.³³ To circumvent this concern

of antibody-dependent enhancement, we have assessed this vaccine with Algel and a TLR7/8 agonist that results in immune responses that are biased to Th1. Previous studies have shown that the toll-like receptors play an integral role in bridging the innate and adaptive immune responses, leading to the differentiation of CD4⁺ T cells into Th1 cells, which produce IFN- γ .³⁴ Geeraedts and colleagues³⁵ reported that the stimulation of TLR7 by an influenza whole-virion inactivated vaccine was a significant determinant of a greater immune response and Th1 polarisation. Thus, it is imperative to develop such whole-virion inactivated vaccines with adjuvants that can synergistically contribute to the full potential. Algel-IMDG contains an imidazoquinoline class TLR7/8 agonist adsorbed to Algel. Preclinical studies on BBV152 adjuvanted with this molecule reported a Th1-biased response in mice.⁷ Furthermore, in a non-human primate and hamster live viral challenge studies, Algel-IMDG formulations

led to higher neutralising antibodies, which might have resulted in improved upper and lower airway viral clearance (after challenge).^{8,9}

This study was done at a time of rapidly increasing daily diagnoses of COVID-19. Among all 897 individuals screened for this trial, 70 (8%) had positive SARS-CoV-2 nucleic acid test results and 63 (7%) had positive SARS-CoV-2 serology results. Seroconversion (at day 28) in the control group was reported in six (8%) of 75 participants from five separate study sites. Because substantial SARS-CoV-2 was observed at enrolment and some of the control group recipients seroconverted, post-vaccination titres from the vaccinated recipients might be slightly inflated, in the event of natural exposure to SARS-CoV-2. No symptomatic COVID-19 cases were reported in the control group.

Because this is an interim report, we are not reporting any data on the persistence of vaccine-induced antibody responses or long-term safety outcomes. The results reported here do not permit efficacy assessments. The analysis of safety outcomes requires more extensive phase 2 and 3 clinical trials. Pre-vaccination laboratory values were similar to values after vaccination. However, transient laboratory abnormalities might have been resolved by day 28. The analysis of T-cell responses by Th2 cytokines was not done and is planned for phase 2. We were unable to assess other immune responses of convalescent serum because of insufficient number of samples. The proportion of samples collected from asymptomatic individuals was high (39%), and no additional data on the severity of disease from symptomatic individuals was obtained. This study population did not have ethnic diversity and most of the participants were men, further underscoring the importance of assessing BBV152 in other populations.

However, this study has several strengths. To ensure generalisability, this study was conducted with participants from diverse geographic locations within India (appendix p 13), enrolling 375 participants across 11 hospitals. The first 50 participants were enrolled into the 3 µg with Algel-IMDG and control groups. Before granting the recommendation to proceed with the enrolment of other cohorts, masked safety data was reviewed by the data safety monitoring board. As a result, no operational bias was introduced. Despite enrolment occurring during a national lockdown, which led to several operational challenges, the overall participant retention rate was 97%. The sample size was intentionally large to enable the inference of meaningful conclusions regarding neutralising responses. With several reports questioning the efficacy of SARS-CoV-2 vaccines against antigenically divergent strains, we report neutralising responses to homologous and heterologous strains. The BBV152 vaccine strain, based on the Asp614Gly mutation, has been reported to have differential sensitivity to neutralisation by vaccine-elicited antibodies or by antibodies produced by natural infection.^{36,37} The increase

in Asp614Gly infectivity results in the virus being more susceptible to neutralising antibodies,³⁸ which is corroborated by marginal reductions in neutralising titres in the PRNT₅₀ assays with heterologous strains, which are devoid of the Asp614Gly mutation.

BBV152 induced binding and neutralising antibody responses and with the inclusion of the Algel-IMDG adjuvant, this is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1-biased response. BBV152 is stored at 2–8°C, which is compatible with immunisation cold-chain requirements. Both Algel-IMDG formulations were selected for the phase 2 immunogenicity trials. Further efficacy trials are warranted.

Contributors

RE and KMV accessed and verified the data. HJ, BG, PY, and GS led the immunogenicity experiments. KMV, SPr, VS, and RE contributed to the analysis and manuscript preparation. SR was the study coordinator and helped immensely with the protocol design and interim report generation. PA, SPr, NG, and BB contributed various neutralising antibody assays and participated in the writing of this manuscript. SPa reviewed the manuscript. PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG were involved with the scientific review of this manuscript. KE was responsible for overall supervision of the project and review of the final paper.

Declaration of interests

RE, HJ, BG, KMV, SPr, VS, KE, and SR are employees of Bharat Biotech, with no stock options or incentives. KE is the Chairman and Managing Director of Bharat Biotech. PY, GS, PA, NG, SPa, and BB are employees of The Indian Council of Medical Research. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

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Supplementary Appendix to Manuscript Entitled

Safety and immunogenicity trial of an inactivated SARS-CoV-2 vaccine-BBV152: a phase 1, double-blind, randomised control trial

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Supplemental methods

i. RT-PCR (conducted at Dr. Dangs Lab, New Delhi) at Screening

TRUPCR SARS-CoV-2 RT qPCR (V 3.2) is a single tube, in vitro nucleic acid amplification test for the qualitative detection of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2)specific RNA from respiratory specimens (nasopharyngeal or oropharyngeal aspirates, washes or swabs, bronchoalveolar lavage, sputum and tracheal aspirates) using Real-time PCR. The human RNaseP gene serves as an endogenous internal positive control for human nucleic acid is also included in this kit.

E gene: For the detection of Sarbecovirus RdRp gene and N gene_dual targets for the detection of SARS-CoV-2

RNase P gene: endogenous internal control, which qualifies the sample for testing and is essential for testing Viral RNA in host organism. According to the Centre for Disease Control and prevention, Respiratory Viruses Branch, Division of Viral Diseases, all clinical samples should be tested for human RNase P gene to assess specimen quality for RT PCR for detection of 2019-Novel Coronavirus

The assay runs for 38 cycles; however for any interpretation, threshold cut off cycle Ct is 35.

Interpretation is as follows:

Amplification Signals In

- a) RNase P +/- , E Gene +, RdRp&N gene + : SARS-CoV-2 POSITIVE
- b) RNase P +/- , E Gene -, RdRp&N gene + : SARS-CoV-2 POSITIVE
- c) RNase P +/- , E Gene +, RdRp&N gene - : SARBECoVIRUS POSITIVE
- d) RNase P + , E Gene -, RdRp&N gene - : NEGATIVE
- e) RNase P - , E Gene -, RdRp&N gene - : INVALID

100 percent concordance of results for submitted samples with ICMR designated QC Lab (AIIMS for Dr. Dangs Lab)

ii. CLIA (conducted at Dr. Dangs Lab, New Delhi) at Screening

The liaison SARS-CoV-2 IgG assay performed on the Liaison XL analyzer is an indirect chemiluminescence Immunoassay (CLIA) for the Quantitative determination of anti-S1 and anti- S2 antibodies to SARS-CoV-2 in human serum or plasma. The sensitivity of the above assay is 97.4 percent for 15 days post-diagnosis and specificity 98.9 percent for Laboratory routine testing. Testing of assay-specific calibrators allows the detected Relative light unit (RLU) to adjust the assigned master curve. The analyzer automatically calculates SARS-CoV- S1/S2 IgG antibody concentrations as arbitrary units (AU/mL) and grades the results.

Results are interpreted as follows:

Less than 12 AU/mL: NEGATIVE (A negative result may indicate the absence or a very low level of IgG antibodies to the Pathogen. The test could score negative in infected patients during the incubation period and during the early stages of infection) >or equal to 12 and less than 15 AU/mL: Equivocal (Retest in duplicate. Samples with 2 out of 3 results more than or equal to 15 or less than 12 should be reported as positive or negative, respectively. A second sample should be collected and tested no less than one to two weeks later if the results are repeatedly equivocal) >or equal to 15: Positive (A positive result generally indicates exposure of the subject to the pathogen)

iii. Enzyme-linked immunosorbent assay (ELISA) (conducted at Bharat Biotech)

ELISA tests were performed as per standard protocols. Briefly, Microtiter plates were coated with SARS-CoV-2 specific antigens (Whole inactivated SARS CoV-2 antigen, spike (S1) (Syngene, Bangalore, India, Batch No# PRB026913/Receptor Binding Domain (RBD), Syngene, Bangalore, India, Batch No# PRB025485/ nucleocapsid (N), Syngene, Bangalore, India, Batch No# PRB025627 at a concentration of 1µg/ml, 100µl/well in PBS pH 7.4). After overnight incubation, wells were blocked and added serially diluted sera. After incubation, wells were added with Goat anti-Human IgG HRP conjugate (Sigma-Aldrich, Cat# A8667, dilution 1:5000) and incubated for 1hr at RT. Tetramethyl benzidine used as a substrate and measured absorbance at 450/630nm. Threshold value (Mean + 3SD) was established by taking the absorbance of Day 0 sera samples and antigen-specific endpoint titers were determined for Day 28 sera samples. The reciprocal antibody dilution, at which absorbance is above the threshold, was taken as antigen-specific antibody endpoint titers.

Plaque Reduction Neutralisation Test (PRNT₅₀) (conducted at Bharat Biotech and National Institute of Virology)

The Plaque reduction neutralisation test was performed in a biosafety level 3 facility. To perform PRNT₉₀, Vero CCL-81 cell suspension (1.0×10^5 /mL/well) was added in duplicates in 24-well tissue culture plates and cultured in a CO₂ incubator at 37°C for 16-24 hrs. Serum samples from all enrolled participants were inactivated by keeping in a 56°C-water bath for 30 min. Serial dilutions (4 fold) of serum samples were mixed with the virus, which can form 50 plaque-forming units and then incubated for 1 h at 37°C. The virus-serum mixtures were added onto the preformed Vero CCL-81 cell monolayers and incubated 1 h at 37°C in a 5% CO₂ incubator. The number of plaques was counted, and the Neutralizing antibody titer was determined based on the 50% reduction in the number of plaque count, which was further analyzed using 50% Probit Analysis (10.4103/ijmr.IJMR_2382_20). A neutralisation antibody titer < 1:20 considered negative, while that of > 1:20 considered as positive.

iv. Microneutralisation assay (MNT) (conducted at Bharat Biotech)

The serum collected from all enrolled participants were inactivated at 56°C in a water bath for 30 min. Serum was successively diluted 1:8 to the required concentration by a 2-fold series, and an equal volume of challenge virus solution containing 100 CCID₅₀ viruses was added. After neutralisation in a 37°C incubator for two hours, a 1.0×10^5 /mL cell suspension was added to the wells (0.1 mL/well) and cultured in a CO₂ incubator at 37°C for 3-5 days. The Karber method (Ramakrishnan, 2016) by observing the CPE was used to calculate the neutralisation endpoint (convert the serum dilution to logarithm), which means that the highest dilution of serum that can protect 50% of cells from infection by challenge with 100 CCID₅₀ virus is the antibody potency of the serum. A neutralisation antibody potency < 1:20 is negative, while that R 1:20 is positive.

v. Intracellular Staining: (conducted at Bharat Biotech)

Human PBMCs (1×10^6 /ml) were cultured in 24 well plates and stimulated with inactivated SARS-COV-2 antigen (1.2 µg/ml) or PMA (25 ng/ml, cat # P8139; Sigma) and Ionomycin (1 µg/ml, cat # I0634, Sigma) along with Protein transport inhibitor (Monensin, 1.3 µl/ml cat # 554724, BD biosciences) for 12-16hrs in CO₂ incubator at 37°C. Cells were washed and centrifuged at 1000rpm for 5-10min and stained with cell surface markers BV421 Mouse Anti Human CD3 (clone: UCHT1, Cat # 562427, BD Biosciences), APC- Cy7 Mouse Anti Human CD4 (Clone: SK3 Cat # 566319, BD Biosciences), PE- Mouse Anti Human CD8a (Clone: HIT8a, Cat # 555635, BD Biosciences) and Per Cp-Cy5.5 Mouse Anti Human IL-4 (Clone: 8D4-8, Cat # 561234) for 30 minutes at 4°C. Cells were again washed twice with PBS and fixed using fixation/Permeabilize solution (Cat # 554722, BD Biosciences) for 20 mins at 4°C. Following fixation/permeabilization, cells were washed with 1x permeabilization buffer and stained with intracellular cytokines IFN-γ (APC Mouse Anti Human IFN-γ, Clone: 4S.B3, cat # 551385, BD Biosciences) for 30 mins at 4°C. Cells were washed and resuspended in 500 µl FACS buffer (Cat # 554657, BD Biosciences). All samples were acquired using BD FACSVerser (BD Biosciences).

vi. SARS-CoV2 Antibody (IgG1/IgG4) Isotyping:

Th1-dependent IgG1 vs. Th2 -dependent IgG4 antibody subclasses were determined by ELISA from sera collected from all vaccinated groups as described earlier. Briefly, 96 well microtiter plates were coated with spike (S1) protein (Cat: SYNG-PRB026913, Make: Syngene), at a concentration of 1 µg/ml, in PBS pH 7.4) and blocked with 1% BSA in PBS, pH 7.4. Serially diluted (1:50 to 1:204800) individual sera were added and incubated for 2hrs at 37°C followed by the addition of mouse anti-human IgG1 (Cat No: 409904, Make: Biolegend) or IgG4 (Cat No: 411202, Make: Biolegend) antibodies at a concentration of 25ng/well. After incubation of the plate for 1hr at RT, wells were again washed, and added Anti Mouse IgG HRP Conjugate (Cat No: A4416, Make: Sigma Aldrich) at a dilution of 1:2500. Later, 3,3',5,5'-tetramethylbenzidine (TMB) solution (Cat No: AR1002, Make: deNovo Biolabs) was added as a substrate to develop color. Absorbance was read at 450nm. Cut off was determined as 1:50 dilution, by calculating Mean+3SD of absorbance obtained at all dilutions of known negative control (unvaccinated and uninfected sera). Th1:Th2 index was calculated by taking ratios of end point antibody titer (sera dilution at which absorbance was above the cut off) of IgG1 & IgG4.

vii. ELISPOT for IFN- γ (conducted at Indoor Biotechnologies, Bangalore):

To determine the frequency of IFN- γ producing T cells generated by the vaccine, we performed an ELISPOT assay using the IFN- γ ELISPOT kit (MABTECH), as per the manufacturer's instructions. Briefly, ELISPOT plates precoated with IFN- γ antibody were used, these were further seeded with 300,000 PBMCs obtained from the study subjects. The PBMCs were stimulated with SARS-CoV-2 peptide matrix (SARS-CoV-2 S1 scanning pool) (MABTECH) at a concentration of 5 μ g/ml for 18 hours. Unstimulated cells and anti-CD3 stimulated cells were used as a negative and positive controls, respectively. Subsequently, the plates were washed and incubated with a biotinylated detection antibody, followed by Streptavidin-ALP (Alkaline Phosphatase). The plates were developed with the BCIP-NBT substrate (5-bromo-4-chloro-3'-indolylphosphate and nitro-blue tetrazolium) as per the manufacturer's instructions until distinct spots emerged. The number of blue spots per well was determined by using an ELISPOT reader (AiD) or under a dissection microscope (Leica). The frequency of positive cells was calculated after subtracting the number of spots in unstimulated cells from the peptide stimulated cells, and the results were expressed as SFU/10⁶ PBMCs.

viii. Database Handling/Procedures and Data Management Plan

The database used for this study is a fully validated, FDA 21 CFR Part 11 compliant system, proprietary, SAS (software as a Service) based clinical data management system. Error rates for clinical database are controlled and do not exceed 0.5% as an industry-wide standard. For critical data zero errors based on a 100% review of data are obtained. This is controlled and documented by database audits against the study CRFs. Based on Data Management Plan (DMP) document a road map to handle the data under projected circumstances and describes the CDM activities was followed in the trial. The DMP describes the annotations, database design, data entry and data tracking guidelines, quality control measures, SAE reconciliation guidelines, discrepancy management, data transfer/extraction, and database locking guidelines. Along with the DMP, a Data Validation Plan (DVP) containing all edit-checks was performed and the calculations for derived variables are also prepared. The edit check programs in the DVP help in cleaning up the data by identifying the discrepancies.

Table S1: Ethic Committees from All Participating Trial Sites with Reference Numbers:

| Site Name | Reference Number |
|--|----------------------------|
| Nizam's Institute of Medical Science, Hyderabad, Telangana | ECR/303/INST/AP/2013/RR-19 |
| All India Institute of Medical Science, New Delhi | ECR/547/INST/DL/2014/RR-17 |
| PGIMS, Rohtak, Haryana | ECR/293/Inst/HR/2013/RR-19 |
| All India Institute of Medical Science, Patna | ECR/1387/INST/BR/2020 |
| Redkar Hospital & Research Centre, Goa | ECR/902/INST/GA/2018 |
| IMS & SUM Hospital, Odisha | ECR/627/INST/OR/2014/RR-17 |
| Jeevan Rekha Hospital, Belgaum, Karnataka | ECR/1242/INST/KA/2019 |
| Gillukar Multispeciality Hospital, Nagpur | ECR/1374/INST/MH/2020 |
| Rana Hospital and Trauma Center, Gorakhpur, Utter Pradesh | ECR/1332/INST/UP/2020 |
| Prakhar Hospital, Kanpur, Utter Pradesh | ECR/1017/INST/UP/2017 |
| SRM Medical College Hospital & Research Centre, Chennai Tamil Nadu | ECR/431/INST/TL/2013/RR-19 |

Table S2: Grading Scales for Local Adverse Events and Systemic

| S. No. | Event Name | None=1 | Mild =2 | Moderate=3 | Severe=4 | Potentially life threatening=5 |
|--------------------------------|------------------------------------|-------------------------|--|--|--|--|
| Local Adverse Events | | | | | | |
| 1 | Pain at injection site | Absent | Does not interfere with activity | Interferes with activity or repeated use of non-narcotic pain reliever >24hrs | prevents daily activity or repeated use of narcotic pain reliever | Emergency room (ER) visit or hospitalization |
| 2 | Tenderness/Soreness | Absent | Mild discomfort to touch | Discomfort with movement | Significant discomfort at rest | Emergency room (ER) visit or hospitalization |
| 3 | Redness/Erythema | Absent | 2.5-5cm | 5.1-10cm | >10 cm | Necrosis or exfoliative dermatitis |
| 4 | Swelling/Induration | Absent | 2.5-5cm and does not interfere with daily activity | 5.1-10cm or interferes with daily activity | >10 cm prevents daily activity | Necrosis |
| 5 | Pruritus associated with injection | Absence of any Pruritus | itching localized to injection site and relieved spontaneously or with <48 hours treatment | Itching beyond injection site not generalized or localized itching requiring >48 hours treatment | Itching causing inability to perform usual social & functional activities | NA |
| 6 | Any other Local AE's | Absent | Does not interfere with daily activity | interferes with daily activity, | prevents daily activity | Emergency room (ER) visit or hospitalization |
| Systemic Adverse Events | | | | | | |
| 1 | Pain | Absent | Does not interfere with activity | Repeated use of non-narcotic pain reliever > 24 hours or interferes with daily activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| 2 | Fever | <38.00C (<100.40 F) | 38.0-38.40 C(100.4-101.10F) | 38.5-38.90 C(101.2-102.00F) | 39.0-400C C(102.1-1040F) | > 400 C (>1040 F) |
| 3 | Nausea/Vomiting | Absent | No interference with daily activity or 1-2 episodes/24 hours | Some interference with daily activity or > 2 episodes/24 hours | Prevents daily activity, requires outpatient IV hydration | Emergency room (ER) visit or hospitalization for hypotensive shock |
| 4 | Headache | Absent | No interference with daily activity | some interference with daily activity or repeated use of non-narcotic pain reliever | Significant, prevents daily activity or repeated use of narcotic pain reliever | Emergency room (ER) visit or hospitalization |
| 5 | Fatigue | Absent | No interference with daily activity | some interference with daily activity | Significant, prevents daily activity | Emergency room (ER) visit or hospitalization |
| 6 | Myalgia | Absent | No interference with daily activity | some interference with daily activity | Significant, prevents daily activity | Emergency room (ER) visit or hospitalization |
| 7 | Acute Allergic Reaction | Absent | No interference with daily activity | some interference with daily activity | Prevents daily activity | Emergency room (ER) visit or hospitalization |
| 8 | Rash | Rash Absent | rashes covering <10%BSA with or without symptoms (pruritus, burning, | rashes covering 10-30 %BSA (Body Surface Area) with or without symptoms (pruritus, | rashes covering >30 %BSA with or without symptoms (pruritus, burning, | NA |

| | | | | | | |
|----|-------------------------------|--------|---|---|---|--|
| | | | tightness) | burning, tightness), interferes with daily activity | tightness), prevents with daily activity | |
| 9 | Joint pain | Absent | Does not interfere with daily activity | Repeated use of non- narcotic pain reliever > 24 hours or interferes with daily activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| 10 | Any other Systemic AE's | Absent | Does not interfere with daily activity | interferes with daily activity | prevents daily activity | Emergency room (ER) visit or hospitalization |

Abbreviation: NA, not available

Table S3: Summary of Demographics and Baseline Characteristics of the First 50 Subjects.

| Parameter | | 3 µg with Algel-IMDG n=40 | Control Arm n=10 | |
|--------------------------------|----------------------|------------------------------|---------------------|-------------|
| Age (Years) | (Mean±SD) | 31.2 ± 9.2 | 29.4 ± 6.7 | |
| | Median | 29 | 26.5 | |
| | (Q1;Q3) | (23.3, 39.3) | (25;34) | |
| Age-wise (Years) | ≥18-<25 | 16 (40%) | 3(30%) | |
| | ≥26-<40 | 16(40%) | 6(60%) | |
| | >40-<55 | 8(20%) | 1(10%) | |
| Sex (Gender) | Male n (%) | 35 (35%) | 10 (10%) | |
| Body Mass index‡ | (Mean±SD) | 24.2 ± 3.0 | 22.7 ± 2.9 | |
| | Median | 24.1 | 22.89 | |
| | (Q1;Q3) | (22.5, 25.8) | (19.8;25.7) | |
| Temperature (°F) | (Mean±SD) | 97.7 ± 0.7 | 98.0 ± 0.7 | |
| | Median | 97.7 | 98.15 | |
| | (Q1;Q3) | (97.4;98.2) | (97.5;98.3) | |
| Blood Pressure (mm Hg) | Systolic (mm Hg) | (Mean±SD) | 124.6 ± 7.9 | 128 ± 7.59 |
| | | Median | 126.5 | 127 |
| | | (Q1;Q3) | (118.5;128) | (123;132) |
| | Diastolic (mm Hg) | (Mean±SD) | 79.5 ± 6.4 | 78.6 ± 8.63 |
| | | Median | 80 | 81.5 |
| | | (Q1;Q3) | (76.5;84) | (75;84) |
| Respiratory Rate (Breaths/min) | (Mean±SD) | 16.7 ± 2.3 | 16.6 ± 2.5 | |
| | Median | 16 | 16 | |
| | (Q1;Q3) | (16;18) | (16;18) | |
| Pulse Rate (Beats/min) | (Mean±SD) | 78.8 ± 7.9 | 76.6 ± 6.9 | |
| | Median | 80 | 78 | |
| | (Q1;Q3) | (74;85.5) | (75;80) | |

Results reported here are unblinded. However, the study was performed in a dose-escalation manner wherein after completing vaccination in the first 50 participants with 3 µg with Algel-IMDG (the lowest antigen concentration) and the control (randomisation ratio 4:1); the participants were monitored for seven days for safety. Based on the independent Data Safety Monitoring Board (DSMB) reviewal of blinded safety data, the trial was allowed to continue with enrollment of the remaining participants into all groups.

Table S4: Adverse Events of the first 50 participants (blinded) after the first Dose of Vaccine Administration.

| Adverse Events after the First Dose | |
|--|---|
| ADVERSE EVENT | 3 µg with Algel-IMDG and Control Arms n=50 |
| Headache | 1 (2%) |
| Feeling Hungry | 2(4%) |
| Nausea | 1(2%) |
| Fatigue | 2(4%) |
| Pain at injection site | 3(6%) |
| Total Adverse Events | 9(18%) |

The study was performed in a dose-escalation manner wherein after completing vaccination in the first 50 participants with 3 µg with Algel-IMDG (the lowest antigen concentration) and the control (randomisation ratio 4:1); the participants were monitored for seven days for safety. Based on the independent Data Safety Monitoring Board (DSMB) reviewal of blinded safety data, the trial was allowed to continue with enrollment of the remaining participants into all groups.

Table S5: Proportion of Subjects Experiencing Solicited Adverse Events By Symptom, Severity, Dose Number, and Dose Group.

| Symptoms | Dose Group | Severity | | | | | |
|---------------------|---------------------|--------------|------------------|----------------|--------------|------------------|----------------|
| | | Dose 1 | | | Dose 2 | | |
| | | Mild n(%) | Moderate n(%) | Severe n(%) | Mild n(%) | Moderate n(%) | Severe n(%) |
| Local | | | | | | | |
| Pain | 3µg with Algel-IMDG | 4 (4) | 1 (1) | - | 2 (2) | - | - |
| | 6µg with Algel-IMDG | 4 (4) | 1 (1) | - | 1 (1) | - | - |
| | 6µg with Algel | 1 (1) | - | - | 1 (1) | - | - |
| | Control | 2 (2.7) | - | - | - | - | - |
| Swelling | 3µg with Algel-IMDG | - | - | - | - | - | - |
| | 6µg with Algel-IMDG | - | - | - | - | - | - |
| | 6µg with Algel | - | - | - | - | - | - |
| | Control | 1 (1.3) | - | - | - | - | - |
| Systemic | | | | | | | |
| Fever | 3µg with Algel-IMDG | - | - | - | 2 (2) | - | - |
| | 6µg with Algel-IMDG | 1 (1) | 1 (1) | - | 1 (1) | - | - |
| | 6µg with Algel | 1 (1) | 2 (2) | - | 1 (1) | - | - |
| | Control | - | - | - | - | - | - |
| Body ache | 3µg with Algel-IMDG | - | - | - | - | 1 (1) | - |
| | 6µg with Algel-IMDG | 1 (1) | 1 (1) | - | - | - | - |
| | 6µg with Algel | - | 1 (1) | - | - | - | - |
| | Control | - | - | - | - | - | - |
| Fatigue | 3µg with Algel-IMDG | 1 (1) | 2 (2) | - | 1 (1) | 1 (1) | - |
| | 6µg with Algel-IMDG | - | 3 (3) | - | - | - | - |
| | 6µg with Algel | - | - | - | 3 (3) | - | - |
| | Control | - | - | - | - | - | - |
| Headache | 3µg with Algel-IMDG | 1 (1) | - | - | - | - | - |
| | 6µg with Algel-IMDG | 2 (2) | 3 (3) | - | - | - | - |
| | 6µg with Algel | - | 2 (2) | - | - | - | - |
| | Control | 5 (6.7) | - | - | - | - | - |
| Nausea/ Vomiting | 3µg with Algel-IMDG | 1 (1) | - | - | - | - | - |
| | 6µg with Algel-IMDG | 2 (2) | - | - | - | - | - |
| | 6µg with Algel | 2 (2) | - | - | - | - | - |
| | Control | 2 (2.7) | - | - | - | - | - |

Table S6: Number of unsolicited, non-serious, adverse events classified by MedDRA® System Organ Class, severity, and investigator-assigned relationship to study vaccine/control

| MedDRA SOC | Dose Group | Adverse Events | Severity | | | Relationship to IP | |
|--|---------------------|---|------------|----------------|--------------|--------------------|---------|
| | | | Mild n (%) | Moderate n (%) | Severe n (%) | Not Related | Related |
| Gastrointestinal Disorders | 3µg with Algel-IMDG | GERD (1) | 1 (1) | - | - | 1 (1) | - |
| | 6µg with Algel-IMDG | Stomach pain (1) | 1 (1) | - | - | 1 (1) | - |
| | 6µg with Algel | Abdominal Pain/discomfort (3) | - | 3 (3) | - | - | 3 (3) |
| | Control | - | - | - | - | - | - |
| General Disorders and administrative site conditions | 3µg with Algel-IMDG | Feeling hungry (3) | 1 (1) | 2 (2) | - | 3 (3) | - |
| | | Fever (2) | 1 (1) | - | 1 (1) | 2 (2) | - |
| | | Chills (1) | - | - | 1 (1) | 1 (1) | - |
| | | Sweating (1) | - | 1 (1) | - | - | 1 (1) |
| | 6µg with Algel-IMDG | Feeling hungry (1) | - | 1 (1) | - | 1 (1) | - |
| | | Shivering of hand (2) | - | 2 (2) | - | - | 2 (2) |
| | | Shivering (1) | - | 1 (1) | - | - | 1 (1) |
| | | Sweating (1) | - | 1 (1) | - | - | 1 (1) |
| | 6µg with Algel | Fever (3) | 1 (1) | 2 (2) | - | 2 (2) | 1 (1) |
| | Control | Fever (2) | 2 (2.7) | - | - | 2 (2.7) | - |
| Infections and Infestations | 6µg with Algel-IMDG | Conjunctivitis (1) | 1 (1) | - | - | 1 (1) | - |
| Nervous system disorders | 3µg with Algel-IMDG | Tremor (2) | - | 2 (2) | - | - | 2 (2) |
| | | Dizziness (2) | - | 2 (2) | - | - | 2 (2) |
| | | Headache (1) | 1 (1) | - | - | 1 (1) | - |
| | 6µg with Algel-IMDG | Dizziness (1) | 1 (1) | - | - | 1 (1) | - |
| | | Sleeping disturbance (1) | - | 1 (1) | - | 1 (1) | - |
| | 6µg with Algel | Giddiness (1) | 1 (1) | - | - | 1 (1) | - |
| | | Headache (2) | - | 2 (2) | - | 2 (2) | - |
| | Control | Giddiness (1) | 1 (1.3) | - | - | 1 (1.3) | - |
| Vertigo (1) | | 1 (1.3) | - | - | 1 (1.3) | - | |
| Respiratory, thoracic and mediastinal disorders | 3µg with Algel-IMDG | - | - | - | - | - | |
| | 6µg with Algel-IMDG | Cold (1) | - | 1 (1) | - | - | 1 (1) |
| | | Cough (2) | 1(1) | 1 (1) | - | 1 (1) | 1 (1) |
| | 6µg with Algel | Cold (2) | 1 (1) | 1 (1) | - | - | 2 (2) |
| | | Cough (1) | 1 (1) | - | - | - | 1 (1) |
| | Control | Cold (1) | 1 (1.3) | - | - | - | 1 (1.3) |
| Throat pain (1) | | 1 (1.3) | - | - | - | 1 (1.3) | |
| Skin and subcutaneous tissue disorders | 3µg with Algel-IMDG | Folliculitis on the anterior aspect of right shoulder (1) | 1 (1) | - | - | 1 (1) | - |
| | 6µg with Algel-IMDG | - | - | - | - | - | |
| | 6µg with Algel | - | - | - | - | - | |
| | Control | - | - | - | - | - | |

GERD: Gastroesophageal reflux disease, COLD: the lowest level term (LLT) in the MedDRA for the preferred term (PT) Nasopharyngitis is cold.

Table S7: Abnormal Laboratory Parameters after two dose Vaccinations in the Phase 1 Clinical Trial.

a. Biochemistry

| Lab Parameters | 3 µg with Algel-IMDG N=100 | | 6 µg with Algel-IMDG N=100 | | 6 µg with Algel N =100 | | Control Arm N=75 | |
|---|-------------------------------|---------------|-------------------------------|---------------|---------------------------|---------------|---------------------|---------------|
| | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 |
| | Total n=64 | Total n=71 | Total n=65 | Total n=69 | Total n=64 | Total n=57 | Total n=65 | Total n=45 |
| Bilirubin Direct | 11 (17.2%) | 19 (26.4%) | 9 (13.9%) | 11 (15.9%) | 13 (20.3%) | 12 (21.1%) | 8 (12.3%) | 5 (11.1%) |
| Bilirubin Indirect | 13 (20.3%) | 15 (20.8%) | 9 (13.9%) | 12 (17.4%) | 11 (17.2%) | 14 (24.6%) | 9 (13.9%) | 4 (8.9%) |
| Bilirubin Total | 15 (23.4%) | 18 (25%) | 7 (10.8%) | 15 (21.7%) | 16 (25.0%) | 17 (29.8%) | 9 (13.9%) | 7 (15.6%) |
| Blood Glucose | 1 (1.6%) | 5 (6.9%) | 1 (1.5%) | 4 (5.8%) | 1 (1.6%) | 2 (3.5%) | 3 (4.6%) | 2 (4.4%) |
| C-Reactive Protein | 10 (15.6%) | 10 (13.9%) | 11 (16.9%) | 12 (17.4%) | 10 (15.6%) | 9 (15.8%) | 6 (9.2%) | 6 (13.3%) |
| Serum Creatinine | 1 (1.6%) | (0%) | (0%) | 1 (1.4%) | 1 (1.6%) | 1 (1.8%) | 3 (4.6%) | 2 (4.4%) |
| Gamma glutamyl transferase (GGT) | (0%) | 4 (5.6%) | 6 (9.2%) | 5 (7.3%) | 3 (4.7%) | 1 (1.8%) | 3 (4.6%) | 3 (6.7%) |
| Serum Albumin | 14 (21.9%) | 7 (9.7%) | 10 (15.4%) | 13 (18.8%) | 16 (25%) | 7 (12.3%) | 21 (32.3%) | 10 (22.2%) |
| Serum Alkaline Phosphate | 2 (3.1%) | 4 (5.6%) | 9 (13.9%) | 7 (10.1%) | 10 (15.6%) | 5 (8.8%) | 3 (4.6%) | (0%) |
| Serum Lipase | 1 (1.6%) | 10 (13.9%) | 4 (6.2%) | 7 (10.1%) | 2 (3.1%) | 5 (8.8%) | 4 (6.2%) | 5 (11.1%) |
| SGOT | 8 (12.5%) | 10 (13.9%) | 7 (10.8%) | 5 (7.3%) | 11 (17.2%) | 7 (12.3%) | 9 (13.9%) | 10 (22.2%) |
| SGPT | 18 (28.1%) | 18 (25%) | 15 (23.1%) | 14 (20.3%) | 20 (31.3%) | 19 (33.3%) | 20 (30.8%) | 18 (40%) |
| Cholesterol | 24 (37.5%) | 21 (29.2%) | 28 (43.1%) | 25 (36.2%) | 22 (34.4%) | 13 (22.8%) | 19 (29.2%) | 15 (33.3%) |
| Blood Urea Nitrogen | 1 (1.6%) | (0%) | (0%) | (0%) | (0%) | (0%) | (0%) | (0%) |

n represents total number of subjects with abnormal parameters within the arm. Percentages are the results of counts divided by n.

a. Haematology

| Lab Parameters | 3 µg with Algel-IMDG N=100 | | 6 µg with Algel-IMDG N=100 | | 6 µg with Algel N =100 | | Control Arm N=75 | |
|------------------------------|-------------------------------|---------------|-------------------------------|---------------|---------------------------|---------------|---------------------|---------------|
| | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 |
| | n=19 | n=79 | n=20 | n=69 | n=14 | n=66 | n=15 | n=51 |
| Basophils | (0%) | (0%) | (0%) | (0%) | (0%) | (0%) | 1 (6.67%) | (0%) |
| Eosinophils | 4 (21.1%) | 21 (26.6%) | 1 (5.0%) | 13 (18.8%) | 2 (14.3%) | 10 (15.2%) | 1 (6.7%) | 14 (27.5%) |
| ESR | 17 (89.5%) | 49 (62.0%) | 16 (80.0%) | 30 (43.5%) | 10 (71.4%) | 31 (46.9%) | 8 (53.3%) | 27 (52.9%) |
| Hemoglobin | 19 (100%) | 14 (17.7%) | 20 (100%) | 17 (24.6%) | 14 (100%) | 12 (18.2%) | 15 (100%) | 16 (31.4%) |
| Lymphocytes | 4 (21.1%) | 10 (12.7%) | (0%) | 16 (23.2%) | 2 (14.3%) | 16 (24.2%) | 3 (20.0%) | 10 (19.6%) |
| MCH | 8 (42.1%) | 37 (46.8%) | 10 (50.0%) | 25 (36.2%) | 5 (35.7%) | 17 (25.8%) | 7 (46.7%) | 25 (49.0%) |
| MCHC | 8 (42.1%) | 27 (34.2%) | 14 (70.0%) | 22 (31.9%) | 4 (28.6%) | 24 (36.4%) | 8 (53.3%) | 23 (45.1%) |
| MCV | 5 (26.3%) | 26 (32.9%) | 12 (60.0%) | 17 (24.6%) | 5 (35.7%) | 14 (21.2%) | 7 (46.7%) | 16 (31.4%) |
| Monocytes | (0%) | 1 (1.3%) | 2 (10.0%) | 2 (2.9%) | (0%) | (0%) | (0%) | (0%) |
| Neutrophils | 1 (5.3%) | 2 (2.5%) | (0%) | 1 (1.5%) | (0%) | 2 (3.0%) | (0%) | 2 (3.9%) |
| PCV | 15 (78.9%) | 22 (27.9%) | 15 (75.0%) | 19 (27.5%) | 12 (85.7%) | 21 (31.8%) | 13 (86.7%) | 20 (39.2%) |
| Platelet Count | 1 (5.3%) | 4 (5.1%) | (0%) | 3 (4.4%) | (0%) | 4 (6.1%) | (0%) | 1 (1.9%) |
| Total Leucocyte Count | 1 (5.3%) | 1 (1.3%) | 1 (5.0%) | 4 (5.8%) | 1 (7.1%) | 5 (7.6%) | 1 (6.7%) | 1 (1.9%) |

n represents total number of subjects with abnormal parameters within the arm. Percentages are the results of counts divided by n.

b. Routine Urine Analysis

| Lab Parameters | 3 µg with Algel-IMDG N=100 | | 6 µg with Algel-IMDG N=100 | | 6 µg with Algel N =100 | | Control Arm N=75 | |
|-----------------------------|-------------------------------|---------------|-------------------------------|---------------|---------------------------|---------------|---------------------|---------------|
| | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 | Day 0 | Day 28 |
| | n=18 | n=39 | n=27 | n=33 | n=30 | n=27 | n=24 | n=28 |
| Appearance | 7 (38.9%) | 18 (46.2%) | 16 (59.3%) | 27 (81.8%) | 17 (56.7%) | 22 (81.5%) | 12 (50%) | 17 (60.7%) |
| Bacteria | (0%) | (0%) | 1 (3.7%) | (0%) | 2 (6.7%) | (0%) | 1 (4.2%) | 1 (3.6%) |
| Bile pigments | 1 (5.6%) | 1 (2.6%) | (0%) | 3 (9.1%) | 1 (3.3%) | 3 (11.1%) | (0%) | (0%) |
| Crystals | 10 (55.6%) | 9 (23.1%) | 5 (18.5%) | 13 (39.4%) | 9 (30%) | 8 (29.6%) | 9 (37.5%) | 7 (25%) |
| Urobilinogen | 1 (5.6%) | (0%) | 1 (3.7%) | (0%) | (0%) | (0%) | (0%) | (0%) |
| Urine Ketones | (0%) | 1 (2.6%) | (0%) | (0%) | (0%) | (0%) | (0%) | (0%) |
| Leucocytes Pus cells | 3 (16.7%) | 2 (5.1%) | 7 (25.9%) | 3 (9.1%) | 8 (26.7%) | 3 (11.1%) | 1 (4.2%) | 2 (7.1%) |
| Nitrite | (0%) | (0%) | 1 (3.7%) | (0%) | 3 (10%) | (0%) | 1 (4.2%) | 1 (3.6%) |
| pH | 1 (5.6%) | 1 (2.6%) | (0%) | (0%) | 1 (3.3%) | (0%) | (0%) | 1 (3.6%) |
| RBC | 3 (16.7%) | 23 (58.9%) | 3 (11.1%) | 2 (6.1%) | 8 (26.7%) | 5 (18.5%) | 5 (20.8%) | 7 (25%) |
| Urine Glucose | 1 (5.6%) | 1 (2.6%) | 1 (3.7%) | 2 (6.1%) | 2 (6.7%) | 3 (11.1%) | 3 (12.5%) | 1 (3.6%) |
| Urine Protein | 5 (27.8%) | 1 (2.6%) | 4 (14.8%) | 1 (3.0%) | 6 (20%) | 1 (3.7%) | 5 (20.8%) | 3 (10.7%) |

n represents total number of subjects with abnormal parameters within the arm. Percentages are the results of counts divided by n.

Table S8: Immunogenicity Parameters analyzed.

| Total Parameters / Vaccine Formulation | | | 3 µg with Algel –IMDG | 6 µg with Algel-IMDG | 6 µg with Algel | Control |
|--|-----------------|-------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | | | GMT (95% CI) | GMT (95% CI) | GMT (95% CI) | GMT (95% CI) |
| ELISA GMT (95% CI) | S1- Protein | Day 0 | 500 (500,500) | 500 (500,500) | 500 (500,500) | 500 (500,500) |
| | | Day 28 | 4897.5 (4154.9,5772.7) | 5771.1 (4793.6,6948.0) | 6380.6 (5440.6,7482.9) | 2000.0 (1654.6,2417.5) |
| | RBD- Protein | Day 0 | 500 (500,500) | 500 (500,500) | 500 (500,500) | 500 (500,500) |
| | | Day 28 | 2571.9 (2265.8,2919.4) | 3146.7 (2753.3,3596.4) | 3745.8 (3234.6,4337.7) | 1606.1 (1359.1,1897.9) |
| | N- Protein | Day 0 | 500 (500,500) | 500 (500,500) | 500 (500,500) | 500 (500,500) |
| | | Day 28 | 3110.6 (2667.2,3627.6) | 4053.7 (3376.4,4866.8) | 2695.8 (2544.9,3456.2) | 1620.2 (1357.3,1934.1) |
| ELISA SCR (95% CI) | S1- Protein | Day 28 | 93.8% (87.7,97.5) | 93.3% (86.6,97.3) | 97.9% (92.6,99.7) | 65.8% (54.3,76.1) |
| | RBD- Protein | Day 28 | 83.2% (74.9,89.6) | 91.4% (84.2,95.9) | 94.7% (88.1,98.3) | 55.7% (44.1,66.9) |
| | N- Protein | Day 28 | 89.9% (82.2,94.4) | 85.6% (77.5,91.2) | 89.5% (81.5,94.8) | 49.4% (37.9,60.9) |
| Isotype Mean (95% CI) | Day 28 | 3.3 (2.2, 4.5) | 3.3 (2.2, 4.4) | 2.2 (1.4, 3.1) | -- | |
| MNT ₅₀ GMT (95% CI) | Day 0 | 6.21 (5.9, 6.5) | 6.01 (5.8,6.2) | 5.95 (5.8,6.1) | 6.13 (5.8,6.4) | |
| | Day 14 | 9.14 (8.1,10.4) | 11.20 (9.6,13.0) | 9.45 (8.2,10.9) | 6.07 (5.9, 6.3) | |
| | Day 28 | 61.70 (49.5,76.9) | 66.4 (53.4,82.4) | 48.00 (37.7,61.1) | 7.20 (6.4,8.1) | |
| MNT ₅₀ SCR (95% CI) | Day 28 | (87.88%) (81.5,94.3) | (91.92%) (86.6,97.3) | (82.8%) (75.1,90.5) | (8.22%) (1.9, 14.5) | |
| Homologous/ Heterologous Strain Challenge- PRNT ₅₀ (95% CI) | NIV-2020-770 | 219.6 (137.5, 350.9) | 376.4 (269.2, 526.20) | 253.7 (147.9, 434.9) | 0.30 (0.04, 2.5) | |
| | nCoV-Q111 | 215.1 (127.3, 363.3) | 157.5 (53.0, 467.9) | 170.84 (98.4, 296.8) | 0.25 (0.04, 1.5) | |
| | nCov-Q100 | 106.0 (75.1, 149.7) | 132.7 (84.2, 209.1) | 119.2 (72.4, 196.3) | 0.2 (0.04, 1.3) | |
| SARS-CoV-2 Cell-mediated Responses Median (95% CI) | % CD3 | 0.5 (0.3,1.2) | 0.7 (0.4, 2.1) | 0.2 (0.1,0.5) | 0.07 (0.04, 0.6) | |
| | %CD 4 | 0.4 (0.2,1.0) | 0.8 (0.3, 1.0) | 0.1 (0.1, 0.3) | 0.08 (0.02, 0.3) | |
| | % CD8 | 0.04 (0.01,0.2) | 0.05 (0.01,1.3) | 0.02 (0.01, 0.05) | 0.01 (0.01, 0.04) | |
| Elispot Median (IQR) | Day 0 | 1.0 (0.0, 5.0) | 1.0 (1.0, 5.0) | 7.0 (3.5, 21.0) | 1.0 (0.0, 12.0) | |
| | Day 28 | 105 (8.5, 166.0) | 55.0 (22.0, 173.8) | 31.5 (16.0, 121.0) | 3.0 (1.0, 23.0) | |

Seroconversion rates (SCR) were defined by the proportion of the titre's achieving ≥4-Fold above baseline.

FIGURE S1: INDIAN CITIES SELECTED FOR THE PHASE 1 STUDY.

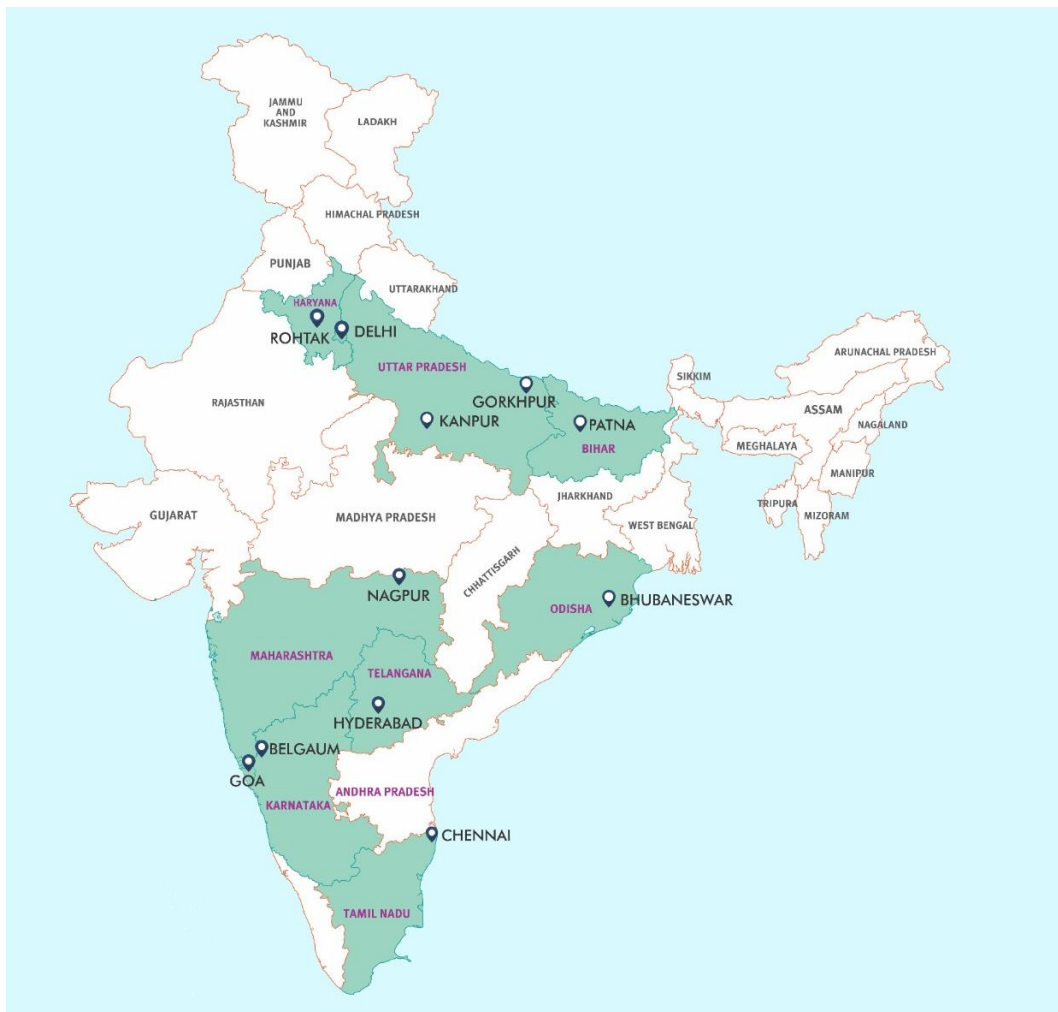
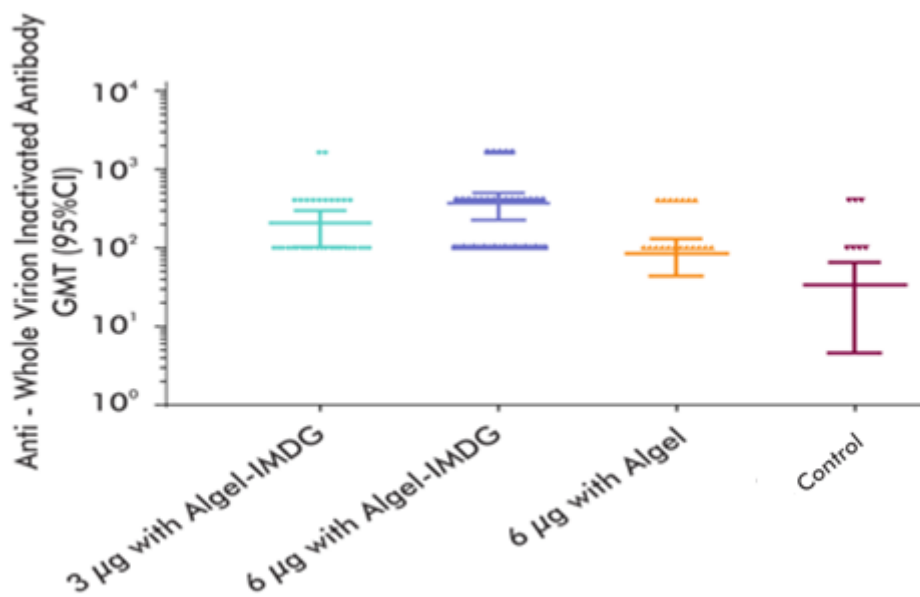
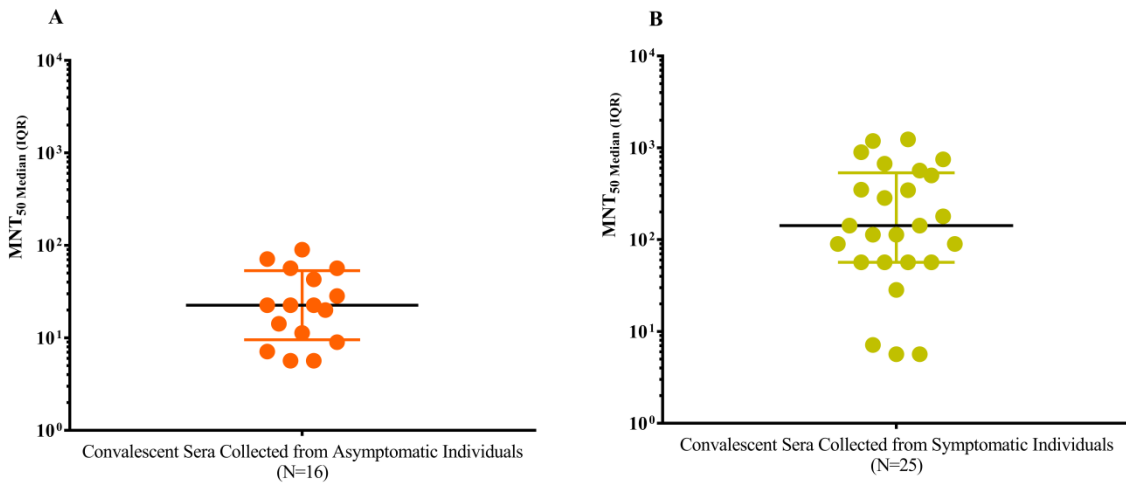


Figure S2: Anti-Whole Virion Inactivated Antibody (ELISA)



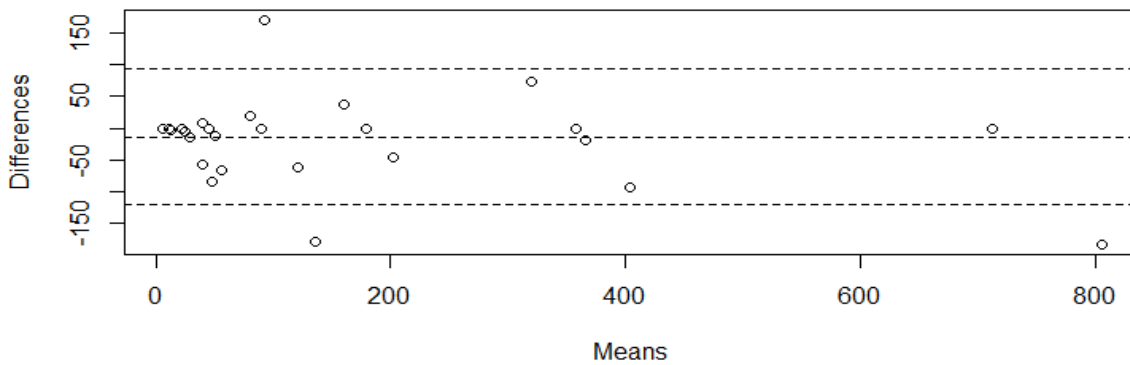
Shown are geometric mean IgG titers towards the whole virion inactivated antigen at 2 weeks after the second vaccination (day 28) for the 3 µg and 6 µg with Algel-IMDG groups, the 6 µg with Algel group, and the Algel-only control arm.

Figure S3: Microneutralisation of the Human Convalescent Serum Samples.



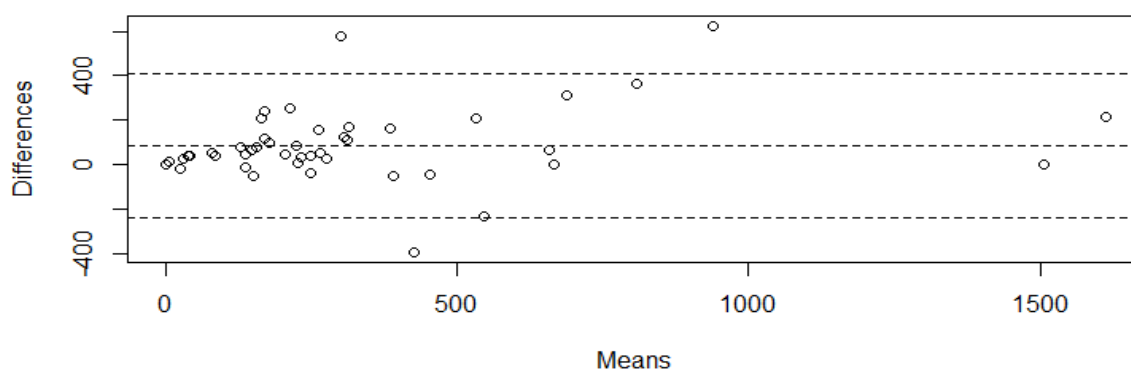
Shown are medians (IQR) of human convalescent serum samples. The human convalescent serum panel included specimens from PCR-confirmed symptomatic/asymptomatic COVID-19 participants obtained at least 30 days after diagnosis (41 samples for MNT₅₀).

Figure S4: Comparison Between MNT₅₀ Assays at the Two Labs (Bharat Biotech and National Institute of Virology)



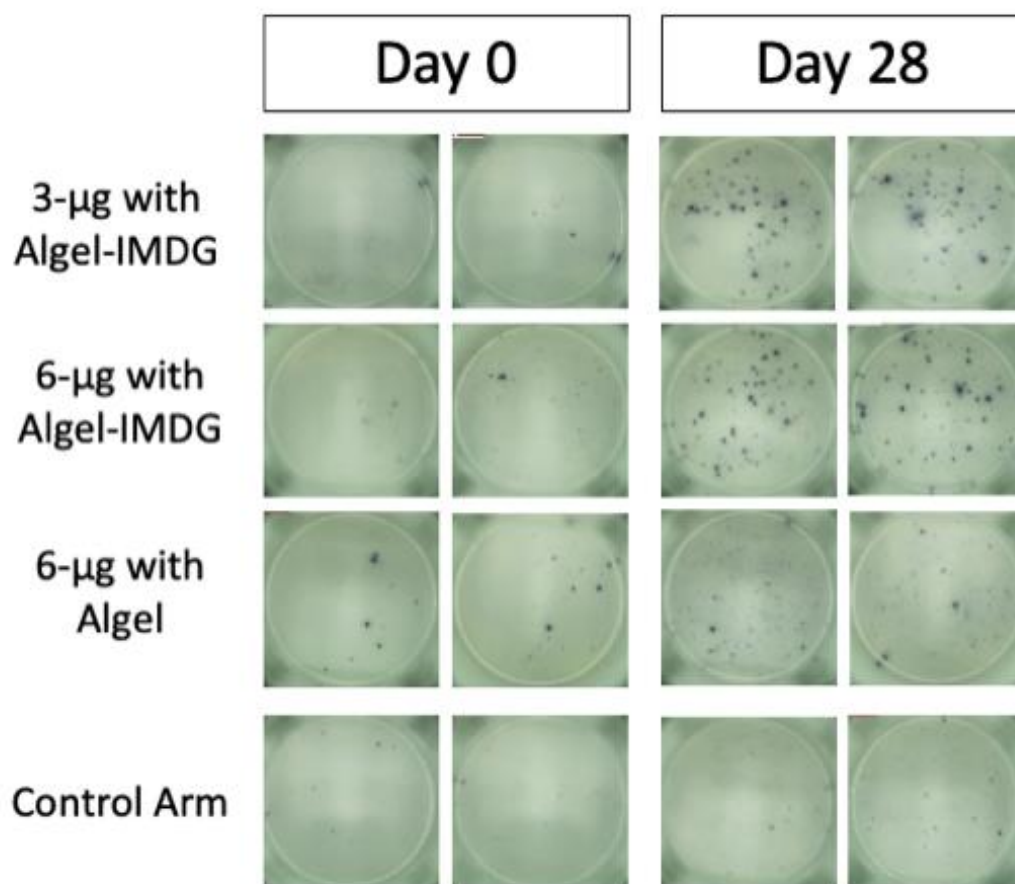
The Bland–Altman plot for comparing two measurements of the same variable (microneutralisation [MNT₅₀]) analyzed at both laboratories. A strong agreement between the laboratories was established.

Figure S5: Comparison Between PRNT₅₀ Assays at The Two Labs (Bharat Biotech and National Institute of Virology)



The Bland–Altman plot for comparing two measurements of the same variable (microneutralisation [PRNT₅₀]) analyzed at both laboratories. A strong agreement between the laboratories was established.

Figure S6: ELISpot Assay of PBMC’s Stimulated with S1 Peptides.



Representative results from the ELISpot assay of PBMCs stimulated with S1 peptide pool on day 0 and day 28. Each row represents the vaccine formulation that they received.

ANNEXURE-2



Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial

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Summary

Background BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine (3 µg or 6 µg) formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel). We previously reported findings from a double-blind, multicentre, randomised, controlled phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) and one Algel-only control (no antigen), with the first dose administered on day 0 and the second dose on day 14. The 3 µg and 6 µg with Algel-IMDG formulations were selected for this phase 2 study. Herein, we report interim findings of the phase 2 trial on the immunogenicity and safety of BBV152, with the first dose administered on day 0 and the second dose on day 28.

Methods We did a double-blind, randomised, multicentre, phase 2 clinical trial to evaluate the immunogenicity and safety of BBV152 in healthy adults and adolescents (aged 12–65 years) at nine hospitals in India. Participants with positive SARS-CoV-2 nucleic acid and serology tests were excluded. Participants were randomly assigned (1:1) to receive either 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. Block randomisation was done by use of an interactive web response system. Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to treatment group allocation. Two intramuscular doses of vaccine were administered on day 0 and day 28. The primary outcome was SARS-CoV-2 wild-type neutralising antibody titres and seroconversion rates (defined as a post-vaccination titre that was at least four-fold higher than the baseline titre) at 4 weeks after the second dose (day 56), measured by use of the plaque-reduction neutralisation test (PRNT₅₀) and the microneutralisation test (MNT₅₀). The primary outcome was assessed in all participants who had received both doses of the vaccine. Cell-mediated responses were a secondary outcome and were assessed by T-helper-1 (Th1)/Th2 profiling at 2 weeks after the second dose (day 42). Safety was assessed in all participants who received at least one dose of the vaccine. In addition, we report immunogenicity results from a follow-up blood draw collected from phase 1 trial participants at 3 months after they received the second dose (day 104). This trial is registered at ClinicalTrials.gov, NCT04471519.

Findings Between Sept 5 and 12, 2020, 921 participants were screened, of whom 380 were enrolled and randomly assigned to the 3 µg with Algel-IMDG group (n=190) or 6 µg with Algel-IMDG group (n=190). Geometric mean titres (GMTs; PRNT₅₀) at day 56 were significantly higher in the 6 µg with Algel-IMDG group (197·0 [95% CI 155·6–249·4]) than the 3 µg with Algel-IMDG group (100·9 [74·1–137·4]; p=0·0041). Seroconversion based on PRNT₅₀ at day 56 was reported in 171 (92·9% [95% CI 88·2–96·2]) of 184 participants in the 3 µg with Algel-IMDG group and 174 (98·3% [95·1–99·6]) of 177 participants in the 6 µg with Algel-IMDG group. GMTs (MNT₅₀) at day 56 were 92·5 (95% CI 77·7–110·2) in the 3 µg with Algel-IMDG group and 160·1 (135·8–188·8) in the 6 µg with Algel-IMDG group. Seroconversion based on MNT₅₀ at day 56 was reported in 162 (88·0% [95% CI 82·4–92·3]) of 184 participants in the 3 µg with Algel-IMDG group and 171 (96·6% [92·8–98·8]) of 177 participants in the 6 µg with Algel-IMDG group. The 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations elicited T-cell responses that were biased to a Th1 phenotype at day 42. No significant difference in the proportion of participants who had a solicited local or systemic adverse reaction in the 3 µg with Algel-IMDG group (38 [20·0%; 95% CI 14·7–26·5] of 190) and the 6 µg with Algel-IMDG group (40 [21·1%; 15·5–27·5] of 190) was observed on days 0–7 and days 28–35; no serious adverse events were reported in the study. From the phase 1 trial, 3-month post-second-dose GMTs (MNT₅₀) were 39·9 (95% CI 32·0–49·9) in the 3 µg with Algel-IMDG group, 69·5 (53·7–89·9) in the 6 µg with Algel-IMDG group, 53·3 (40·1–71·0) in the 6 µg with Algel group, and 20·7 (14·5–29·5) in the Algel alone group.

Interpretation In the phase 1 trial, BBV152 induced high neutralising antibody responses that remained elevated in all participants at 3 months after the second vaccination. In the phase 2 trial, BBV152 showed better reactogenicity and

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For the Hindi translation of the abstract see Online for appendix 1

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safety outcomes, and enhanced humoral and cell-mediated immune responses compared with the phase 1 trial. The 6 µg with Algel-IMDG formulation has been selected for the phase 3 efficacy trial.

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Introduction

The novel human coronavirus SARS-CoV-2 has spread worldwide. To date, 194 vaccine candidates are being developed to prevent COVID-19.¹ Vaccines from multiple manufacturers will be needed to address the global need for SARS-CoV-2 vaccines. Several such vaccines (inactivated, viral vector, or mRNA) have received emergency use authorisation for immunisation of health-care workers and at-risk individuals.^{2–5} There is currently an insufficient supply of vaccines, and the mRNA-based vaccines have cold chain hurdles that countries need to overcome.

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor (TLR) 7/8 agonist molecule adsorbed to alum (Algel-IMDG). BBV152 is stored between 2°C and 8°C, which will ease immunisation cold chain requirements.

Preclinical studies in mice, rats, and rabbits showed appropriate safety profiles and humoral and cell-mediated responses.⁶ Live viral challenge protective efficacy studies in hamsters and non-human primates showed rapid viral clearance in the lower and upper respiratory tracts, and the absence of lung pathology after viral challenge.^{7,8}

We previously reported interim findings from a double-blind, randomised, phase 1 trial on the safety and immunogenicity of three different formulations of BBV152 (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, and 6 µg with Algel) and one Algel only control (without antigen).⁹ This phase 1 trial was done with the intention of selecting two formulations. Based on acceptable safety outcomes, and humoral and cell-mediated responses, the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations were selected for progression to a phase 2 trial. The decision to change the dosing schedule from a

Research in context

Evidence before this study

We searched PubMed on Jan 23, 2021, using the search terms “SARS-CoV-2”, “COVID-19”, “vaccine”, and “clinical trial”. We searched for research articles published from database inception to the date of the search, with no language restrictions. We found 12 clinical trials of COVID-19 mRNA, adenovirus vectored, protein subunit, and inactivated virus vaccines. A preferred characteristic of any COVID-19 vaccine candidate is its ability to induce T-helper-1 (Th1) responses. Whole-virion inactivated vaccines are mostly developed with alum (Algel) as the adjuvant. The response generated by alum is primarily biased to Th2. Clinical trial results from two other inactivated virus vaccines (manufactured by Sinovac and Sinopharm) reported humoral responses but minimal cell-mediated responses. Bharat Biotech developed a Vero cell-based whole-virion inactivated SARS-CoV-2 vaccine (BBV152), formulated with alum and a toll-like receptor 7/8 agonist, producing a Th1-skewed response. BBV152 showed protection in non-human primate and hamster challenge models. Data from a phase 1 study suggested adequate safety and immunogenicity findings. In January 2021, serum samples taken from 38 participants in the 6 µg with Algel-IMDG group at 4 weeks after the second dose (day 56) in the phase 2 trial were found to effectively neutralise a SARS-CoV-2 variant of concern (B.1.1.7 or 20B/501Y.V1).

Added value of this study

We report preliminary analyses for the immunogenicity and safety of BBV152 in 380 vaccinated adults and adolescents.

BBV152 led to enhanced immune responses and induced T-cell responses that were biased to Th1. Due to the difference in dosing regimens between phase 1 (two doses given 2 weeks apart) and phase 2 (two doses given 4 weeks apart) trials, neutralisation responses were significantly higher in the phase 2 trial than in the phase 1 trial. Immunological differences between men and women, and across age groups were not observed. Overall, both 3 µg with Algel-IMDG and 6 µg with Algel-IMDG vaccine groups had similar safety outcomes. Follow-up data from the phase 1 trial shows that BBV152 induces durable humoral and cell-mediated immunity at 3 months after the second dose (day 104).

Implications of all the available evidence

Humoral immune responses from other inactivated SARS-CoV-2 vaccine candidates are consistent with the findings of this study. However, this is the only study of an inactivated COVID-19 vaccine candidate to report a thorough evaluation of cell-mediated responses. The 6 µg with Algel-IMDG formulation has been selected for the phase 3 efficacy trial. BBV152 (developed using a well established manufacturing platform) was safe, immunogenic (persisting for 3 months), and can be stored at 2–8°C, which is compatible with the immunisation cold chain requirements of most countries. Follow-up studies to assess efficacy and immune responses in older adults and in people with comorbidities are underway.

14-day interval between the first and second doses (phase 1 trial), to a 28-day interval between the two doses (phase 2 trial) was based on ensuring commonality with other licensed COVID-19 vaccines. In the phase 1 trial, no difference in the safety and immunogenicity between the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups was observed. In this phase 2 trial, the inclusion of a placebo group was not planned. Our objective was to increase the sample size to establish whether there are differences in immunogenicity between the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups. Therefore, no control or Algel alone group was included in this study.

Herein, we report interim findings from the phase 2 trial on the immunogenicity and safety of 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations of BBV152. Additionally, this paper reports follow-up immunological results from the phase 1 trial at 3 months after participants received the second dose (day 104).

Methods

Study design and participants

This is a randomised, multicentre, phase 2 clinical trial to evaluate the immunogenicity and safety of the whole-virion inactivated SARS-CoV-2 vaccine BBV152 in healthy male and female volunteers at nine hospitals across nine states in India. Participants were aged 12–65 years at the time of enrolment. At the screening visit, participants were tested using both SARS-CoV-2 nucleic acid and serology tests, which were done at a central laboratory (Dr Dangs Laboratory, New Delhi, India) using commercially available assays. If individuals were positive for either test, they were excluded from the trial. The median time between the screening visit and vaccination visit was 3 days (range 2–4). Individuals aged older than 65 years, pregnant or lactating women, and individuals with comorbidities were excluded. All study-related activities and the opportunity to decline or withdraw from the study were explained to participants. All participants were screened for eligibility on the basis of their health status, including their medical history, vital signs, and physical examination results, and were enrolled after providing signed and dated informed consent forms. Details of the inclusion and exclusion criteria can be found in the protocol (appendix 2 pp 50–51).

The trial was approved by the National Regulatory Authority (India) and the respective ethics committees of each participating hospital and was conducted in compliance with all International Council for Harmonization Good Clinical Practice guidelines.

Randomisation and masking

The master randomisation list was uploaded to the interactive web response system, which contained the randomisation number and intended allocation. A central depot manager uploaded the kit numbers to the

respective sites. At the site-level, the system would set the randomisation number and the allotment of the kit without displaying the true group allocation; the system would allocate the same treatment group for the second visit. A block size of four was used to randomly assign (1:1) participants to either the 3 µg with Algel-IMDG group or the 6 µg with Algel-IMDG group. An unmasked contract research organisation (Sclin Soft Technologies, Hyderabad, India) generated the master randomisation code, and dispatched and labelled the vaccine vials.

Participants, investigators, study coordinators, study-related personnel, and the sponsor were masked to the treatment group allocation (excluding the unmasked contract research organisation). Participants were assigned a computer-generated randomisation code that maintained masking. A masked study nurse prepared and administered the vaccines. Each vial contained a unique code that ensured appropriate masking.

Procedures

BBV152 (manufactured by Bharat Biotech) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain was isolated from a patient with COVID-19, sequenced at the Indian Council of Medical Research-National Institute of Virology, and provided to Bharat Biotech.¹⁰ Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform aided the rapid development of BBV152. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by an aspartic acid to glycine shift at amino acid position 614 of the spike protein.¹⁰ Studies suggest that the mutation is associated with higher viral loads in patients and animal models compared with the wild-type strain¹¹ and that NIV-2020-770 is considered to be the dominant strain in the pandemic.¹²

The candidates were formulated with the Algel-IMDG adjuvant, which is an imidazoquinoline class molecule (TLR 7/8 agonist) adsorbed onto Algel. After confirming their eligibility, participants were randomly assigned to the two groups. Both vaccines were stored at 2–8°C in a single-use glass vial. The appearance, colour, and viscosity of the two formulations were identical.

Vaccines were provided as a sterile liquid that was injected through an intramuscular route (deltoid muscle) at a volume of 0.5 mL per dose in a two-dose regimen on day 0 and day 28. Each glass vial contained a single dose of one of the vaccine formulations and required no additional dilution steps, therefore, no on-site dose preparation was required. No prophylactic medication (ibuprofen or acetaminophen) was prescribed either before or after vaccination. The follow-up visits were scheduled on days 42, 56, 118, and 208 after vaccination for blood collection.

Anti-IgG responses against the spike (S1) glycoprotein, receptor-binding domain (RBD), and nucleocapsid protein

See Online for appendix 2

See Online for appendix 3

of SARS-CoV-2 were assessed by ELISA (Syngene, Bangalore, India), and are expressed as geometric mean titres (GMTs). Wild-type virus neutralising antibody titres in serum samples were analysed with a micro-neutralisation test (MNT₅₀) and a plaque-reduction neutralisation test (PRNT₅₀) at Bharat Biotech in a masked manner. MNT₅₀ and PRNT₅₀ were developed in-house. Seroconversion was defined as a post-vaccination titre at least four-fold higher than the pre-vaccination titre. To ensure the validity of our assay, an arbitrary number of serum samples (n=40) were selected at random and tested by PRNT₅₀ at the National Institute of Virology.

Due to the absence of established SARS-CoV-2-specific correlates of protection, to compare vaccine-induced immune responses with those elicited by natural SARS-CoV-2 infections, 50 convalescent serum samples (collected 1–2 months after a nucleic acid test-based diagnosis) were tested by PRNT₅₀ and MNT₅₀. These serum samples were collected from self-reported symptomatic (n=35) and asymptomatic (n=15) adult (age-range not known) patients with COVID-19, and were provided by the National Institute of Virology (Pune, India). For symptomatic patients, ascertainment of severity grading and the requirement for supplemental oxygen was not available.

Cell-mediated responses were assessed in a subset of participants at three sites on day 42 and day 56. The contract research organisation generated a random code containing randomisation numbers, which was provided to the staff to identify this subset of participants. Blood (3–5 mL) was collected from participants who consented to have additional blood volume collected on day 42. Serum was used to evaluate Th1-dependent and Th2-dependent antibody isotypes, and peripheral blood mononuclear cells (PBMCs) were used to assess Th1 and Th2 cytokines. PBMCs were collected from 58 participants (29 from each group). Ten pre-vaccination samples (five from each group) collected on day 0 served as the control. Formal sample size estimations for cell-mediated responses were not done. PBMCs collected on day 42 were used to assess Th1 (interferon- γ [IFN γ], tumour necrosis factor- α [TNF α], and IL-2) and Th2 (IL-5, IL-10, and IL-13) cytokines using a Luminex multiplex assay (Luminex Corporation, Austin, TX, USA) at Indoor Biotechnologies (Bangalore, India).

PBMCs collected on day 56 were used to assess Th1 and Th2 cytokines using a cytokine bead array multiplex assay (CBA Kit, BD Biosciences, New Jersey, USA). These tests were done at Bharat Biotech.

PBMCs from a subset of randomly selected participants who consented to the additional blood volume were collected on day 104 of the phase 1 trial, and used to assess T-cell memory responses (CD4⁺CD45RO⁺ T cells and CD4⁺CD45RO⁺CD27⁺ T cells) at Bharat Biotech. Wild-type virus neutralisation assays (GMTs and seroconversion [MNT₅₀] assays) were done in phase 1 participants at day 104. After antigen stimulation of these PBMCs, culture

supernatants were collected on day 3 to assess cytokines and secreted SARS-CoV-2 IgG antibodies (by ELISA) on day 6. All samples were analysed in a masked manner. The details of all assay methods can be found in appendix 3 (pp 3–4).

Outcomes

The primary outcome was SARS-CoV-2 wild-type neutralising antibody titres and seroconversion rates at 4 weeks after the second dose (day 56).

A key secondary outcome was the number and proportion of participants with solicited local and systemic reactogenicity. Participants were observed for 2 h post-vaccination to assess reactogenicity. They were instructed to record local and systemic reactions within 7 days (days 0–7 and days 28–35) post-vaccination using a paper-based memory aid. The memory aid contained fields for symptom onset, severity, time to resolution, and concomitant medications, and participants were instructed to complete the form daily. The form was collected during the next visit to the site. Routine telephone calls were scheduled following the first 7 days after each vaccination. Solicited local adverse events were pain and swelling at the injection site, and systemic adverse events were fever, fatigue or malaise, myalgia, body aches, headache, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. All unsolicited adverse events were reported by participants throughout the study. The grading scale for most adverse events was based on the US Food and Drug Administration (FDA) document for the toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Adverse events for which grading was not described in the FDA guidance document were graded by use of the Common Terminology Criteria for Adverse Events. Adverse events were graded according to severity score (mild, moderate, or severe) and whether they were related or unrelated to the investigational vaccine, as detailed in the protocol (appendix 2).

Statistical analysis

We calculated that 171 participants per group were required for 90% power to detect a significant difference between GMTs in two equally sized groups, assuming the log₁₀ (titre) is normally distributed with an SD of 0.5, the true GMT ratio is 1.5, and the groups are compared with a two-sample *t* test on log₁₀ (titre) at a two-sided 5% significance level. Assuming a 10% loss of participants due to drop-out during the study, the sample size was calculated as 190 participants in each group. Sample size was calculated by use of PASS 13 software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

The primary outcome was assessed in all participants who received two doses of the vaccine. Safety was assessed in all participants who received at least one dose of the vaccine. Safety endpoints are described as frequencies. GMTs with 95% CIs are presented for immunological endpoints. For continuous variables

(those with <20 observations), medians and IQRs are reported. The exact binomial calculation was used for the CI estimation of proportions. Wilson's test was used to test differences in proportions. CI estimation for the GMT was based on the \log_{10} (titre) and the assumption that the \log_{10} (titre) was normally distributed. GMTs were compared with *t* tests using the means of the \log_{10} (titre). Significance was set at $p < 0.05$ (two-sided).

This preliminary report presents results regarding immunogenicity (days 0–56) and safety outcomes (days 0–42). Descriptive and inferential statistics were assessed using SAS, version 9.2.

The trial is registered at ClinicalTrials.gov, NCT04471519.

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, or writing of this report or the statistical report, but was involved in study design. Data cleaning and analysis was done by the third party contract research organisation (Sclin Soft Technologies). Masked laboratory assessments were done at the respective laboratories, and masked datasheets were sent to the contract research organisation for decoding and analysis. The unmasked randomisation list was not shared with the study sponsor.

Results

Between Sept 5 and 12, 2020, 921 potential participants were screened, 380 of whom were enrolled and randomly assigned to either the 3 μg with Algel-IMDG group ($n=190$) or the 6 μg with Algel-IMDG group ($n=190$; figure 1). Among the 541 individuals who were initially screened but excluded, 48 had positive nucleic acid tests and 123 had positive serology tests for SARS-CoV-2. Due to competitive recruitment, 190 individuals who were screened and found to be eligible were not enrolled. Other notable exclusions were due to inconclusive RT-PCR results ($n=168$). The retention rates at day 56 were 97% (184 of 190 participants) in the 3 μg with Algel-IMDG group and 93% (177 of 190 participants) in the 6 μg with Algel-IMDG group. The demographic characteristics of participants are shown in table 1.

GMTs (PRNT_{50}) at day 0 were 0.1 (95% CI 0.1–0.1) in both groups, increasing to 100.9 (74.1–137.4) in the 3 μg with Algel-IMDG group and 197.0 (155.6–249.4) in the 6 μg with Algel-IMDG group at day 56 (figure 2A). The GMT (PRNT_{50}) at day 56 was significantly higher in the 6 μg with Algel-IMDG group than in the 3 μg with Algel-IMDG group ($p=0.0041$), and was not significantly different to the GMT (PRNT_{50}) observed in convalescent serum collected from patients who had recovered from COVID-19 ($p=0.54$). Seroconversion based on PRNT_{50} at day 56 was reported in 171 (92.9% [95% CI 88.2–96.2]) of 184 participants in the 3 μg with Algel-IMDG group and 174 (98.3% [95.1–99.6]) of 177 participants in the 6 μg with Algel-IMDG group (figure 2B).

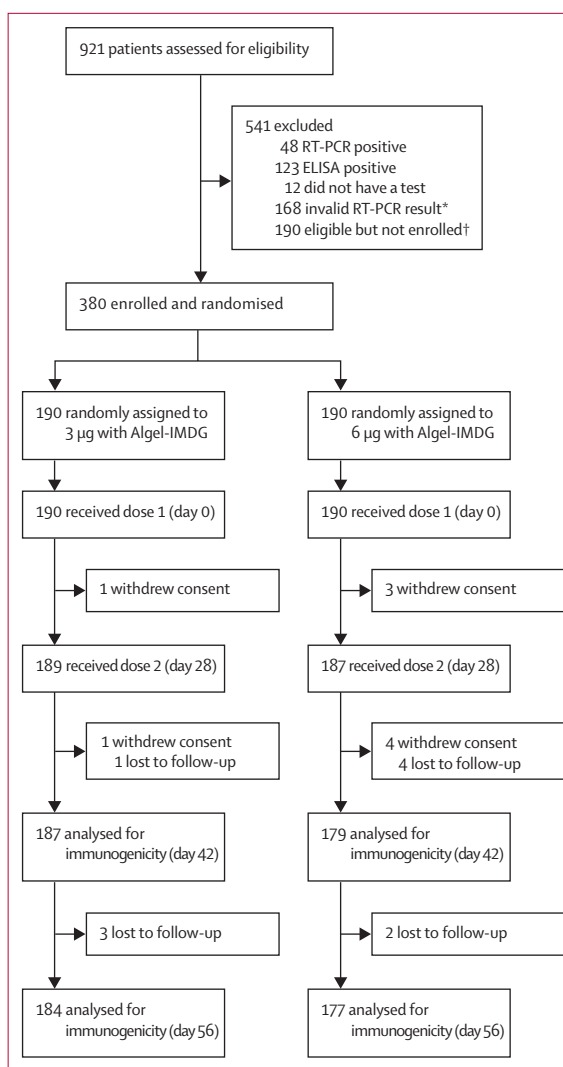


Figure 1: Trial profile

*Caused by cold chain excursions during transport of the nasopharyngeal swabs from the field site to the central laboratory. †Due to competitive recruitment, all sites were screening participants individually; therefore, there was an excess of eligible participants who were not enrolled because the recruitment target was met.

GMTs (MNT_{50}) at day 56 were 92.5 (95% CI 77.7–110.2) in the 3 μg with Algel-IMDG group and 160.1 (135.8–188.8) in the 6 μg with Algel-IMDG group (figure 2C). Seroconversion based on MNT_{50} at day 56 was reported in 162 (88.0% [95% CI 82.4–92.3]) of 184 participants in the 3 μg with Algel-IMDG group and 171 (96.6% [92.8–98.8]) of 177 participants in the 6 μg with Algel-IMDG group (figure 2D; appendix 3, p 6). The PRNT_{50} and MNT_{50} GMTs at day 56 were significantly higher in the 6 μg with Algel-IMDG group than the 3 μg with Algel-IMDG group. No differences in the GMTs (PRNT_{50}) were observed in a subset of paired serum samples from both groups (20 samples from each group) analysed at the National Institute of Virology and Bharat

Biotech on day 42 (2 weeks after the second vaccination; appendix 3, p 13). Seroconversion rates and GMTs across three age groups (≥ 12 to < 18 year, ≥ 18 to < 55 year, and ≥ 55 to ≤ 65 year groups) and between both sexes were

| | 3 μg with Algel-IMDG (n=190) | 6 μg with Algel-IMDG (n=190) |
|-------------------------------------|---|---|
| Age, years | | |
| Median | 34.0 (26.0–41.8) | 35.0 (27.0–44.0) |
| ≥ 12 to < 18 | 10 (5%) | 4 (2%) |
| ≥ 18 to < 55 | 173 (91%) | 176 (93%) |
| ≥ 55 to ≤ 65 | 7 (4%) | 10 (5%) |
| Sex | | |
| Female | 50 (26%) | 45 (24%) |
| Male | 140 (74%) | 145 (76%) |
| Body-mass index*, kg/m ² | 25.1 (3.4) | 24.9 (2.8) |

Data are median (IQR), n (%), or mean (SD). The intention-to-treat population included all participants who received at least one dose. *Calculated by the participant's weight (kg) divided by the square of their height (m), measured at the time of screening.

Table 1: Demographics of participants in the intention-to-treat population

similar, but only small numbers of participants were included in the youngest and oldest age groups (appendix 3, p 7).

IgG antibody titres (GMTs) to all epitopes (spike glycoprotein, receptor-binding domain, and nucleocapsid protein) were detected after the administration of both doses (table 2). Anti-spike glycoprotein IgG GMTs at day 56 were 10 413.9 (95% CI 9142.4–11862.2) in the 3 μg with Algel-IMDG group and 9541.6 (8245.9–11041.0) in the 6 μg with Algel-IMDG group. Both the 3 μg and 6 μg with Algel-IMDG groups showed similar anti-spike glycoprotein, anti-receptor-binding domain, and anti-nucleocapsid protein GMTs. At day 42, the anti-spike isotype mean ratios (IgG1/IgG4) were 2.4 (95% CI 1.9–2.9) in the 3 μg with Algel-IMDG group and 2.2 (1.7–2.6) in the 6 μg with Algel-IMDG group.

The Th1/Th2 cytokine ratio indicated bias to a Th1 cell response at day 42 (figure 3A). Th2 responses were detected at minimal levels in both vaccine groups, as shown by IL-5, IL-10, and IL-13 levels (figure 3B). We observed a significant increase in the levels of Th1 cytokines, IFN γ , IL-2, and TNF α , on day 56 compared with

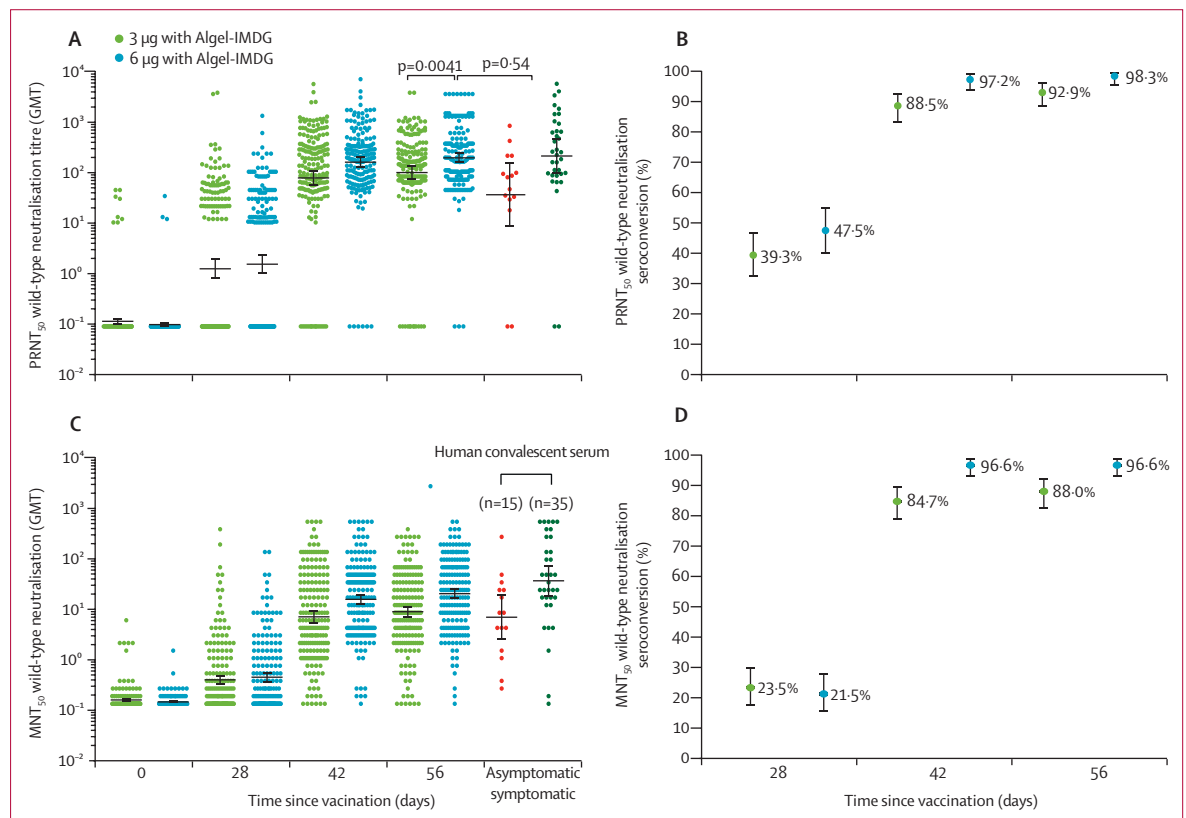


Figure 2: SARS-CoV-2 wild-type PRNT₅₀ GMTs (A), and seroconversion rates (B), and wild-type MNT₅₀ GMTs (C) and seroconversion rates (D) SARS-CoV-2 wild-type PRNT₅₀ and MNT₅₀ GMTs at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) in the 3 μg with Algel-IMDG (n=190) and 6 μg (n=190) with Algel-IMDG groups are shown. Seroconversion rates were defined by the proportion of post-vaccination titres that were at least four-fold higher than baseline. In A and C, the human convalescent sera panel included specimens from participants with PCR-confirmed symptomatic and asymptomatic COVID-19 obtained at least 30–60 days after diagnosis (50 samples); dots represent individual datapoints, the horizontal bars show the GMTs, and the error bars represent the 95% CIs. In B and D, the dots represent the seroconversion rates and error bars represent 95% CIs. PRNT₅₀=plaque-reduction neutralisation test. GMT=geometric mean titre. MNT₅₀=microneutralisation assay.

| | Geometric mean titre (95% CI) | | Seroconversion rate* (95% CI) | |
|---|-------------------------------|--------------------------|-------------------------------|----------------------|
| | 3 µg with Algel-IMDG | 6 µg with Algel-IMDG | 3 µg with Algel-IMDG | 6 µg with Algel-IMDG |
| Anti-spike glycoprotein IgG | | | | |
| Day 0 | 500.0 (500.0–500.0) | 500.0 (500.0–500.0) | .. | .. |
| Day 28 | 2574.2 (2228.9–2973.1) | 2240.5 (1942.4–2584.5) | 71.2% (64.1–77.6) | 65.0% (57.5–72.0) |
| Day 42 | 11528.8 (10002.7–13287.8) | 10040.0 (8667.0–11630.5) | 98.4% (95.3–99.7) | 98.3% (95.1–99.7) |
| Day 56 | 10413.9 (9142.4–11862.2) | 9541.6 (8245.9–11041.0) | 98.4% (95.3–99.7) | 96.6% (92.8–98.8) |
| Anti-receptor binding domain IgG | | | | |
| Day 0 | 500.0 (500.0–500.0) | 500.0 (500.0–500.0) | .. | .. |
| Day 28 | 1962.7 (1726.2–2231.6) | 2031.6 (1777.3–2322.3) | 58.7% (51.2–65.9) | 58.2% (50.6–65.6) |
| Day 42 | 5572.3 (4897.5, 6339.9) | 4980.8 (4366.7, 5681.3) | 94.0% (89.6, 97.0) | 93.2% (88.5, 96.5) |
| Day 56 | 5874.0 (5194.8, 6642.0) | 5558.0 (4859.9, 6356.5) | 96.2% (92.3, 98.5) | 94.4% (89.9, 97.3) |
| Anti-nucleocapsid protein IgG | | | | |
| Day 0 | 500.0 (500.0–500.0) | 500.0 (500.0–500.0) | .. | .. |
| Day 28 | 2734.1 (2375.1–3147.5) | 2490.4 (2161.7–2869.2) | 72.3% (65.2–78.6) | 71.2% (63.9–77.7) |
| Day 42 | 8957.2 (7778.6–10314.3) | 9211.2 (7939.3–10686.8) | 97.3% (93.8–99.1) | 95.5% (91.3–98.0) |
| Day 56 | 8626.0 (7528.6–9883.4) | 8754.0 (7589.4–10097.4) | 97.3% (95.3–100.0) | 96.6% (92.8–98.8) |

ELISA results at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) for the 3 µg with Algel-IMDG and the 6 µg with Algel-IMDG groups are shown. The number of participants in the 3 µg with Algel-IMDG group included in the immunogenicity analysis was 190 on day 0, 189 on day 28, 187 on day 42, and 184 on day 56. The number of participants in the 6 µg with Algel-IMDG group included in the immunogenicity analysis was 190 on day 0, 187 on day 28, 179 on day 42, and 177 on day 56. The cutoff for detectable antibodies was 1/500. Endpoint titre dilution for days 28, 42, and 56 sera samples were established with baseline (day 0) and interpolated from the raw optical density data of the corresponding day 0 sample. The cutoff (mean ±3 SD) for day 0 was calculated considering the absorbance of all sera dilutions (1/500 to 1/32 000) tested, except the lowest dilution (1/500). *Defined as a post-vaccination IgG titre that was at least four-fold higher than the baseline titre.

Table 2: SARS-CoV-2 IgG titres against the spike glycoprotein, receptor-binding domain, and nucleocapsid protein

day 0 ($p < 0.0001$), as measured with the Luminex multiplex assay (appendix 3, p 12).

Solicited local adverse reactions after dose 1 (days 0–7) were reported in nine (4.7% [95% CI 2.2–8.8]) of 190 participants in the 3 µg with Algel-IMDG group and eight (4.2% [1.8–8.1]) of 190 participants in the 6 µg with Algel-IMDG group (table 3). Solicited systemic adverse reactions after dose 1 were reported in nine (4.7% [2.2–8.8]) participants in the 3 µg with Algel-IMDG group and 14 (7.4% [4.1–12.1]) participants in the 6 µg with Algel-IMDG group. Solicited local adverse reactions after dose 2 (days 28–35) were reported in eight (4.2% [1.8–8.1]) participants in the 3 µg with Algel-IMDG group and seven (3.7% [1.6–7.7]) participants in the 6 µg with Algel-IMDG group. Solicited systemic adverse reactions after dose 2 were reported in 12 (6.3% [3.3–10.8]) participants in the 3 µg with Algel-IMDG group and 11 (5.8% [3.0–10.1]) participants in the 6 µg with Algel-IMDG group (table 3; unsolicited adverse events are included in appendix 3, p 9).

No association between the dose of vaccine and the number of adverse events was observed. After both doses, the most common solicited adverse events were injection site pain, reported in five (2.6% [95% CI 0.9–6.0]) of 190 participants in the 3 µg with Algel-IMDG group and six (3.2% [1.2–6.8]) of 190 participants in the 6 µg with Algel-IMDG group. Most adverse events were mild (69 [89%] of 78 participants) and resolved within 24 h of onset. At 7 days after the second dose, solicited local and systemic adverse reactions were

reported in 38 (20.0% [14.7–26.5]) of 190 participants in the 3 µg with Algel-IMDG group and 40 (21.1% [15.6–27.7]) of 190 participants in the 6 µg with Algel-IMDG group.

In the phase 1 trial, 97 (97%) of 100 participants in the 3 µg with Algel-IMDG group, 95 (95%) of 100 participants in the 6 µg with Algel-IMDG group, 92 (92%) of 100 participants in the 6 µg with Algel group, and 69 (92%) of 75 participants in the Algel-only control group were followed up to day 104 (3 months after the second dose). GMTs (MNT_{50}) at day 104 were 39.9 (95% CI 32.0–49.9) in the 3 µg with Algel-IMDG group, 69.5 (53.7–89.9) in the 6 µg with Algel-IMDG group, 53.3 (40.1–71.0) in the 6 µg with Algel group, and 20.7 (14.5–29.5) in the Algel-only control group (figure 4A). Seroconversion based on MNT_{50} was reported in 72 (73.5% [95% CI 63.6–81.9]) participants in the 3 µg with Algel-IMDG group, 76 (81.1% [71.4–88.1]) participants in the 6 µg with Algel-IMDG group, and 68 (73.1% [62.9–81.8]) participants in the 6 µg with Algel group (figure 4B). GMTs in the 6 µg with Algel-IMDG group were significantly higher than the 3 µg with Algel-IMDG group (appendix 3, p 7). There were no significant differences in GMTs between day 42 (2 weeks after the second dose) and 104 (3 months after the second dose) across the vaccine groups (appendix 3, p 7). Post-hoc analyses of MNT_{50} wild-type neutralising antibody responses in phase 1 and phase 2 participants in the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups, showed that GMTs were significantly higher in phase 2 participants (at day 56)

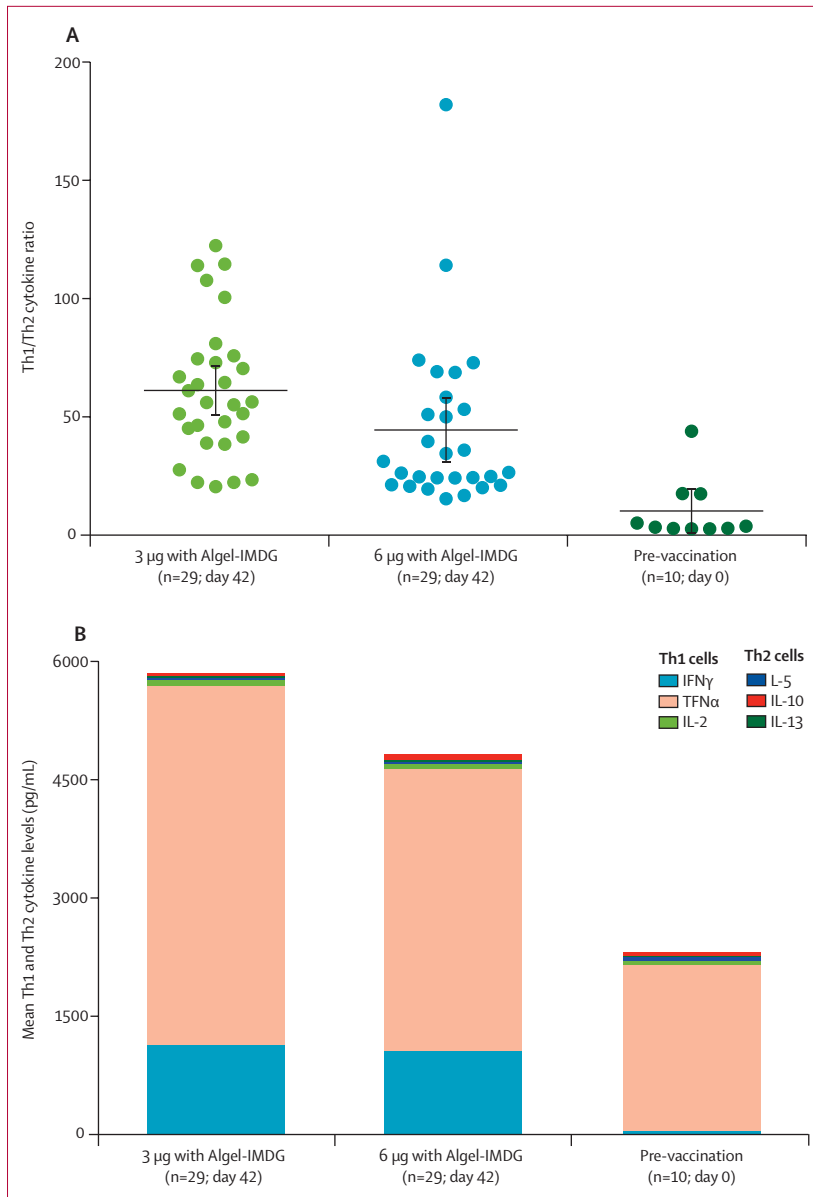


Figure 3: Th1/Th2 cytokine ratios (A) and mean Th1 and Th2 cytokine levels (B) at day 42 in phase 2 participants. In A and B, cell-mediated responses in blood samples from 58 participants (29 each from the 3 µg with Algel-IMDG and 6 µg with Algel-IMDG groups), with proliferative responses to vaccination at 2 weeks after the second dose (day 42), and in ten control participants (five pre-vaccination samples from each group) are shown. In A, the Th1/Th2 ratio was calculated by the sum of IFN γ plus IL-2 cytokine levels divided by the sum of IL-5 plus IL-13 cytokine levels; horizontal bars show the mean ratios and error bars show the 95% CIs. In B, mean cytokine levels in the cell culture supernatants obtained from PBMCs stimulated with SARS-CoV-2 peptides are shown; Th1 (IFN γ , IL-2, and TNF α) and Th2 (IL-5, IL-13, and IL-10) cytokines are represented by stacked bars. Th=T-helper. IFN γ =interferon- γ . TNF α =tumour necrosis factor- α . IL=interleukin.

than in phase 1 participants (at day 42) at 4 weeks after receiving the second dose (figure 4C). At 4 weeks after the second dose of 6 µg with Algel-IMDG, the phase 1–2 GMT (MNT₅₀) ratio was 1.9 (95% CI 1.5–2.6).

PBMCs from a subset of phase 1 participants at one site were collected to evaluate T-cell memory responses at day 104. Formulations with Algel-IMDG generated a

T-cell memory response, as shown by an increase in the frequency of effector memory CD4⁺CD45RO⁺ T cells and CD4⁺CD45RO⁺CD27⁺ T cells compared with pre-vaccination (day 0) samples (figure 4D, E). Samples from Algel-alone recipients also showed a T-cell memory response. We also detected secreted IgG antibodies in the cell culture supernatant by ELISA, and the antibody titres ranged from neat (undiluted) to 1/64 (appendix 3 p 8). Further effector function of activated and differentiated T cells was shown by the levels of Th1 cytokines (appendix 3 p 8).

In phase 2 participants, nine (33%) of 27 unsolicited adverse events were reported to be related to the vaccine, as judged by a masked investigator. No significant difference in the number of unsolicited adverse events was observed between the groups (appendix 3 p 9). Severity grading scales for adverse events and the evaluation of adverse events related to the vaccine are described in appendix 3 (pp 10–11). No symptomatic SARS-CoV-2 infections were reported to the site investigators (via follow-up telephone calls or site visits) between days 0 and 118 (a scheduled visit) in phase 2 participants. However, illness visits were not scheduled and no routine SARS-CoV-2 nucleic acid testing was done. No serious adverse events were reported up to day 118 in phase 2 participants.

No new solicited or unsolicited adverse events that occurred between days 42 and 104 in phase 1 participants were considered to be related to the vaccine by the investigators. Additionally, no new serious adverse events were reported. One case of symptomatic COVID-19 was reported in the Algel-only control group. This participant received the first dose on July 17, 2020, but was considered to be lost to follow-up before the second dose was administered. The participant visited the site on Nov 27, 2020, with complaints of chronic anosmia and a history of a positive SARS-CoV-2 rapid antigen test on Aug 16, 2020.

Discussion

In this report, we present interim findings from the phase 2 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The overall participant retention rates were 97% in the 3 µg with Algel-IMDG group and 93% in the 6 µg with Algel-IMDG group. Neutralising antibody titres were similar to a panel of convalescent serum samples. All elicited cytokine responses to BBV152 were biased to Th1 cells. The vaccine was well tolerated in both groups with no serious adverse events. Long-term follow-up of phase 1 trial participants showed that neutralising antibody titres persisted, and T-cell memory responses were more pronounced in the 6 µg with Algel-IMDG group compared with pre-vaccination samples.

The most common adverse event in the phase 2 trial was pain at the injection site, followed by headache, fatigue, and fever. No severe or life-threatening (ie, grade 4 and 5) solicited adverse events were reported. No

significant differences in safety were observed between the two groups. However, the study was not powered to compare such differences. After either dose, the combined incidence of local and systemic adverse events in this study is lower than that of other SARS-CoV-2 vaccine platform candidates,^{13–16} and similar to that of other inactivated SARS-CoV-2 vaccine candidates.^{17,18} However, other vaccine studies have enrolled different populations and have employed varying approaches to measure adverse events.

BBV152 induced antibody binding (to spike glycoprotein and nucleocapsid protein epitopes) and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.^{17,18} Studies have reported the variable persistence of humoral and cell-mediated responses acquired from natural infection.^{19,20} In the phase 1 trial of BBV152, we evaluated an accelerated schedule, in which the two doses were administered 2 weeks apart. At day 104 (3 months after the second dose), we observed detectable humoral and cell-mediated responses to SARS-CoV-2. Serum neutralising antibodies were detected in all phase 1 participants at day 104, and the levels of these antibodies were similar to the panel of convalescent serum samples. These findings are in accordance with those of the mRNA-1273 (Moderna) vaccine, which has received emergency use authorisation.^{2,21} A sizeable T-cell memory population was also observed at this timepoint. A routine schedule, in which the two doses are administered 4 weeks apart, was evaluated in the phase 2 trial of 3 µg with Algel-IMDG and 6 µg with Algel-IMDG. We found that immune responses (MNT₅₀) were significantly higher with the routine schedule (phase 2) than with the accelerated schedule (phase 1), which is consistent with other reports.^{5,22}

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG. An imidazoquinoline molecule (IMDG), which is a TLR7/8 agonist, has been used to augment cell-mediated responses.^{23,24} Both 3 µg with Algel-IMDG and 6 µg with Algel-IMDG formulations induced responses that were biased to a Th1 phenotype, with IgG1/IgG4 ratios greater than 1. The ratio of Th1/Th2 cytokines was clearly biased to a Th1 response, with increased IFN γ generation.

In the present study, BBV152 induced T-cell memory responses, which was shown by an increased frequency of antigen-specific CD4⁺ T cells expressing the memory phenotype marker CD45RO⁺. The increase in the CD4⁺CD45RO⁺CD27⁺ T-cell population also indicates the activation of the co-stimulatory marker CD27, and confirms the antigen recall memory T-cell response.²⁵ Further, the effector function of these cells was supported by the Th1 cytokine secretion observed in ex vivo responses after stimulation of PBMCs for 3 days.²⁶ These results further corroborate our phase 1 results showing an increased frequency of CD4⁺ T cells producing IFN γ in participants who received Algel-IMDG-containing

| | Dose 1 | | Dose 2 | |
|---------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | 3 µg with Algel-IMDG (n=190) | 6 µg with Algel-IMDG (n=190) | 3 µg with Algel-IMDG (n=190) | 6 µg with Algel-IMDG (n=190) |
| Local reactions | | | | |
| Pain at injection site | | | | |
| Mild | 5 (3%) | 6 (3%) | 7 (4%) | 4 (2%) |
| Moderate | 1 (1%) | 0 | 0 | 1 (1%) |
| Redness at injection site | | | | |
| Mild | 1 (1%) | 1 (1%) | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Itching | | | | |
| Mild | 1 (1%) | 1 (1%) | 0 | 2 (1%) |
| Moderate | 0 | 0 | 0 | 0 |
| Stiffness in upper arm | | | | |
| Mild | 1 (1%) | 0 | 0 | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Weakness in injection arm | | | | |
| Mild | 0 | 0 | 1 (1%) | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Systemic reactions | | | | |
| Body ache | | | | |
| Mild | 0 | 2 (1%) | 1 (1%) | 2 (1%) |
| Moderate | 0 | 1 (1%) | 0 | 0 |
| Fever | | | | |
| Mild | 2 (1%) | 5 (3%) | 5 (3%) | 4 (2%) |
| Moderate | 1 (1%) | 3 (2%) | 0 | 0 |
| Headache | | | | |
| Mild | 2 (1%) | 1 (1%) | 1 (1%) | 2 (1%) |
| Moderate | 0 | 0 | 0 | 1 (1%) |
| Malaise | | | | |
| Mild | 4 (2%) | 1 (1%) | 3 (2%) | 0 |
| Moderate | 0 | 0 | 0 | 0 |
| Weakness | | | | |
| Mild | 0 | 0 | 1 (1%) | 2 (1%) |
| Moderate | 0 | 1 (1%) | 0 | 0 |
| Rashes | | | | |
| Mild | 0 | 0 | 1 (1%) | 0 |
| Moderate | 0 | 0 | .. | 0 |

Data are n (%). The safety analysis set includes all participants who received one dose of the vaccine (n=380). The number of participants who had a solicited adverse event after receiving dose 1 (days 0–7) and dose 2 (days 28–35) is shown.

Table 3: Mild and moderate solicited adverse events in the safety analysis set

formulations. Samples from participants in the Algel-only control group also showed a T-cell memory response, which corroborates a recent study published in 2020 indicating the presence of cross-reactive T-cells in individuals unexposed to SARS-CoV-2.²⁷ Additionally, two participants in the Algel-only group showed high neutralising antibody titres and IL-6 levels at day 104 of the phase 1 study. In the phase 1 trial, the ability to secrete anti-spike glycoprotein IgG antibodies at day 104 further shows the long-lasting T-cell memory response generated by BBV152. Similar findings supporting long-term immunity were reported by Sekine and colleagues²⁸ in

convalescent patients who had previously had COVID-19. Memory B-cell responses from BBV152 are currently being evaluated. Thus far, cell-mediated responses after receipt of other SARS-CoV-2 inactivated vaccine candidates have been minimally reported.

This study was done at a time when the number of daily diagnosed COVID-19 cases was increasing rapidly. In the Algel-only control group (phase 1 trial), seroconversion was reported in six (8.2% [95% CI 1.9–14.5]) of 73 participants at day 28, 13 (18.8% [10.8–30.4]) of 69 participants at day 42, and 23 (33.3% [22.7–45.8]) of 69 participants at day 104. These results suggest that both phase 1 and 2 trials are being done during a period of high ongoing SARS-CoV-2 circulation. Since substantial SARS-CoV-2 PCR positivity was observed in the general population during the study period, in the event of natural exposure to SARS-CoV-2, it is possible that post-vaccination antibody titres in vaccinated participants could be slightly inflated. No cases of COVID-19 were reported in either group of the phase 2 trial, whereas one case of symptomatic COVID-19 was reported in the Algel-only control group of the phase 1 trial. However, illness visits were not scheduled, and routine SARS-CoV-2 nucleic acid testing was not done.

The results reported in this study do not permit efficacy assessments. The evaluation of safety outcomes requires extensive phase 3 clinical trials. We were unable to assess other immune responses (ie, binding antibody and cell-mediated responses) in convalescent serum samples due to the low quantity. Furthermore, no additional data on the age of the participant or the severity of disease from symptomatic individuals were obtained. Comparisons between phase 1 and 2 trials were not done in a randomised set of participants, and no adjustments on baseline parameters were made. Conclusions are to be considered as post-hoc analyses. Even though direct comparisons between the phase 1 and 2 trials cannot be made, the reactogenicity assessments reported in this study were substantially better in the phase 2 trial than the phase 1 trial and other trials with a placebo group.⁹ Additionally, the proportion of participants reporting adverse events in the phase 2 trial were lower than in the phase 1 trial. The study coordinators had verified all source documents to ensure that no data were missing or that errors had occurred. Further corroboration with phase 3 safety results is required. This study enrolled a small number of participants aged 12–18 years and 55–65 years. Follow-on studies are required to establish immunogenicity in children and in those aged 65 years and older. Withdrawals in the 6 µg with Algel-IMDG group were higher than the 3 µg with Algel-IMDG group but were not associated with adverse events. Lastly, this study population lacked ethnic, racial, and gender diversity, further underscoring the importance of evaluating BBV152 in other populations. Longitudinal follow-up of additional post-vaccination visits (at months 3, 6, and 12) is important for understanding the durability of immune responses, and is ongoing.

This study has several strengths. To ensure generalisability of the results, this study included participants from diverse geographic locations, enrolling 380 participants across nine hospitals across nine states in India. Based on follow-up data from the phase 1 trial, despite a marginal expected decline in neutralising antibody titres at day 104, BBV152 has shown the potential to provide durable humoral and cell-mediated immune responses. With several reports questioning the efficacy of SARS-CoV-2 vaccines against antigenically divergent strains, we previously reported neutralising antibody responses in homologous and heterologous strain assessments.⁹ Day 56 serum samples from 38 participants in the 6 µg with Algel-IMDG group of the phase 2 trial effectively neutralised a SARS-CoV-2 variant of concern (lineage B.1.1.7 or 20B/501Y. V1).²⁹ On the basis of superior cell-mediated responses in the phase 1 trial, the 6 µg with Algel-IMDG formulation was selected for the phase 3 efficacy trial, which involves 25 800 volunteers and is currently underway (NCT04641481). BBV152 (COVAXIN) has received emergency use authorisation in India.

Contributors

All authors met the criteria for authorship set forth by the International Committee for Medical Editors. HJ, DD, DR, UP, BG, PY, and GS did the immunogenicity experiments. The contract research organisation (SciSoft Technologies) was responsible for analysing the data and generating the report. KMV, SRe, VS, SP, and RE contributed to the manuscript preparation. SRe was the study coordinator and helped immensely with designing the protocol and generating the interim report. PA, SP, NG, and BB from the Indian Council of Medical Research contributed to the writing of this paper. KE was responsible for overall supervision of the project and review of the final paper. All principal investigators (PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG) were involved in the scientific review of this paper. All authors and the contract research organisation had full access to masked data in the study and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

RE, HJ, BG, KMV, SRe, DD, DR, UP, SP, and VS are employees of Bharat Biotech, with no stock options or incentives. KE is the Chairman and Managing Director of Bharat Biotech. PY, GS, PA, NG, SP, and BB are employees of the Indian Council of Medical Research. PR, SV, SKR, CS, SVR, CSG, JSK, SM, VR, and RG were principal investigators representing the study sites.

Data sharing

The study protocol is provided in appendix 2. De-identified, individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after the approval of a proposal, data can be shared through a secure online platform.

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**Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine,
BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of
immune responses from a phase 1 follow-up report**

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**This supplementary material has been provided by the authors to give readers additional information
about their work.**

Supplemental methods

- i. RT-PCR (conducted at Dr. Dangs Lab, New Delhi) at Screening

TRUPCR SARS-CoV-2 RT qPCR (V 3.2) is a single tube, in vitro nucleic acid amplification test for the qualitative detection of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2)specific RNA from respiratory specimens(nasopharyngeal or oropharyngeal aspirates,washes or swabs, bronchoalveolar lavage, sputum and tracheal aspirates)using Real-time PCR. The human RNasePgene serves as an endogenous internal positive control for human nucleic acid is also included in this kit.

E gene: For the detection of SarbecovirusRdRp gene and N genedual targets for the detection of SARS-CoV-2

RNase P gene:endogenous internal control, which qualifies the sample for testing and is essential for testing Viral RNA in host organism. According to the Centre for Daises Control and prevention, Respiratory Viruses Branch, Division of Viral Diseases, all clinical samples should be tested for human RNase P gene to assess specimen quality for RT PCR for detection of 2019-Novel Coronavirus

The assay runs for 38 cycles;however for any interpretation,threshold cut off cycle Ct is 35.

Interpretation is as follows:

Amplification Signals In

- a) RNase P +/- , E Gene +, RdRp&N gene + : SARS-CoV-2 POSITIVE
- b) RNase P +/- , E Gene -, RdRp&N gene + : SARS-CoV-2 POSITIVE
- c) RNase P +/- , E Gene +, RdRp&N gene - : SARBECOVIRUS POSITIVE
- d) RNase P + , E Gene -, RdRp&N gene - : NEGATIVE
- e) RNase P - , E Gene -, RdRp&N gene - : INVALID

100 percent concordance of results for submitted samples with ICMR designated QC Lab(AIIMS for Dr. Dangs Lab) **ii.** CLIA (conducted at Dr. Dangs Lab, New Delhi) at Screening

The liaison SARS-CoV-2 IgG assay performed on the Liaison XL analyzer is an indirect chemiluminescence Immunoassay (CLIA) for the Quantitative determination of anti-S1 and anti- S2 antibodies to SARS-CoV-2 in human serum or plasma.The sensitivity of the above assay is 97.4 percent for 15 days post-diagnosis and specificity 98.9 percent for Laboratory routine testing. Testing of assay-specific calibrators allows the detected Relative light unit (RLU)to adjust the assigned master curve.The analyzer automatically calculates SARS-CoV-S1/S2 IgG antibody concentrations as arbitrary units (AU/mL)and grades the results.

Results are interpreted as follows:

Less than 12 AU/mL: NEGATIVE (A negative result may indicate the absence or a very low level of IgG antibodies to the Pathogen. The test could score negative in infected patients during the incubation period and during the early stages of infection)>or equal to 12 and less than 15 AU/mL: Equivocal (Retest in duplicate. Samples with 2 out of 3 results more than or equal to 15 or less than 12 should be reported as positive or negative, respectively.A second sample should be collected and tested no less than one to two weeks later if the results are repeatedly equivocal)>or equal to 15: Positive (A positive result generally indicates exposure of the subject to the pathogen) **iii.** Enzyme-linked immunosorbent assay (ELISA) (conducted at Bharat Biotech)

ELISA tests were performed as per standard protocols. Briefly, Microtiter plates were coated with SARS-CoV-2 specific antigens (Whole inactivated SARS CoV-2 antigen, spike (S1) (Syngene, Bangalore, India, Batch No# PRB026913/Receptor Binding Domain (RBD), Syngene, Bangalore, India, Batch No#PRB025485/ nucleocapsid (N), Syngene, Bangalore, India, Batch No# PRB025627 at a concentration of 1µg/ml, 100µl/well in PBS pH 7.4). After overnight incubation, wells were blocked and added serially diluted sera. After incubation, wells were added with Goat anti-Human IgG HRP conjugate (Sigma-Aldrich, Cat# A8667, dilution 1:5000) and incubated for 1hr at RT. Tetramethyl benzidine used as a substrate and measured absorbance at 450/630nm. Threshold value (Mean + 3SD) was established by taking the absorbance of Day 0 sera samples and antigen-specific endpoint titers were determined for Days 28, 42, and 56 sera samples. The reciprocal antibody dilution, at which absorbance is above the threshold, was taken as antigen-specific antibody endpoint titers. Since, Bharat Biotech is a vaccine manufacturing company, all serological assays such as ELISA/ PRNT50 were routinely performed for various vaccines before releasing every batch into the market. All methods were validated with respect to sensitivity and specificity. In the case of SARS-CoV-2 vaccine development, all these methods were used, while maintaining proper negative and positive controls.

Known unvaccinated and uninfected individual serum was used as a negative control. Simultaneously, ELISA blank (without coating antigen) was also maintained as a negative control. Apart from this, cut off (Mean+3SD)

was drawn from the absorbance obtained at various dilutions (1:1000 to 1:32000) of sera collected on day 0 (before vaccination), who is found negative for RT-PCR and Serology test.

iv. Plaque Reduction Neutralisation Test (PRNT₅₀) (conducted at Bharat Biotech)

The Plaque reduction neutralisation test was performed in a biosafety level 3 facility. To perform PRNT₅₀, Vero CCL-81 cell suspension (1.0×10^5 /mL/well) was added in duplicates in 24-well tissue culture plates and cultured in a CO₂ incubator at 37°C for 16-24 hrs. Serum samples from all enrolled participants were inactivated by keeping in a 56°C-water bath for 30 min. Serial dilutions (4 fold) of serum samples were mixed with the virus, which can form 50 plaque-forming units and then incubated for 1 h at 37°C. The virus-serum mixtures were added onto the preformed Vero CCL-81 cell monolayers and incubated 1 h at 37°C in a 5% CO₂ incubator. The number of plaques was counted, and the Neutralizing antibody titer was determined based on the 50% reduction in the number of plaque count, which was further analyzed using 50% Probit Analysis (10.4103/ijmr.IJMR_2382_20). Inoculation dose used was 100 CCID₅₀ in 50 microlitre.

v. Microneutralisation assay (MNT) (conducted at Bharat Biotech)

The serum collected from all enrolled participants were inactivated at 56°C in a water bath for 30 min. Serum was successively diluted with start dilution 1:8 to the required concentration by a 2-fold series, and an equal volume of challenge virus solution containing 100 CCID₅₀ viruses was added. After neutralisation in a 37°C incubator for two hours, a 1.0×10^5 /mL cell suspension was added to the wells (0.1 mL/well) and cultured in a CO₂ incubator at 37°C for 3-5 days. The Karber method (Ramakrishnan, 2016) by observing the CPE was used to calculate the neutralisation endpoint (MNT₅₀) (convert the serum dilution to logarithm), which means that the dilution of serum that can protect 50% of cells from infection by challenge with 100 CCID₅₀ virus. Inoculation dose used was 100 PFU in 100 microlitre

During each assay, known antibody titre from animal sera is used as a positive control. Pre-immune sera used as a negative control. T-cell Memory Response (Phase 1 PBMCs collected on Day 104):

PBMCs were cultured in 24 well plate with 0.5×10^6 cells/ml/well and stimulated with Whole virion Inactivated SARS CoV2 antigen (1.2 µg/ml) for 6 days by keeping the plate at 37°C in 5% CO₂ incubator. Cells stimulated with phorbol 12-myristate 13-acetate (PMA) (25 ng/ml, Sigma) and Ionomycin (1 µg/ml, Sigma) were used as positive control and unstimulated cells and PBMCs collected on Day 0 stimulated with inactivated SARS CoV 2 antigen were used as negative control. On Day 6, cells were harvested and stained with human specific fluorochrome conjugated B & T cell surface marker antibodies for 30 minutes at 4°C. The list of fluorochrome conjugated cell surface marker antibodies procured from BD Biosciences, USA are as follows, Mouse anti- human CD3 BV450 (clone# UCHT1, Cat# 560365), Mouse anti- human CD4 PE-Cy 7 (clone# SK3, Cat# 348789), Mouse anti- human CD8 APC-H7 (clone# SK1, Cat# 560179), Mouse anti- human CD19 PE (clone# SJ25C1, Cat# 340364) and Mouse anti- human CD27 APC (clone# M-T271, Cat# 558664). Mouse anti- human CD45RO PerCp Cy5.5 (clone# UCHL1, Cat# 130-113-552) was procured from Miltenyi Biotec, Germany). Cells were again washed twice with PBS and resuspended in 500µl FACS buffer (BD Biosciences). All samples were acquired using BD FACSVerser (BD Biosciences, CA, USA) and data was analyzed using FlowJo software (Tree Star). To assess the T cell memory responses, gating was done from CD3⁺T cell population and to CD4⁺ T cell population and to assess the B cell memory response, gating was done on CD3⁻ lymphocyte population. Additionally, on Day 3, 50µl cell culture supernatant was tested to determine Th1/Th2/Th17 cytokine profile using human CBA kit (Cytokine Bead Array Kit, Cat# 560484, BD Biosciences, USA). Further, Cell culture supernatant collected on Day 6 was also tested for secreted IgG antibodies by ELISA.

vi. T-cell Memory Response (Phase 1 PBMCs collected on Day 104):

PBMCs were cultured in 24 well plate with 0.5×10^6 cells/ml/well and stimulated with Whole virion Inactivated SARS CoV2 antigen (1.2 µg/ml) for 6 days by keeping the plate at 37°C in 5% CO₂ incubator. Cells stimulated with PMA (25 ng/ml, Sigma) and Ionomycin (1 µg/ml, Sigma) were used as positive control and unstimulated cells and PBMCs collected on Day 0 stimulated with inactivated antigen were used as negative control. On Day 6, cells were harvested and stained with human specific fluorochrome conjugated B & T cell surface markers for 30 minutes at 4°C. The list of fluorochrome conjugated cell surface marker antibodies procured from BD Biosciences, USA are as follows, Mouse anti- human CD3 BV450 (clone# UCHT1, Cat# 560365), Mouse anti- human CD4 PE-Cy 7 (clone# SK3, Cat# 348789), Mouse anti- human CD8 APC-H7 (clone# SK1, Cat# 560179), Mouse anti- human CD19 PE (clone# SJ25C1, Cat# 340364) and Mouse anti- human CD27 APC (clone# MT271, Cat# 558664). Mouse anti- human CD45RO PerCp Cy5.5 (clone# UCHL1, Cat# 130-113-552) was procured from Miltenyi Biotec, Germany). Cells were again washed twice with PBS and resuspended in 500µl

FACS buffer (BD Biosciences). All samples were acquired using BD FACSVerse (BD Biosciences, CA, USA) and data was analyzed using FlowJo software (Tree Star). To assess the T cell memory responses, gating was done from CD3⁺T cell population and to CD4⁺ T cell population and to assess the B cell memory response, gating was done on CD3⁻ lymphocyte population. Additionally, on Day 3, 50µl cell culture supernatant was tested to determine Th1/Th2/Th17 cytokine profile using human CBA kit (Cytokine Bead Array Kit, Cat# 560484, BD Biosciences, USA). Further, Cell culture supernatant collected on Day 6 was also tested for secreted IgG antibodies by ELISA.

vii. SARS-CoV2 spike (S1) Antibody (IgG1/IgG4) Isotyping:

Th1-dependent IgG1 vs. Th2 -dependent IgG4 antibody subclasses were determined by ELISA from sera collected from all vaccinated groups as described earlier. Briefly, 96 well microtiter plates were coated with spike (S1) protein (Cat: SYNG-PRB026913, Make: Syngene), at a concentration of 1µg/ml, in PBS pH 7.4) and blocked with 1% BSA in PBS, pH 7.4. Two fold serially diluted (1:50 to 1:204800) individual sera were added and incubated for 2hrs at 37 C followed by the addition of mouse anti-human IgG1 (Cat No: 409904, Make: Biolegend) or IgG4 (Cat No: 411202, Make: Biolegend) antibodies at a concentration of 25ng/well. After incubation of the plate for 1hr at RT, wells were again washed, and added Anti Mouse IgG HRP Conjugate (Cat No: A4416, Make: Sigma Aldrich) at a dilution of 1:2500. Later, 3,3',5,5'-tetramethylbenzidine (TMB) solution (Cat No: AR1002, make: deNovo Biolabs) was added as a substrate to develop color. Absorbance was read at 450nm. Cut off was determined as 1:50 dilution, by calculating threshold (Mean+3SD) of absorbance obtained at remaining all dilutions of known negative control (unvaccinated and uninfected sera). Th1:Th2 index was calculated by taking ratios of end point antibody titer (sera dilution at which absorbance was above the cut off) of IgG1 & IgG4. Th1/Th2 Immunophenotyping (conducted at Indoor Biotechnologies, Bangalore):

viii. Luminex Based Multiplex Assay

PBMCs from the study subject were thawed as per the SOP and washed with RPMI containing 10% FBS twice. Subsequently cells were washed twice with AIM-V Media with 10% Human AB Serum and resuspended at a density of 6x 10⁶ cells per ml. 300,000 cells (50µl) were aliquoted to individual wells in a U bottom tissue culture plate (Nunc Delta-Treated cat no: 163320) and added with 50ul of plain media (for unstimulated condition) or 50µl of COVID peptide cocktail (peptides from S,N & M protein at 2ug/ml(for each peptide))(stimulated condition) or anti-CD3 antibody (Positive Control). Peptides and anti-CD3 were diluted in AIM-V media with 10% AB serum. Each condition was performed in duplicates. The cells were incubated in CO₂ incubator at 37°C for 48 hours.

At the end of 48 hours of incubation the culture supernatant from the wells were collected and analyzed for cytokine levels using a Bio-plex Pro Human Cytokine panel (BIORAD, cat no: M5000031YV). Briefly, array of beads specific for the analytes (via the capture antibody) were either incubated with culture supernatant or standards. After washing the beads, biotinylated detection antibody was added and after washing the bead were incubated with Streptavidin PE. After washing the beads were acquired in a Bio plex 200 (BIORAD) machine. The data was analyzed using the Bioplex Manager software 6.1 **ix.** Cytokine Bead Array based Multiplex Assay

PBMCs collected on Day 56 of Phase II & Day 104 of Phase I from vaccinated individuals were stimulated with whole virion inactivated SARS CoV-2 antigen (1.2µg/ml) for 72hrs. Cell culture supernatants were collected and used for the simultaneous detection of multiple cytokines using Human Th1/Th2/Th17 BD CBA Kit (BD Bioscience, San Jose, CA, USA). Supernatant samples were processed as per the manufacturer's instructions. Briefly, the kit was used for the simultaneous detection of human IL-2, IL-4, IL-6, IFN-γ, TNF, IL-17A, and IL-10 cytokines in a single sample. For each sample, 50 µL of the mixed captured beads, 50 µL of the unknown serum sample or standard dilutions, and 50 µL of phycoerythrin (PE) detection reagent were added consecutively to each assay tube and incubated for 3 h at room temperature in the dark. The samples were washed with 1 mL of wash buffer for 5 min and centrifuged. The bead pellet was resuspended in 300 µL buffer after discarding the supernatant. Samples were measured on the BD FACS Verso and analyzed by FCAP Array Software (BD Bioscience). Unstimulated cells or PBMCs collected on Day 0 were maintained as a negative control. PBMCs stimulated with PMA & ionomycin were maintained as a positive control.

x. Database Handling/Procedures and Data Management Plan

The database used for this study is a fully validated, FDA 21 CFR Part 11 compliant system, proprietary, SAS (software as a Service) based clinical data management system. Error rates for clinical database are controlled and

do not exceed 0.5% as an industry-wide standard. For critical data zero errors based on a 100% review of data are obtained. This is controlled and documented by database audits against the study CRFs. Based on Data Management Plan (DMP) document a road map to handle the data under projected circumstances and describes the CDM activities was followed in the trial. The DMP describes the annotations, database design, data entry and data tracking guidelines, quality control measures, SAE reconciliation guidelines, discrepancy management, data transfer/extraction, and database locking guidelines. Along with the DMP, a Data Validation Plan (DVP) containing all edit-checks was performed and the calculations for derived variables are also prepared. The edit check programs in the DVP help in cleaning up the data by identifying the discrepancies.

xi. Definition of Reactogenicity and Safety.

Reactogenicity refers to a subset of reactions that occur soon after vaccination, and are a physical manifestation of the inflammatory response to vaccination. In clinical trials, information on expected signs and symptoms after vaccination is actively sought (or ‘solicited’). These symptoms may include pain, redness, swelling or induration for injected vaccines, and systemic symptoms, such as fever, myalgia, headache, or rash. The broader term ‘safety’ profile refers to all adverse events (AEs) that could potentially be caused/ triggered or worsened at any time after vaccination, and includes AEs, such as anaphylactic reactions, diseases diagnosed after vaccination and autoimmune events. (Reference: Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how’s and what’s of vaccine reactogenicity. NPJ Vaccines. 2019;4:39.)

Table S1: Ethic Committees from All Participating Trial Sites with Reference Numbers:

| Site Name | Reference Number |
|--|----------------------------|
| Nizam’s Institute of Medical Science, Hyderabad, Telangana | ECR/303/INST/AP/2013/RR-19 |
| All India Institute of Medical Science, New Delhi | ECR/547/INST/DL/2014/RR-17 |
| PGIMS, Rohtak, Haryana | ECR/293/Inst/HR/2013/RR-19 |
| All India Institute of Medical Science, Patna | ECR/1387/INST/BR/2020 |
| Redkar Hospital & Research Centre, Goa | ECR/902/INST/GA/2018 |
| Jeevan Rekha Hospital, Belgaum, Karnataka | ECR/1242/INST/KA/2019 |
| Gillukar Multispecialty Hospital, Nagpur | ECR/1374/INST/MH/2020 |
| Prakhar Hospital, Kanpur, Utter Pradesh | ECR/1017/INST/UP/2017 |
| SRM Medical College Hospital & Research Centre, Chennai Tamil Nadu | ECR/431/INST/TL/2013/RR-19 |

Table S

2: SARS-CoV-2 Neutralising Antibody Responses and Cell-mediated responses.

| Parameters | | 3 µg with Algel-IMDG (n=190) | 6 µg with Algel-IMDG (n=190) |
|--|---|------------------------------------|------------------------------------|
| PRNT ₅₀ GMT (95% CI) | Day 0 | 0.11 (0.10, 0.13) | 0.10 (0.09, 0.11) |
| | Day 28 | 1.23 (0.78, 1.94) | 1.54 (0.99, 2.4) |
| | Day 42 | 78.4 (54.8, 112.0) | 161.8 (126.2, 207.4) |
| | Day 56 | 100.9 (74.1, 137.4) | 197.0 (155.6, 249.4) |
| PRNT ₅₀ SCR (95% CI) | Day 28 | 39.3 (32.2, 46.8) | 47.5 (39.9, 55.1) |
| | Day 42 | 88.5 (83.0, 92.8) | 97.2 (93.5, 99.1) |
| | Day 56 | 92.9 (88.2, 96.2) | 98.3 (95.1, 99.7) |
| MNT ₅₀ GMT (95% CI) | Day 0 | 6.3 (6.02, 6.68) | 6.0 (5.8, 6.1) |
| | Day 28 | 12.6 (10.8, 14.7) | 12.0 (10.2, 14.0) |
| | Day 42 | 78.5 (64.6, 95.2) | 134.8 (144.4, 158.8) |
| | Day 56 | 92.5 (77.7, 110.2) | 160.1 (135.8, 188.8) |
| MNT ₅₀ SCR (95% CI) | Day 28 | 23.5 (17.6, 30.3) | 21.5 (15.7, 28.3) |
| | Day 42 | 84.7 (78.7, 89.6) | 96.6 (92.8, 98.8) |
| | Day 56 | 88.0 (82.4, 92.3) | 96.6 (92.6, 98.5) |
| SARS-CoV-2 Cell mediated Responses (on Day 42) Mean (95% CI) (pg/mL) | IFN – gamma | 1167.2 (445.9, 1888) | 1082.5 (110.9, 2054) |
| | IFN-Alpha | 4577.1 (4015, 5139) | 3612.7 (2918, 4307) |
| | IL-2 | 42.13 (31.0, 53.2) | 28.1 (22.9, 33.3) |
| | IL-5 | 33.4 (29.2, 37.5) | 30.9 (27.2, 34.6) |
| | IL-10 | 27.3 (21.5, 33.1) | 72.2 (53.9, 90.5) |
| | IL-13 | 20.1 (14.6, 25.6) | 16.3 (9.4, 23.1) |
| Th1: Th2 Ratio | (IFN- gamma +TNFAlpha+ IL-2) / (IL-5 + IL-13) | 59.2 (48.5, 69.7) | 42.5 (28.6, 56.3) |

Shown are neutralising antibody and cell-mediated immunity results at baseline (day 0), 4 weeks after the first vaccination (day 28), 2 weeks after the second vaccination (day 42), and 4 weeks after the second vaccination (day 56) for the 3 µg (n=190) and 6 µg (n=190) with Algel-IMDG groups. Shown are the cytokine levels in 2day

Table S

supernatants for 58 participants (n=29 in each the 3 µg- and 6 µg with Algel-IMDG groups) with proliferative responses to BBV152 vaccination whose PBMC were evaluated after stimulation with SARS-CoV-2 peptides.

3: PRNT₅₀ Neutralising antibody titres across age groups and gender on day 56 (four weeks after the second dose).

| Parameter | 3 µg with Algel-IMDG | | | 6 µg with Algel-IMDG | | | |
|-----------|----------------------|--------------------|--------------------|----------------------|-------------------|----------------------|--------------------|
| | Age Group | n | SCR (95%CI) | Median (Q1, Q3) | N | SCR (95%CI) | Median (Q1, Q3) |
| | ≥12-<18 | 10 | 100% (69.2,100) | 231.8 (171.0,1036.5) | 4 | 100% (39.8,100) | 224.5 (76.6,840.7) |
| | ≥18-<55 | 166 | 92.2% (87.0,95.8) | 137.7 (63.9,273.4) | 164 | 98.17% (94.8,99.6) | 182.4 (83.9,423.7) |
| | ≥55-≤65 | 7 | 100% (59,100) | 70.7 (21.6,186.8) | 9 | 100% (66.4,100) | 199.5 (72.3,344.7) |
| Gender | n | SCR (95%CI) | GMT (95%CI) | n | SCR (95%CI) | GMT (95%CI) | |
| Male | 135 | 91.1% (85.0,95.3) | 89.1 (60.3, 131.8) | 137 | 97.8% (93.7,99.6) | 211.3 (158.3, 282.2) | |
| Female | 48 | 97.9% (88.9,100.0) | 143 (93.5, 218.8) | 40 | 100% (91.2,100) | 154.8 (109.9, 218) | |

Table S4: Phase 1 Long term Follow-up immunogenicity analysis.

| Total Parameters | | 3 µg with Algel-IMDG (n=100) | 6 µg with Algel-IMDG (n=100) | 6 µg with Algel (n=100) | Algel alone (n=75) |
|--------------------------------|---------|------------------------------|------------------------------|-------------------------|--------------------|
| MNT ₅₀ GMT (95% CI) | Day 0 | 6.22 (5.9,6.5) | 6.02 (5.8,6.2) | 5.95 (5.8,6.1) | 6.09 (5.1,6.4) |
| | Day 28 | 60.33 (48.5, 75.03) | 65.96 (53.2,81.8) | 48.37 (37.9,61.7) | 7.20 (6.38,8.1) |
| | Day 42 | 45.96 (36.1, 58.5) | 81.95 (64.6, 103.9) | 64.93 (53.7,78.5) | 11.79 (9.4,14.8) |
| | Day 104 | 39.96 (32.0,49.9) | 69.52 (53.7,90.0) | 53.34 (40.1,71.0) | 20.67 (14.5,29.5) |
| MNT ₅₀ SCR (95% CI) | Day 28 | 87.88 (81.5,94.3) | 91.92 (86.6,97.3) | 82.80 (75.1,90.5) | 8.22 (1.9,14.5) |

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| | | | | |
|----------------|----------------------|----------------------|----------------------|----------------------|
| Day 42 | 74.23 (64.2,82.3) | 88.42 (80.94.1) | 91.21 (83.4,96.1) | 18.13 (10.129.3) |
| Day 104 | 73.47 (63.6,81.9) | 81.05 (71.4,88.1) | 73.12 (62.9,81.8) | 32.88 (22.3,44.9) |

Shown are geometric mean titers of the wild-type SARS-CoV-2 microneutralisation assay (MNT_{50}) at baseline (day 0), 2 weeks after the second vaccination (day 28), 4 weeks after the second vaccination (day 42), and 3 months after the second vaccination (day 104) for the 3 μ g and 6 μ g with Algel-IMDG groups, the 6 μ g with Algel group, and the Algel-only control arm (from the immunogenicity cohort). Seroconversion rates (SCR) were defined by the proportion of titers achieving ≥ 4 -fold above baseline.

5: Secreted antibodies upon PBMC stimulation from samples collected on day 104 (three months after the second dose) in the phase 1 trial.

| | 3 μg with Algel –IMDG | 6 μg with Algel-IMDG | 6 μg with Algel | Algel alone |
|-------------|---|--|---------------------------------------|--------------------|
| Mean | 12.63 | 16.60 | 19.73 | 2.33 |

Values represented in Mean \pm SD indicates spike specific secreted IgG titers measured as end point antibody dilution by ELISA from cell culture supernatant, after stimulation of PBMCs with antigen for 6days (*Ex-vivo*). The value for pre-vaccination samples were 0.

Table S6: Further effector function of activated and differentiated T cells from PBMCs from the Phase 1 study (at day 104, three months after the second dose).

| | 3µg Ag+ Algel-IMDG (n=10) | 6µg Ag+ Algel-IMDG (n=10) | 6µg Ag+ Algel (n=10) | Algel Alone (n=6) | Pre-vaccination (n=5) |
|------------------|----------------------------------|----------------------------------|-----------------------------|--------------------------|------------------------------|
| IL-17A | 4.39±4.29 | 3.40±3.41 | 14.70±28.75 | 9.58±8.79 | 5.23±2.97 |
| IFNγ | 82±172.8 | 124.69±224.73 | 13.03±16.50 | 26.77±60.27 | 0.01±0.02 |
| TNF-alpha | 3.99±4.93 | 3.25±5.63 | 1.30±0.58 | 3.37±6.54 | 0.00±0.00 |
| IL-2 | 30.55±46.83 | 55.84±69.15 | 17.05±9.40 | 6.14±8.50 | 0.29±0.36 |
| IL-4 | 0.2±0.29 | 0.35±0.48 | 0.13±0.13 | 0.08±0.16 | 0.00±0.00 |
| IL-10 | 37.87±60.28 | 22.47±41.76 | 6.35±6.76 | 6.23±8.18 | 1.22±1.06 |
| IL-6 | 297.15±410.52 | 464.24±470.51 | 218.54±327.33 | 544.56±1057.95 | 27.61±30.19 |

Values shown in Mean±SD represents cytokines levels measured in pg/ml by CBA method from culture supernatants, obtained after stimulation of PBMCs with antigen for 6days (*Ex-vivo*). Release of Th1 biased cytokines (IFNγ, TNF-α and IL-2) as a function of effector cells of CD4⁺ T cells, which further supports towards T cell dependent memory response. No or negligible levels of Th2 cytokines (IL-4) and IL-17A cytokine levels were observed, whereas, IL-6 cytokine levels were observed in 3µg and 6µg with Algel-IMDG formulation predicted to be due to activation of both T & B cells.

Table S7: Solicited Adverse Events After Two Doses in the Safety Set

| Symptoms | Dose Group | Severity | | | |
|------------------------------------|---------------------|--------------------------------------|------------------|-------------------------------|------------------|
| | | Dose 1 | | Dose 2 | |
| | | Mild n(%) | Moderate n(%) | Mild n(%) | Moderate n(%) |
| Local | | | | | |
| Pain at injection Site | 3µg with Algel-IMDG | 5 (2.63%) | 1 (0.53%) | 7 (3.68%) | - |
| | 6µg with Algel-IMDG | 6 (3.16%) | - | 4 (2.10%) | 1 (0.53%) |
| Redness at Injection site | 3µg with Algel-IMDG | 1 (0.53%) | - | - | - |
| | 6µg with Algel-IMDG | 1 (0.53%) | - | - | - |
| Itching | 3µg with Algel-IMDG | 1 (0.53%) | - | - | - |
| | 6µg with Algel-IMDG | 1 (0.53%) | - | 2 (1.05%) | - |
| Stiffness in upper arm | 3µg with Algel-IMDG | 1 (0.53%) | - | - | - |
| | 6µg with Algel-IMDG | - | - | - | - |
| Weakness in Right Arm | 3µg with Algel-IMDG | - | - | 1 (0.53%) | - |
| | 6µg with Algel-IMDG | - | - | - | - |
| Mild & Moderate (After Dose 1 & 2) | 3µg with Algel-IMDG | 9 (4.7%) (2.2, 8.8) | | 8 (4.2%) (1.8, 8.1) | |
| | 6µg with Algel-IMDG | 8 (4.2%) (1.8,8.1) | | 7 (3.7%) (1.6, 7.7) | |
| Systemic | | | | | |
| Body ache | 3µg with Algel-IMDG | - | - | 1 (0.53%) | - |
| | 6µg with Algel-IMDG | 2 (1.05%) | 1 (0.53%) | 2 (1.05%) | - |
| Fever | 3µg with Algel-IMDG | 2 (1.05%) | 1 (0.53%) | 5 (2.63%) | - |
| | 6µg with Algel-IMDG | 5 (2.63%) | 3 (1.58%) | 4 (2.10%) | - |
| Headache | 3µg with Algel-IMDG | 2 (1.05%) | - | 1 (0.53%) | - |
| | 6µg with Algel-IMDG | 1 (0.53%) | - | 2 (1.05%) | 1 (0.53%) |
| Malaise | 3µg with Algel-IMDG | 4 (2.10%) | - | 3 (1.58%) | - |
| | 6µg with Algel-IMDG | 1 (0.53%) | - | - | - |
| Weakness | 3µg with Algel-IMDG | - | - | 1 (0.53%) | - |
| | 6µg with Algel-IMDG | - | 1 (0.53%) | 2 (1.05%) | - |
| Rashes | 3µg with Algel-IMDG | - | - | 1 (0.53%) | - |
| | 6µg with Algel-IMDG | - | - | - | - |
| Mild & Moderate (After Dose 1 & 2) | 3µg with Algel-IMDG | 9 (4.7%) (95% CI: 2.2, 8.8) | | 12 (6.3%) (95% CI: 3.3, 10.8) | |
| | 6µg with Algel-IMDG | 14 (7.4%) (95% CI: 4.1, 12.1) | | 11 (5.8%) (95% CI: 3.0, 10.1) | |
| Total | | 33 (8.68%) | 7 (1.84%) | 36 (9.47%) | 2 (0.53%) |
| Adverse events after two doses | 3µg with Algel-IMDG | 38 (10.0%) (95% CI: 7.2,13.5) | | | |
| | 6µg with Algel-IMDG | 40 (10.5%) (95% CI: 7.6,14.1) | | | |

The groups received 3 µg with Algel-IMDG or 6 µg with Algel-IMDG. Data are shown as the number of participants who experienced an event (%) after receiving either dose 1 (0-7) or dose 2 (28-35 days). The grading scale for most adverse events was based on the FDA guidance document for the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. For adverse events where grading was not described in the FDA guidance document, we used the Common Terminology Criteria for Adverse Events (CTCAE) grading

Table S8: Number of unsolicited, non-serious, adverse events classified by MedDRA® System Organ Class, severity, and investigator-assigned relationship to study vaccine/control.

| MedDRA SOC | Dose Group | Adverse Events | Severity | | Relationship to IP | |
|--|---------------------|------------------------|---------------|-------------------|--------------------|-----------|
| | | | Mild N (%) | Moderate N (%) | Not Related | Related |
| Gastrointestinal Disorders | 3µg with Algel-IMDG | Mouth Ulcer (1) | 1(0.53%) | - | 1(0.53%) | - |
| | 6µg with Algel-IMDG | Gastric Problem (1) | 1(0.53%) | - | 1(0.53%) | - |
| General Disorders and administrative site conditions | 3µg with Algel-IMDG | Weakness (2) | 2(1.05%) | - | 2(1.05%) | - |
| | 6µg with Algel-IMDG | Fever (1) | - | 1(0.53%) | - | 1(0.53%) |
| | | Body ache (1) | - | 1(0.53%) | - | 1(0.53%) |
| Nervous system disorders | 3µg with Algel-IMDG | Headache (1) | 1(0.53%) | - | 1(0.53%) | - |
| | 6µg with Algel-IMDG | Dizziness (1) | 1(0.53%) | - | - | 1(0.53%) |
| | | Headache (1) | 1(0.53%) | - | 1(0.53%) | - |
| Respiratory, thoracic and mediastinal disorders | 3µg with Algel-IMDG | Cold (3) | 2(1.05%) | 1(0.53%) | 2(1.05%) | 1(0.53%) |
| | | Breathlessness (1) | 1(0.53%) | - | 1(0.53%) | - |
| | | Cough (1) | 1(0.53%) | - | 1(0.53%) | - |
| | | Heaviness in chest (1) | 1(0.53%) | - | 1(0.53%) | - |
| | | Running nose (1) | 1(0.53%) | - | 1(0.53%) | - |
| | 6µg with Algel-IMDG | Cold (2) | 2(1.05%) | - | 2(1.05%) | - |
| | | Running nose (1) | - | 1(0.53%) | - | 1(0.53%) |
| | | Sneezing (1) | 1(0.53%) | - | 1(0.53%) | - |
| Skin and subcutaneous tissue disorders | 3µg with Algel-IMDG | Rashes (1) | - | 1(0.53%) | - | 1(0.53%) |
| | 6µg with Algel-IMDG | - | - | - | - | - |
| Total | | | 16 (76.2%) | 5 (23.8%) | 15 (71.4%) | 6 (28.6%) |

GERD: Gastroesophageal reflux disease, COLD: the lowest level term (LLT) in the MedDRA for the preferred term (PT) Nasopharyngitis is cold

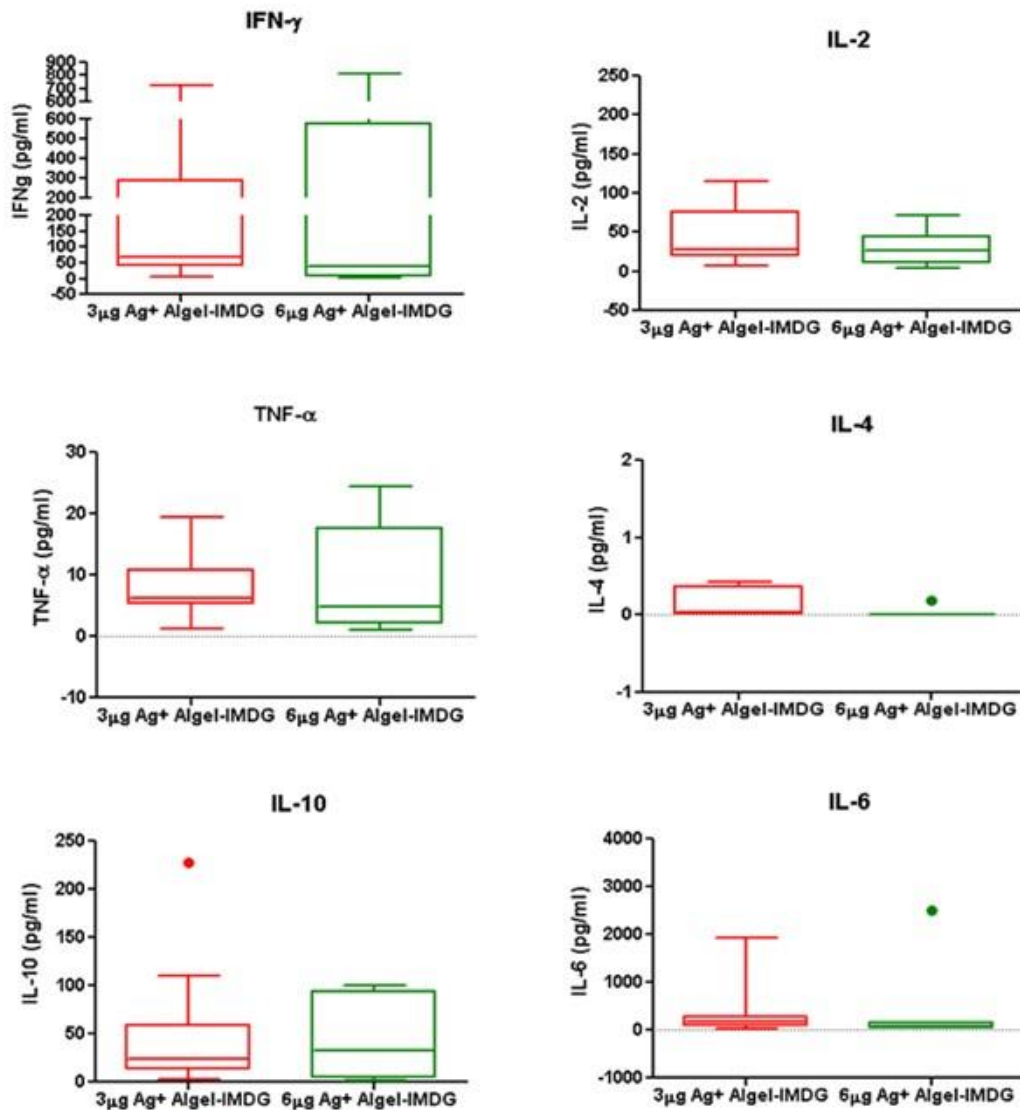
Table S9: Grading Scales for Local and Systemic Adverse Events.

| Event Name | None=1 | Mild =2 | Moderate=3 | Severe=4 | Potentially life threatening=5 |
|------------------------------------|-------------------------|--|--|--|--|
| Local Adverse Events | | | | | |
| Pain at injection site | Absent | Does not interfere with activity | Interferes with activity or repeated use of non-narcotic pain reliever >24hrs | prevents daily activity or repeated use of narcotic pain reliever | Emergency room (ER) visit or hospitalization |
| Tenderness/Soreness | Absent | Mild discomfort to touch | Discomfort with movement | Significant discomfort at rest | Emergency room (ER) visit or hospitalization |
| Redness/Erythema | Absent | 2.5-5cm | 5.1-10cm | >10 cm | Necrosis or exfoliative dermatitis |
| Swelling/Induration | Absent | 2.5-5cm and does not interfere with daily activity | 5.1-10cm or interferes with daily activity | >10 cm prevents daily activity | Necrosis |
| Pruritus associated with injection | Absence of any Pruritus | itching localized to injection site and relieved spontaneously or with <48 hours treatment | Itching beyond injection site not generalized or localized itching requiring >48 hours treatment | Itching causing inability to perform usual social & functional activities | NA |
| Any other Local AE's | Absent | Does not interfere with daily activity | interferes with daily activity, | prevents daily activity | Emergency room (ER) visit or hospitalization |
| Systemic Adverse Events | | | | | |
| Pain | Absent | Does not interfere with activity | Repeated use of nonnarcotic pain reliever > 24 hours or interferes with daily activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| Fever | <38°C (<100.4°F) | 38.0-38.4°C(100.4-101.1°F) | 38.5-38.9°C (101.2-102.0°F) | 39.0-40°C (102.1-104°F) | > 40°C (>104°F) |
| Nausea/Vomiting | Absent | No interference with daily activity or 1-2 episodes/24 hours | Some interference with daily activity or > 2 episodes/24 hours | Prevents daily activity, requires outpatient IV hydration | Emergency room (ER) visit or hospitalization for hypotensive shock |
| Headache | Absent | No interference with daily activity | some interference with daily activity or repeated use of nonnarcotic pain reliever | Significant, prevents daily activity or repeated use of narcotic pain reliever | Emergency room (ER) visit or hospitalization |
| Fatigue | Absent | No interference with daily activity | some interference with daily activity | Significant, prevents daily activity | Emergency room (ER) visit or hospitalization |
| Myalgia | Absent | No interference with daily activity | some interference with daily activity | Significant, prevents daily activity | Emergency room (ER) visit or hospitalization |
| Acute Allergic Reaction | Absent | No interference with daily activity | some interference with daily activity | Prevents daily activity | Emergency room (ER) visit or hospitalization |

| | | | | | |
|-------------------------|-------------|---|--|--|--|
| Rash | Rash Absent | rashes covering <10%BSA with or without symptoms (pruritus, burning, tightness) | rashes covering 10-30 %BSA (Body Surface Area) with or without symptoms (pruritus, burning, tightness), interferes with daily activity | rashes covering >30 %BSA with or without symptoms (pruritus, burning, tightness), prevents with daily activity | NA |
| Joint pain | Absent | Does not interfere with daily activity | Repeated use of nonnarcotic pain reliever > 24 hours or interferes with daily activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| Any other Systemic AE's | Absent | Does not interfere with daily activity | interferes with daily activity | prevents daily activity | Emergency room (ER) visit or hospitalization |

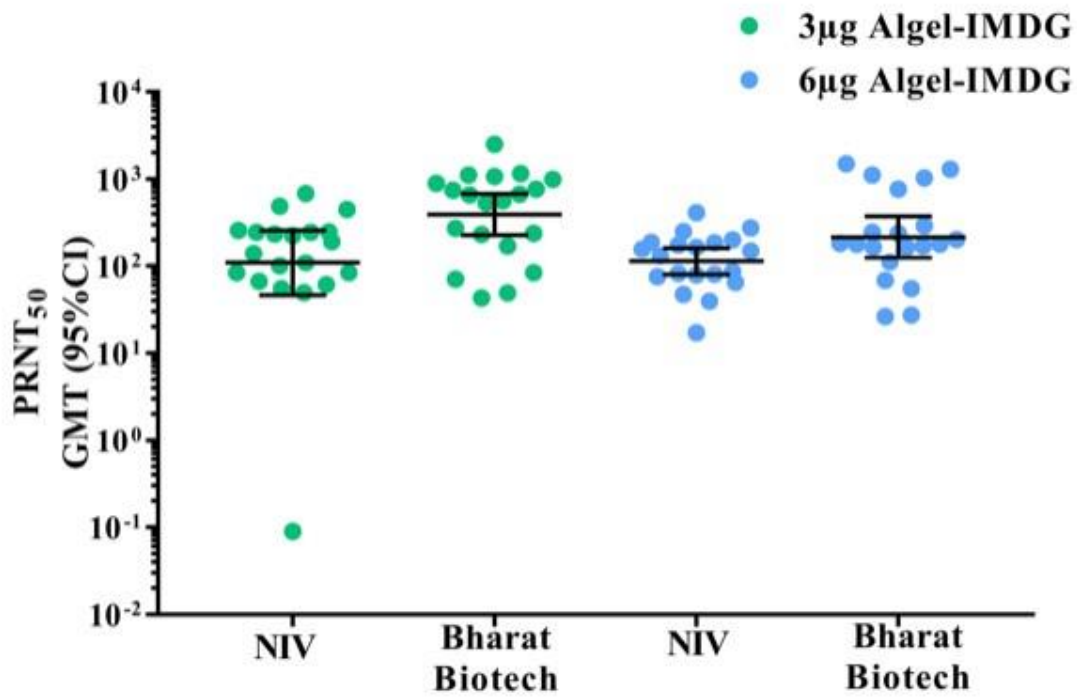
Abbreviation: NA, not available. The grading scale for most AEs was based on the FDA guidance document for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The causality assessment was done based on the investigator's taking the following factors into consideration: Temporal (time-based) relationship between the event and administration of the study vaccine. Possible alternative etiology for the AE, such as concurrent illness or natural history of underlying diseases, or concomitant medications. Adverse events of similar nature having previously been observed with the study vaccine. The adverse event having often been reported in literature for similar types of treatments.

Figure S1: Cytokine profile measured from culture supernatant upon stimulation of PBMCs with antigen

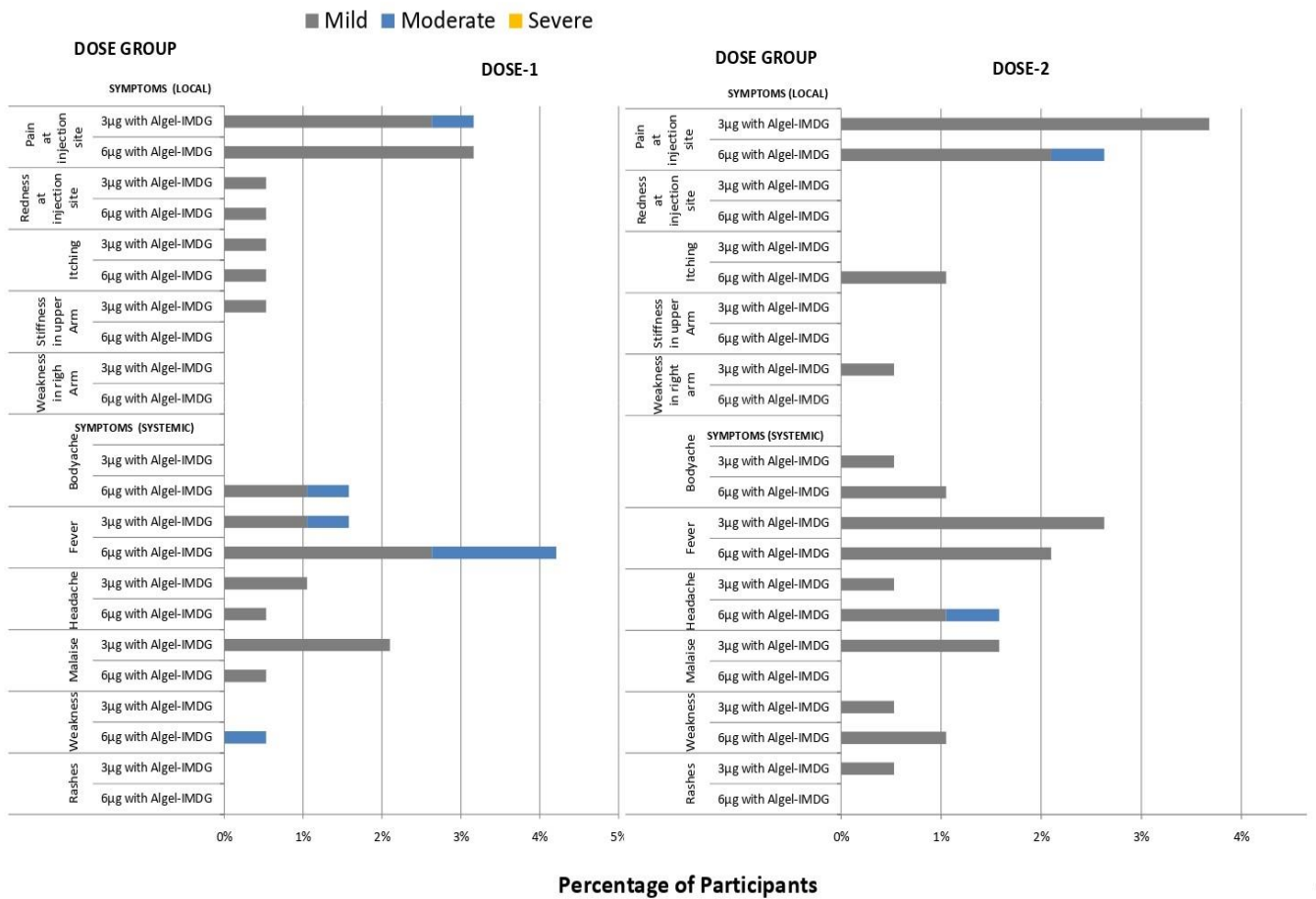


Box plot represents mean with 95% CI values of secreted cytokine levels measured in the cell culture supernatant after 72hrs of whole virion inactivated antigen stimulation. PBMCs collected on Day 56 were used to measure Th1/Th2/Th17 cytokines by CBA method. Graphs and statistics done using Tukey test.

Figure S2: comparison between PRNT₅₀ assays at the two laboratories (Bharat Biotech and National Institute of Virology).



FigureS3: Solicited Adverse Events After Two Doses in the Safety Set



ANNEXURE-3

INTEGRATED CLINICAL AND STATISTICAL REPORT

| | |
|--|---|
| Title: | An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age. |
| Protocol Number: | BBIL/BBV152-C/2020 |
| Design: | This is a randomized, double-blind, phase 3 study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above. |
| Phase: | III |
| Version: | 1.0 |
| Sponsor: | Bharat Biotech International Limited (BBIL), Genome Valley, Shameerpet, Hyderabad, Telangana, India. & Indian Council of Medical Research (ICMR), New-Delhi, India |
| Study Initiation Date: | 16 th November 2020 |
| Study Completion Date: | Ongoing |
| Co-ordination Unit (Responsible for Preparation of the Report) Clinical Operations Management Unit | IQVIA & BHARAT BIOTECH INTERNATIONAL LIMITED |

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GCP Statement: The trial is being conducted in compliance with the protocol, GCP, Schedule Y (Drugs and Cosmetics Act, 2005) and Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research, 2006)

Date of Report: 05th March 2021

Prepared by: Medical Affairs Department
Bharat Biotech International Limited

Study period (years): 1 Year

Date of 1st Dose 1st Subject: November 16, 2020

Date of 1st Dose last subject: January 8, 2021

Trial Registration: CTRI/2020/11/028976

Signature Page:

Study Title: An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age.

Review and approval of the Integrated Clinical and Statistical report.

We have read this report and confirm that, to the best of our knowledge, it accurately describes the conduct and results of the trial.

Signature & Date

Dr. V. Krishna Mohan 06/03/2021

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Title: An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age.

Protocol No.: BBIL/BBV152-C/2020

Investigational Vaccine: Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152B).

Study Population: A total sample size of 25,800 volunteers ages 18 years and above were recruited and administered with vaccine and placebo in 1:1 ratio.

The study was conducted in 25 sites all zone of India.

Study Centres and Investigators:

| S No. | Site Codes | Site Name & Location | Zone |
|-------|------------|---|---------|
| 1 | 308 | MG Medical College, Sri Balaji Vidyapeeth - Dr. PajanivelRanganadin (Pondicherry) | South |
| 2 | 311 | Vydehi institute of medical sciences – Dr. Akshata (Bangalore) | South |
| 3 | 312 | Director of Public Health & Preventive Medicine – Dr. SelvaVinayagam - (Chennai) | South |
| 4 | 317 | Government Fever Hospital, Guntur - Dr. Laxmi Kumari (Guntur) | South |
| 5 | 320 | Nizam's institute of Medical Sciences -Dr. Prabhakar Reddy (Hyderabad) | South |
| 6 | 325 | SRM Hospital & Research Center - Dr. Satyajit Mohapatra (Chennai) | South |
| 7 | 326 | Jeevan Rekha Hospital - Dr Amit Bhate, (Belgaum) | South |
| 8 | 309 | People's University - Dr. Raghavendra Gumashta (Bhopal) | Central |
| 9 | 302 | All India Institute of Medical Sciences – Dr. Chadramani Singh (Patna) | East |
| 10 | 305 | ICMR-National Institute of Cholera and Enteric Diseases - Dr. Suman Kanungo (Kolkata) | East |
| 11 | 318 | (IMS) & SUM Hospital - Dr. E Venkata Rao (Bhubaneswar) | East |
| 12 | 301 | All India Institute of Medical Sciences – Dr. Sanjay Rai (New Delhi) | North |
| 13 | 303 | ESIC Medical College and Hospital – Dr. Anil Pandey (Faridabad) | North |
| 14 | 313 | Aligarh Muslim University - Dr. Md. Shameem (Uttar Pradesh) | North |
| 15 | 321 | PGIMS - Dr. Savita Verma (Rohtak) | North |
| 16 | 323 | Gangaram - Dr Anupam Sachdeva (New Delhi) | North |
| 17 | 324 | Prakhar Hospital – Dr. Jitendra Kushwaha, Kanpur | North |
| 18 | 307 | Lokmanya Tilak Municipal General Hospital-Dr. N.T. Awad (Mumbai) | West |
| 19 | 310 | Rahate Surgical Hospital & ICU - Dr. Manish Multani (Nagpur) | West |
| 20 | 315 | GMERS Medical College and Civil Hospital - Dr. Parul Bhatt (Ahmedabad) | West |
| 21 | 316 | Sir J.J. Group of Hospitals - Dr. PritiMeshram (Mumbai) | West |
| 22 | 322 | Redkar Hospital and Research Centre - Dr. Sagar Redkar (Goa) | West |
| 23 | 327 | Maharaja Agrasen Multi speciality Hospital – Dr. Manish Kumar Jain - (Jaipur) | West |
| 24 | 328 | RCSMGMC & CPR Hospital – Dr. Sunita Jaiprakash Ramanand (Kolhapur) | West |
| 25 | 329 | Prakash Institute of Medical Science & Research – Dr. Vijaykumar Patil (Sangli) | West |

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1. INTRODUCTION

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) has, as on March 05th, 2021, spread to over 216 countries across the globe, with a total of ~115 Million confirmed cases and ~ 2.5 Million deaths. The number of reported SARS-CoV-2 cases in India is also on an increase with ~11 Million confirmed cases and ~157000 deaths(1). Coronaviruses are a severe threat to the humans and other animals, earlier other members of the same family coronaviridae, SARS-CoV infected ~8000 people with a death rate of 10% and another member Middle East Respiratory Syndrome (MERS) virus was outbreaked in the Middle East region and infected ~2000 people with 35% fatality rate(2). Porcine epidemic diarrhea coronavirus (PEDV) has swept throughout the United States of America, causing an almost 100% fatality rate in piglets and wiping out more than 10% of America's pig population in less than a year(2).

Coronaviruses are the enveloped positive-stranded RNA viruses which have the largest genome among all RNA viruses with approximately 27 to 32 kb2. The viral genome is packed inside a helical capsid formed by the nucleocapsid protein (N) which is surrounded by an envelope. SARS-CoV viral envelope is associated with at least three structural proteins: The membrane protein (M) and the envelope protein (E) are involved in virus assembly, whereas the spike protein (S) mediates virus entry into host cells. Among these structural proteins, the spike forms large protrusions from the virus surface, giving coronaviruses the appearance of having crowns(2).

The SARS-CoV-2 virus transmits from person to person mainly through respiratory droplets(3).

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV(4,5). There is local propagation of the virus but a limited innate immune response. At this stage, the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response(6). The symptoms of SARS-CoV-2 infection appear after an incubation period of ~5 days(7). The period from the onset of SARS-CoV-2 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and the status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70(8). The most common symptoms at the onset of SARS-CoV-2 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnoea, and lymphopenia(9).

Till date, no specific treatment was recommended for SARS-CoV-2 infection hence, vaccines are a critical new tool in the battle against COVID-19. Various types of COVID-19 vaccines, such as DNA, RNA- based formulations, Recombinant subunit vaccines containing the viral protein (Spike) epitopes, vector based formulations (eg: Adeno virus) and traditional inactivated vaccines were developed(10–12). Bharat Biotech Int. Ltd., India has developed a whole-virion inactivated Covid-19 vaccine and evaluated for its safety and immunogenicity in a Phase 1 followed by phase 2 study and found that vaccine is safe and immunogenic(13,14). Bharat Biotech has been conducting a phase 3 efficacy study in 25,800 participants to evaluate the efficacy of the vaccine.

2. STUDY DESIGN

The study is an endpoint-driven randomized, double-blind, phase 3 study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above.

A total of 25,800 subjects were enrolled across India in 25 sites (3 Categories) and randomized in a 1:1 ratio to receive BBV152B vaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a NP swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect enrolment of the participant. Participants who are found to be positive for either RT-PCR or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy analysis.

The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B. The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the completion of the study duration.

Case Definition of symptomatic COVID-19

The study is designed to accrue 130 symptomatic COVID-19 cases. This includes any participant who meets any of the two below following criteria:

- Case Definition for Primary Efficacy Symptomatic Endpoint
- Case Definition for Severe Symptomatic COVID-19

Any one of the below mentioned criteria (A or B) must be met, along with a positive SARS-CoV-2 RT-PCR confirmation to be a confirmed symptomatic case

| Criteria A: One or More | | Criteria B: Two or More |
|---|-----|--|
| 1. Shortness of Breath/Difficulty in Breathing 2. New onset Anosmia/Aguesia 3. Oxygen saturation of <94% or escalation by requiring supplemental Oxygen. 4. Pneumonia: diagnosed by chest X ray or CT scan 5. Evidence of Shock 6. ICU Admission/Death | or | 1. Fever 2. Chills 3. New cough 4. Myalgia/Fatigue 5. Headache 6. Sore throat 7. Nausea/Vomiting 8. Diarrhea 9. Congestion/ Runny Nose |
| | AND | |
| Positive SARS-CoV-2 RT-PCR test | | |

SITE CATEGORIES:

Category 1 (Symptomatic): In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 day intervals.

Category 2 (Symptomatic/Asymptomatic): In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of Asymptomatic COVID-19 infection at 1-Month intervals will be collected.

Category 3 (Symptomatic/Asymptomatic+Immunogenicity): In addition to administering the IP, repeated NP swabs for asymptomatic, a series of blood samples will be collected for analyzing serum for immunological assessments.

3. STUDY POPULATION

As per the approved protocol, a total of 25,800 subjects were enrolled and received either vaccine or placebo in 1:1 ratio. Among these 25,800 participants 24,455 were received second dose and detailed site wise enrolled participants, second dose recipients and the participants who were followed up till Day 42 were listed in the Table 1.

TABLE 1: SUMMARY OF ENROLLED SUBJECTS AT EACH SITE

| S No. | Site Name and Location | Subjects completed 1 st dose | Subjects completed 2 nd dose | Subjects Completed follow up (Day 42) |
|--------------------------|---|---|---|---------------------------------------|
| Category 1: Sites | | | | |
| 1 | All India Institute of Medical Sciences - (New Delhi) | 659 | 629 | 629 |
| 2 | All India Institute of Medical Sciences - (Patna) | 1216 | 1137 | 1129 |
| 3 | ESIC Medical College and Hospital - (Faridabad) | 1126 | 1002 | 997 |
| 4 | ICMR-National Institute of Cholera and Enteric Diseases - (Kolkata) | 988 | 969 | 967 |
| 5 | Lokmanya Tilak Municipal General Hospital - (Mumbai) | 197 | 191 | 191 |
| 6 | MG Medical College, Sri Balaji Vidyapeeth - (Pondicherry) | 901 | 868 | 831 |
| 7 | People's University - (Bhopal) | 1725 | 1426 | 1424 |
| 8 | Rahate Surgical Hospital & ICU - (Nagpur) | 1670 | 1594 | 1579 |
| 9 | Vydehi institute of Medical Sciences - (Bangalore) | 496 | 476 | 429 |
| 10 | Director of Public Health & Preventive Medicine - (Chennai) | 29 | 27 | 27 |
| 11 | Gangaram - (New Delhi) | 318 | 276 | 276 |
| 12 | Prakhar Hospital – (Kanpur) | 2250 | 2244 | 2243 |
| 13 | Jeevan Rekha – (Karnataka) | 2227 | 2216 | 2216 |
| 14 | Maharaja Agrasen Multi speciality Hospital - (Jaipur) | 1494 | 1431 | 1124 |
| 15 | Sunita Jaiprakash Ramanand - RCSMGMC & CPR Hospital - (Kolhapur) | 887 | 882 | 737 |
| 16 | Vijaykumar Patil - Prakash Institute of Medical Science & Research - (Sangli) | 611 | 594 | 409 |
| Category 2: Sites | | | | |
| 17 | Aligarh Muslim University - (Uttar Pradesh) | 1008 | 938 | 937 |

| | | | | |
|--------------------------|--|--------------|--------------|--------------|
| 18 | Gmers Medical College and Civil Hospital - (Ahmedabad) | 1081 | 1018 | 1018 |
| 19 | Sir J.J. Group of Hospitals - (Mumbai) | 438 | 379 | 378 |
| 20 | Government Fever Hospital - (Guntur) | 1358 | 1351 | 1350 |
| 21 | (IMS) & SUM Hospital - (Bhubaneswar) | 510 | 495 | 494 |
| 22 | SRM Hospital & Research Center – (Chennai) | 603 | 446 | 404 |
| Category 3: Sites | | | | |
| 23 | Nizam's institute of Medical Sciences - (Hyderabad) | 1998 | 1888 | 1883 |
| 24 | PGIMS - (Rohtak) | 456 | 433 | 433 |
| 25 | Redkar Hospital and Research Centre - (Goa) | 1554 | 1544 | 1544 |
| | Total | 25800 | 24454 | 23649 |

3.1 AT-RISK POPULATION

In this study both healthy volunteers and participants with high risk for Covid-19 who is, either ≥ 60 years of age or < 60 years of age with co-morbid conditions, and HCPs were recruited.

Participants who are < 60 years old will be categorized as at risk for severe COVID-19 illness if they have at least 1 of the following risk factors at Screening:

- Stable chronic lung disease (eg, emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or mild to moderate asthma.
- Stable cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, hypertension, and pulmonary hypertension).
- Severe obesity (body mass index ≥ 35 kg/m²).
- Controlled Diabetes (Type 1, Type 2).
- Stable Liver disease.

Participants who has high risk for Covid-19 were summarized in the Table 2 (>60 Years) and Table 3 (< 60 with Co-morbid condition).

TABLE 2: SUMMARY OF AT RISK PARTICIPANTS

| Description | Treatment Arm | | Total (N = 25,800) n (%) |
|---|---------------------------------|----------------------------------|--------------------------------|
| | BBV152 (N = 12,900) n (%) | Placebo (N= 12, 900) n (%) | |
| At Risk Participants at baseline, Age ≥ 60 years | | | |
| Stable chronic heart disease | 158 (1.22) | 142 (1.10) | 300 (1.16) |
| Stable chronic lung disease | 12 (0.09) | 16 (0.12) | 28 (0.11) |
| Controlled Diabetic | 101 (0.78) | 107 (0.83) | 208 (0.81) |
| Stable Liver Disease | 4 (0.03) | 8 (0.06) | 12 (0.05) |
| Severe obesity (BMI >35) | 2 (0.02) | 2 (0.02) | 4 (0.02) |
| Other stable co-morbid condition | 129 (1.00) | 142 (1.10) | 271 (1.05) |
| None of the above | 32 (0.25) | 28 (0.22) | 60 (0.23) |
| Multiple risk categories* | 245 (1.90) | 296 (2.29) | 541 (2.10) |

* Multiple risk categories count contain for subject selected multiple categories (i.e. more than one)

TABLE 3: SUMMARY OF AT RISK PARTICIPANTS

| Description | Treatment Arm | | Total (N = 25,800) n (%) |
|--|------------------------------|-------------------------------|--------------------------------|
| | BBV152 (N = 12,900) n (%) | Placebo (N= 12, 900) n (%) | |
| At Risk Participants at baseline, Age < 60 years | | | |
| Stable chronic heart disease | 370 (2.87) | 357 (2.77) | 727 (2.82) |
| Stable chronic lung disease | 108 (0.84) | 148 (1.15) | 256 (0.99) |
| Controlled Diabetic | 593 (4.60) | 613 (4.75) | 1206 (4.67) |
| Stable Liver Disease | 17 (0.13) | 17 (0.13) | 34 (0.13) |
| Severe obesity (BMI >35) | 53 (0.41) | 90 (0.70) | 143 (0.55) |
| Other stable co-morbid condition | 613 (4.75) | 676 (5.24) | 1289 (5.00) |
| None of the above | 125 (0.97) | 118 (0.91) | 243 (0.94) |
| Multiple risk categories* | 209 (1.62) | 200 (1.55) | 409 (1.59) |

* Multiple risk categories count contain for subject selected multiple categories (i.e. more than one)

3.2 GENDER AND AGEWISE CLASSIFICATION OF THE PARTICIPANTS:

In the study both the genders were recruited, among 25800 participants 17332 (67.2%) were male and 8468 (32.8%) were female participants. Detailed description of the participants categorized by their age and gender was depicted in the Table 4.

TABLE 4: GENDER AND AGE WISE CLASSIFICATION OF THE PARTICIPANTS

| Gender | ≥18 to ≤50 | ≥51 to ≤60 | ≥61 to above |
|--------|-------------------|-----------------|-----------------|
| Male | 13790 (53.45%) | 2085 (8.08%) | 1457 (5.65%) |
| Female | 6242 (24.19%) | 1250 (4.84%) | 976 (3.78%) |

3.3 INFECTION RATE & SEROPREVALENCE

As per the protocol, all the participants were examined for their status on the Covid-19 infection and seroprevalence at baseline. Nasopharyngeal swab and serum were collected from all the participants and estimated the COVID-19 infection rate and seroprevalence among all the sites across India. The results were reported that 0.82% infection rate and 34.33% of the seroprevalence across the India. Site wise and zone wise seroprevalence and infection rate is depicted in the Table 5.

TABLE 5: INFECTION RATE AND SEROPREVALENCE OF THE COVID-19

| Site Code | Site | RTPCR Tested | RTPCR Positive | Infection Rate (%) | ELISA Samples | Positive | Seroprevalence (%) |
|----------------|----------------------------|--------------|----------------|--------------------|---------------|----------|--------------------|
| NORTH | | | | | | | |
| 301 | AIIMS, Delhi | 658 | 3 | 0.46 | 658 | 293 | 44.53 |
| 303 | ESIC, Faridabad | 1126 | 8 | 0.71 | 1126 | 290 | 25.75 |
| 313 | AMU, Aligarh | 1008 | 20 | 1.98 | 1002 | 311 | 31.04 |
| 321 | PGIMS, Rohtak | 456 | 14 | 3.07 | 456 | 72 | 15.79 |
| 323 | Gangaram, New-Delhi | 319 | 2 | 0.63 | 319 | 107 | 33.54 |
| 324 | PRAKHAR, Kanpur | 2250 | 5 | 0.22 | 2250 | 1031 | 45.82 |
| | | | | 1.18 | | | 32.75 |
| EAST | | | | | | | |
| 302 | AIIMS, Patna | 1216 | 20 | 1.64 | 1216 | 801 | 65.87 |
| 305 | NICED, Kolkata | 989 | 8 | 0.81 | 989 | 264 | 26.69 |
| 318 | IMS, Odisha | 510 | 3 | 0.59 | 510 | 123 | 24.12 |
| | | | | 1.01 | | | 38.89 |
| WEST | | | | | | | |
| 307 | Sion Hospital, Mumbai | 202 | 3 | 1.49 | 197 | 105 | 53.30 |
| 310 | RAHATE, Nagpur | 1672 | 11 | 0.66 | 1672 | 192 | 11.48 |
| 315 | GMERS, Ahmadabad | 1081 | 25 | 2.31 | 1081 | 387 | 35.80 |
| 316 | JJ Hospital, Mumbai | 437 | 5 | 1.14 | 437 | 200 | 45.77 |
| 322 | REDKAR, Goa | 1554 | 1 | 0.06 | 1554 | 497 | 31.98 |
| 326 | Jeevan Rekha, Belgavi | 2227 | 4 | 0.18 | 2227 | 936 | 42.03 |
| 327 | MAMSH, Jaipur | 1494 | 12 | 0.80 | 1494 | 698 | 46.72 |
| 328 | RCSMGMC & CPR, Kolhapur | 887 | 0 | 0.00 | 887 | 248 | 27.96 |
| 329 | PIMSR, Sangli, MH | 611 | 0 | 0.00 | 611 | 198 | 32.41 |
| | | | | 0.74 | | | 36.38 |
| SOUTH | | | | | | | |
| 308 | MGMCR, Pondicherry | 901 | 3 | 0.33 | 901 | 433 | 48.06 |
| 311 | VIMS, Bangalore | 496 | 2 | 0.40 | 496 | 172 | 34.68 |
| 312 | DPH, Chennai | 29 | 1 | 3.45 | 29 | 13 | 44.83 |
| 317 | Guntur, AP | 1358 | 5 | 0.37 | 1358 | 380 | 27.98 |
| 320 | NIMS, Hyderabad | 1998 | 31 | 1.55 | 1998 | 423 | 21.17 |
| 325 | SRM, Chennai | 605 | 0 | 0.00 | 605 | 453 | 74.88 |
| | | | | 1.02 | | | 41.93 |
| CENTRAL | | | | | | | |
| 309 | Peoples University, Bhopal | 1746 | 26 | 1.49 | 1736 | 234 | 13.48 |
| TOTAL | | | | 0.82 | | | 34.33 |

4. SAFETY

There are 25,800 participants were recruited in the study. It is decided to consider all AEs reported till 11 am (IST) March 1, 2021 for first 8000 enrolled participants. All the participants were followed up telephonically for 7 days after each dose of vaccination and reported all the solicited AEs. Unsolicited AEs from all the participants were reported throughout follow-up period (Till Day 42). A total of 655 adverse events were reported and equally distributed in both vaccine and placebo groups. Among these 655 AEs 605 were mild, 34 were moderate and 16 were severe and the severity of the AEs is similar in both the groups. All the AEs except 20 were resolved without sequelae. Detailed AEs list is summarized in the Table 6.

TABLE 6: SUMMARY OF ADVERSE EVENTS

| Description | Treatment Arm | | Total (N=7,865) n (%) |
|---|------------------------------|-------------------------------|-----------------------------|
| | BBV152 (N=4,061) n (%) | Placebo (N=3,804) n (%) | |
| No of Subject with at least one Adverse Event | 335 (8.25) | 300 (7.89) | 635 (8.07) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 99 (2.44) | 94 (2.47) | 193 (2.45) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 55 (1.35) | 39 (1.03) | 94 (1.20) |
| No of Subjects with at least one Systemic Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 94 (2.31) | 55 (1.45) | 149 (1.89) |
| No of subjects with at least one Systemic Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 30 (0.74) | 23 (0.60) | 53 (No 0.67) |
| No of subjects with at least one Unsolicited Adverse Events | 50(1.23) | 67(1.76) | 117 (1.49) |
| All Ongoing Adverse Events | 9 (0.22) | 11 (0.29) | 20 (0.25) |
| Severity | | | |
| Mild | 317 (7.81) | 288 (7.57) | 605 (7.69) |
| Moderate | 17 (0.42) | 17 (0.45) | 34 (0.43) |
| Severe | 9 (0.22) | 7 (0.18) | 16 (0.20) |

4.1 SERIOUS ADVERSE EVENTS

All the participants (25800) were followed up for serious adverse events (SAEs) and 43 SAEs were reported till date and among those cases 33 were resolved, 3 cases are ongoing and 7 deaths were reported. All the SAEs were not related to the vaccine and distributed equally among the two treatment groups. Detailed description of the SAEs is given in the Table 7.

TABLE 7: SAEs Line Listing

| S. No | Study site (Screening Number) | Date of administration | Date of occurrence of SAE | Seriousness Criteria | Diagnosis of the Event | Causality Assessment by PI | Causality Assessment by Sponsor | Outcome of the Event |
|-------|---|--|---------------------------|----------------------|--|----------------------------|---------------------------------|---|
| 1 | NIMS, Hyderabad (32000107) | 19-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 20-11-2020 | Hospitalization | Road traffic accident (RTA)- Crush Injury left foot and Fracture neck of 2 nd 3 rd and 4 th metatarsal. | Unrelated | Unrelated | Recovered and discharged from hospital on 23 rd Nov 2020. |
| 2 | NIMS, Hyderabad (32000073) | 18-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 29-11-2020 | Hospitalization | Uncontrolled Type-2 Diabetes mellitus with Diabetic ketoacidosis and dyselectrolytemia | Unlikely | Unrelated | Recovered and discharged from hospital on 12 th Dec 2020 |
| 3 | PGIMS, Rohtak (32100001) | 20-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from hospital 30 th Dec 2020 in stable condition |
| 4 | NIMS, Hyderabad (32000428) | 28-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | Shortness of breath, pedal edema and fever (3 days). | Unlikely | Unrelated | Recovered and discharged from hospital 6 th Dec 2020 in stable condition |
| 5 | NIMS, Hyderabad (32000272) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 11 th Dec 2020 in stable condition |
| 6 | NIMS, Hyderabad (32000242) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 10-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 15 th Dec 2020 in stable condition |
| 7 | Grant Medical College & JJ Hospital, Mumbai (31600192) | 08-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 12-12-2020 | Hospitalization | Homocysteine | Unrelated | Unrelated | Recovered and discharged from hospital in stable condition on 26 th Dec 2020 |
| 8 | SRM Medical College & Hospital, Chennai (32500018) | 07-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 15-12-2020 | Hospitalization | Clinical enteric fever with dehydration. | Unrelated | Unrelated | Recovered and discharged from hospital on 17 th Dec 2020 |
| 9 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900546) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 17-12-2020 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from hospital on 18 th Dec 2020 with advice to follow up for further treatment plan |
| 10 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900809) | 12-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 21-12-2020 | Death | Death | Unrelated | Unrelated | Fatal |
| 11 | MGMCRI-SBV, Puducherry (30800390) | 26-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) | 01-01-2020 | Hospitalization | "Hollow viscus perforation with Acute Kidney Injury -? Cause" | Unrelated | Unrelated | Recovered |

| | | | | | | | | |
|----|---|--|--|-----------------|---|-----------|-----------|--|
| | | 2 nd dose was not administered | | | | | | |
| 12 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900578) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 06-01-2021 | Hospitalization | Liver abscess | Unrelated | Unrelated | Recovered and discharged from hospital on 15 th Jan 2021 |
| 13 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore. (31100060) | 09-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-12-2020 (Date of awareness of SAE:06-01-2021) | Hospitalization | Left lung opacity-LRTI | Unrelated | Unrelated | Recovered and discharged from Hospital on 23 rd December 2020 |
| 14 | People's College of medical research center, Bhopal, Madhya Pradesh (30900546) | 10/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-01-2021 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from Hospital on 21 st Jan 2021. |
| 15 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901496) | 18-12-2020 (1 st Dose) (Vaccine/Placebo; blinded) 2 nd dose was not administered | 08-01-2021 | Hospitalization | Injury in both the lower limbs (ankle) | Unrelated | Unrelated | Recovered and discharged from Hospital on 19 th Feb 2021. |
| 16 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901257) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 30-12-2020 (Date of awareness of SAE:13/01/2021) | Hospitalization | Mature cataract | Unrelated | Unrelated | Recovered and discharged from hospital on 1 st Jan 2021. |
| 17 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901279) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 03/01/2021 (Date of awareness of SAE: 13/01/2021) | Hospitalization | CAD with hypertension with B/L Pneumonitis /ACS/TVD. She was also positive with COVID-19. | Unrelated | Unrelated | Recovered and discharged from hospital on 6 th Jan 2021. |
| 18 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901436) | 17/12/2020 (1 st Dose) 14/01/2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 15/01/2021 | Hospitalization | Acute cholecystitis and cholelithiasis. | Unrelated | Unrelated | Recovered and discharged from the hospital on 22 -01-2021 |
| 19 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901004) | 14-12-2020 (1 st Dose) 11-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 18-01-2021 | Hospitalization | Renal Calculi with Hepatomegaly. | Unrelated | Unrelated | Recovered and discharged from the hospital on 19-01-2021 |
| 20 | NIMS, Hyderabad (32001145) | 21-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-01-2021 (Date of awareness of the SAE:21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 21 | Jawaharlal Nehru Medical college and Hospital,AMU, Aligarh (31300207) | 25-11-2020 (1 st Dose) 24-12-2020 (2 nd dose) (Vaccine/Placebo; Blinded) | 10-01-2021 (Date of awareness of the SAE- 21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |

| | | | | | | | | |
|----|---|--|--|-----------------|---|-----------|-----------|--|
| 22 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100290) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 11-01-2021 (Date of awareness of the SAE: 14-01-2021) | Hospitalization | Atypical viral pneumonia | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-01-2021 |
| 23 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901512) | 18-12-2020 (1 st Dose) 20-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 21-01-2021 | Hospitalization | Generalised body pain | Unrelated | Unrelated | Recovered and discharged from the hospital on 25-01-2021 |
| 24 | AIIMS, New Delhi (30100090) | 5-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 22-01-2021 (Date of SAE Awareness: 24-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 25 | GMERS Medical College and Civil Hospital, Sola, Ahmedabad (31500928) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 08-01-2021 (Date of awareness of SAE: 27-01-2021) | Death | Death | Unlikely | Unlikely | Fatal |
| 26 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900901) | 13-12-2020 (1 st Dose) 10-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-02-2021 | Hospitalization | Right eye mature cataract and left eye pseudophakia | Unrelated | Unrelated | Recovered and discharged from Hospital on 12 th Feb 2021. |
| 27 | SRM Medical College Hospital & Research Centre, Kanchipuram, Tamil Nadu (32500447) | 28-12-2020 (1 st Dose) 25-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 31-01-2021 (Date of awareness by Sponsor: 01-02-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 28 | SRM Medical College Hospital & Research Centre Kanchipuram, Tamil Nadu (32500303) | 23-12-2021 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 27-01-2021 (Date of awareness-02-02-2021) | Hospitalization | Viral pneumonia due to COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 9 th Feb 2021 in stable condition |
| 29 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900770) | 12-12-2020 (1 st Dose) 09-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Chronic Otitis media | Unrelated | Unrelated | Recovered and discharged from the hospital on 18-02-2021 |
| 30 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Bronchial asthma | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-02-2021 |
| 31 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700845) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |
| 32 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700848) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |

| | | | | | | | | |
|----|---|--|---|-----------------|----------------------------------|---------------------------------------|------------------|---|
| 33 | AIIMS, New Delhi (30100013) | 27-11-2020 (1 st Dose) 26-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-02-2021 (Date of awareness-06-02-2021) | Hospitalization | Immune Thrombocytopenia Purpura. | Could be associated with the vaccine. | Under Evaluation | Recovered and discharged from the hospital on 08-02-2021 |
| 34 | Director of Public Health & Medicine study site, Chennai (31200001) | 09-12-2020 (1 st Dose) 06-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 16-02-2021 |
| 35 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900391) | 07-12-2020 (1 st Dose) 05-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | Chronic otitis media | Unrelated | Unrelated | Recovered and discharged from the hospital on 22-02-2021 |
| 36 | Prakash Institute of Medical Science & Research, Sangli, Maharashtra (32900012) | 30-12-2020 (1 st Dose) 26-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 13-02-2021 | Hospitalization | Fever, headache, and cough | Unrelated | Unrelated | Recovered and discharged from the hospital on 14-02-2021 |
| 37 | AIIMS, New Delhi (30100044) | 02-12-2020 (1 st Dose) 30-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 19-02-2021 | Hospitalization | Myocardial infarction (MI) | Unlikely | Unrelated | Recovered and discharged from the hospital on 01-03-2021 |
| 38 | NIMS, Hyderabad (32001185) | 22-12-2020 (1 st Dose) 19-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | COVID-19 | Unlikely | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 39 | Sir Ganga Ram Hospital Marg, Rajinder Nagar, New Delhi (32300066) | 19-12-2020 (1 st Dose) 20-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | Fever and body ache | Under Evaluation | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 40 | Aligarh Muslim University, Aligarh (31300560) | 30-11-2020 (1 st Dose) 31-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 27-02-2021) | Hospitalization | Epistaxis | Unrelated | Under Evaluation | Recovered and discharged from the hospital on 27-02-2021 |
| 41 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 03-03-2021) | Hospitalization | Acute exacerbation of COPD | Unrelated | Under Evaluation | Ongoing |
| 42 | AIIMS, New Delhi (30100314) | 26-12-2020 (1 st Dose) 23-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 05-03-2021) | Hospitalization | Cholecystitis | Unlikely | Under Evaluation | Recovered and discharged from the hospital on 02-03-2021 |
| 43 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100476) | 06-01-2021 (1 st Dose) 03-02-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-03-2021 (Date of Awareness: 05-03-2021) | Death | Death | Under Evaluation | Under Evaluation | Fatal |

5. IMMUNOGENICITY

The Immunogenicity assessment was planned on the subset of the 600 participants who were recruited in the category 3 sites. All the blood samples from these participants were collected on Day 0, Day 28, Day 56 and these samples are being analysed. The immunogenicity data in terms geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer will be submitted to CDSCO.

6. EFFICACY (INTERIM ANALYSIS)

We are considering first 43 RT-PCR (1/3 of 130 as proposed in 1st interim analysis) positive events and analysis has been done by taking data confirmed by sites. Participants who received two doses and not having PD (protocol deviation) are considered in efficacy population. The first interim analysis is based on 43 cases, of which 36 cases of COVID-19 were observed in the placebo group versus 7 cases observed in the BBV152 (COVAXIN[®]) group, resulting in a point estimate of vaccine efficacy of 80.6%.

TABLE 7: EFFICACY of BBV152

| Description | Treatment Arm | | Total (N =24417) |
|---|-----------------------|-----------------------|---------------------|
| | BBV152 (N = 12218) | Placebo (N=12199) | |
| First occurrence of Virologically confirmed (RT-PCR) n (%) | 7(0.057) | 36(0.295) | 43(0.176) |
| VE (%) | 80.6 | | |
| 95% CI | [78.1, 82.7] | | |
| p value | <0.0001 | | |

7. CONCLUSIONS

Phase 3 study is conducted to evaluate the efficacy and safety of the COVAXIN[®] vaccine. A total of 25800 participants were recruited, among these 67.2% were males and 32.8% were females. At-risk population, ages > 60 years (9.4%), participants (<60 Years) with co-morbid conditions (16.7%) were enrolled. COVID-19 seroprevalence was assessed among these 25800 participants at baseline and results reported that 34.3% of the participants were Seropositive.

All the participants were followed up for their safety, 43 SAEs were reported and among these 33 were resolved, 3 were ongoing and 7 deaths were reported. Among 25800 participants first 8000 enrolled participants AEs were recorded. A total of 655 AEs were reported and most of them were mild in severity. All the reported SAEs were not related to the vaccine.

COVAXIN[®] vaccine efficacy was assessed based on the 43 accrued COVID-19 cases and reported that the vaccine efficacy is 81%.

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ANNEXURE-4

INTERIM CLINICAL REPORT - RESTRICTED USE OF COVAXIN[®] UNDER CLINICAL TRIAL MODE

TITLE: Restricted use of COVAXIN[®] under clinical trial mode.

PROTOCOL NO.: Protocol No: BBIL/COVAXIN/2021

VERSION NO.: 4.0; Date: 12-01-2021

PRODUCT DETAILS: Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152),
COVAXIN[™]

SPONSOR: Bharat Biotech International Limited (BBIL),
Genome Valley, Shameerpet, Hyderabad,
Telangana, India.

INITIATION DATE: 16/JAN/2021

DATE OF INTERIM

REPORT: 06/MAR/2021

VERSION: 1.0

PREPARED BY: Medical Affairs Department, Bharat Biotech International
Limited and Sclin Soft technologies Pvt. Ltd.

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Signature Page:

TITLE: Restricted use of COVAXIN[®] under clinical trial mode.

PROTOCOL NO.: Protocol No: BBIL/COVAXIN/2021

VERSION NO.: 4.0; Date: 12-01-2021

We have read this report and conform that, to the best of our knowledge it accurately describes the conduct and results of the trial.

Signature & Date

Dr. V. Krishna Mohan,
Executive Director,
Bharat Biotech International Limited
Genome Valley, Hyderabad, India

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1. INTRODUCTION:

Bharat Biotech International Limited (BBIL) in collaboration with Indian Council of Medical Research (ICMR) has developed an inactivated whole virion COVID-19 vaccine, COVAXIN[®]. The COVAXIN[®] has been evaluated for safety, reactogenicity and immunogenicity in phase 1 and 2 clinical trials and the trial reports were submitted to the Central Drugs Standard Control Organization (CDSCO) India. COVAXIN[®] has been approved under emergency use authorization with permission number MF/BIO/21/000002, dated 03.01.2021, F. No: BIO/MA/20/000103. This permission is given for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, where COVAXIN[®] vaccine will be administered to the vaccine recipients and they will be followed up for safety.

COVAXIN[®] (prepared under Good manufacturing practices, as required under the Drugs and Cosmetics Act, 1940 and the NCDT Rules 2019) has been approved by CDSCO for Restricted Use in Emergency situation in Public Interest as an abundant precaution in Clinical Trial Mode, in India on 3rd January 2021.

2. ROLE OF ICMR:

The scientists of ICMR have played a substantial role in the “Implementation Plan” of Restricted use of COVAXIN[®] under clinical trial mode. Scientists and research associates from the following institutes were involved:

- National Institute of Nutrition, Hyderabad
- ICMR-RMRCNE, Dibrugarh
- ICMR-RIRMS, Patna
- ICMR-National Institute of Malaria Research, New Delhi
- ICMR-NICPR, Noida
- ICMR-NCDIR, Bengaluru
- ICMR-National AIDS Research Institute. Pune
- ICMR-RMRC, Bhubaneswar
- ICMR-DMRC, Jodhpur
- ICMR-National Institute for Research in Tuberculosis, Chennai
- ICMR- RMRC, Gorakhpur

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3. IMPLEMENTATION PLAN – PROCEDURES:

Bharat Biotech along with ICMR has taken approval for the Implementation Plan from the Central Ethic Committee of ICMR and SEC committee of CDSCO. Subsequently, BBIL has sent lakhs of hard copies of Fact Sheets, Informed Consent forms and Information Leaflets to each designated vaccination sites across the country.

1. The Fact sheet in regional language was provided to the vaccine recipient before vaccination and vaccine recipients were given time to read (in case of inability to read – it was read out to him/her by vaccination staff) to understand it. Opportunity was given to the vaccine recipients to ask clarifying questions to the vaccinator. Vaccinator has used the information leaflet to answer the queries raised by the vaccine recipient. Following questions and clarifications, the fact sheet was returned by the vaccine recipients to the vaccinator.
2. If the vaccine recipient agrees to be vaccinated with COVAXIN[®], he/she has to sign an informed consent form (ICF) (in case of inability to write, he/she has put a left thumb impression on the ICF). Only after signing the informed consent, the vaccine recipients were vaccinated with COVAXIN[®].
3. The informed consent is required at the time of first dose only. The separate consent is not required for subsequent dose.

3.1 Vaccination Procedure:

Vaccine recipients were provided information in local language pertaining to the vaccine administration with the help of a Fact Sheet containing details about COVAXIN[®]. On day 01 (Visit 1) and day 28 (Visit 2) recipients were administered with the doses of the COVAXIN[®] via the intramuscular route.

After Day 1 and Day 28 vaccination, Vaccine recipients were given Adverse Event Form to record the adverse events and they were made to remain for at least 30 minutes after vaccination for observation to record any adverse event.

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3.2 Adverse Events and SAEs Collection Procedure:

1. The designated staff has collated the consent forms obtained on the previous day for record keeping. These were files with date of vaccination, session site specifications and planning unit mentioned on it. A team, consisting of about 150 BBIL sales and marketing employees and ICMR employees, was set-up at the regional level to telephonically contact and enquire about the adverse events based on grouping of vaccine recipients as follows:
 - Day 7 after dose 1 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 28 after dose 1 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 7 after dose 2 including symptoms related to Covid-19 and positive RT-PCR test (if any)
 - Day 28 after dose 2, including symptoms related to Covid-19 and positive RT-PCR test (if any)
2. The list of the vaccine recipients was generated on a daily basis with contact numbers.
3. Adverse events and serious adverse events following immunization (AEFI) informed during the aforementioned contacts were recorded application against the respective personnel identified of a vaccine recipient.
4. Grouping of the vaccine recipients in minor, severe and serious adverse event (as the case may be) was done by District Immunization Officer (DIO) on a daily basis. For all serious and severe cases, the Case Report Form (CRF) has been raised for further investigation by District AEFI Committee.
5. In case of any serious adverse events linked to the COVAXIN™ immunization program, the details of the serious adverse events were recorded by the designated Immunization officers or Health care workers of the vaccination site. BBIL has coordinated through email/telephone/other means to coordinate with the Immunization officers/Health care

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workers to get the required details of SAE. Upon receipt of these details, submitted SAE report to DSMB, ICMR Central Ethics Committee CDSCO/DCGI.

6. Causality of all SAEs was assessed by the Immunization officer, BBIL, ICMR Central Ethics Committee.
7. Drug regulators (Drugs Controller General of India, DCGI) has been provided with the collated data for review and assessment on vaccine safety, on a monthly basis.
8. The end point and the final outcome of the aforementioned AEFI monitoring related to COVAXIN was based on the recommendations made by the regulatory authority (DCGI).

A toll-free number and an email, the details of which are in the fact sheet, were assigned at BBIL to answer the queries of vaccine beneficiaries. Numerous queries via telephone and emails were addressed on a daily basis.

4. COVERAGE OF COVAXIN[®]:

As of 05th March 2021, a total of approximately 13.9 lakh doses of COVAXIN[®] have been administered in approximately 13.3 lakh beneficiaries. The beneficiaries included healthcare workers and frontline workers as designated by the Ministry of Health, Government of India. These doses were administered in 18 States across India. A total of 20 Serious Adverse events have been reported in these beneficiaries. The cumulative coverage report of COVAXIN[®] across India, as of 05th March 2021, is given in **Table 1**.

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Table 1: Cumulative Coverage Report of COVAXIN (05.03.2021)

| Cumulative Coverage of COVAXIN | | | | | | | | |
|--------------------------------|----------------|------------------------|--------------|----------------|----------------------|----------|-----------------|----------|
| S.No. | State/UT | Cumulative Achievement | | | AEFI reported | | | |
| | | | | | Severe/Serious AEFIs | | Deaths reported | |
| | | 1st Dose | 2nd Dose | Total | 1st Dose | 2nd Dose | 1st Dose | 2nd Dose |
| 1 | Andhra Pradesh | 74405 | 4219 | 78624 | 0 | 0 | 0 | 0 |
| 2 | Assam | 40772 | 2876 | 43648 | 1 | 0 | 0 | 0 |
| 3 | Bihar | 30777 | 5629 | 36406 | 0 | 0 | 0 | 0 |
| 4 | Delhi | 89743 | 4076 | 93819 | 9 | 0 | 0 | 0 |
| 5 | Gujarat | 222166 | 11096 | 233262 | 1 | 0 | 0 | 0 |
| 6 | Haryana | 37484 | 2619 | 40103 | 0 | 0 | 0 | 0 |
| 7 | Jharkhand | 32333 | 83 | 32416 | 0 | 0 | 0 | 0 |
| 8 | Karnataka | 6169 | 3111 | 9280 | 0 | 0 | 0 | 0 |
| 9 | Kerala | 64003 | 0 | 64003 | 0 | 0 | 0 | 0 |
| 10 | Madhya Pradesh | 123006 | 0 | 123006 | 1 | 0 | 0 | 0 |
| 11 | Maharashtra | 19673 | 2420 | 22093 | 1 | 0 | 0 | 0 |
| 12 | Odisha | 47920 | 12972 | 60892 | 1 | 0 | 0 | 0 |
| 13 | Punjab | 1307 | 0 | 1307 | 0 | 0 | 0 | 0 |
| 14 | Rajasthan | 177407 | 4696 | 182103 | 2 | 0 | 0 | 0 |
| 15 | Tamil Nadu | 13076 | 2411 | 15487 | 3 | 0 | 0 | 0 |
| 16 | Telangana | 48103 | 0 | 48103 | 1 | 0 | 0 | 0 |
| 17 | Uttar Pradesh | 173971 | 5951 | 179922 | 0 | 0 | 0 | 0 |
| 18 | West Bengal | 130175 | 282 | 130457 | 0 | 0 | 0 | 0 |
| Total | | 1332490 | 62441 | 1394931 | 20 | 0 | 0 | 0 |

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5. FOLLOW-UP OF THE BENEFICIARIES:

The list of beneficiaries was generated on a daily basis with contact numbers. A team, consisting of about 150 BBIL sales and marketing employees and ICMR employees, was set-up at the regional level to telephonically contact and enquire about the adverse events. Adverse events and serious adverse events following immunization (AEFI) informed during the calls were recorded application against the respective personnel identified as a beneficiary.

With the best efforts of both BBIL and ICMR teams, we connected with the vaccine beneficiaries. Most of the telephonic calls were not answered and in many cases the phone numbers of the beneficiaries were incorrectly give. The summary of adverse events of enrolled beneficiaries is given in **Table 2**. The State-wise data of beneficiaries is given in **Table 3**.

A total of 20 serious adverse events have been reported in this implementation plan. Despite numerous attempts by BBIL and ICMR, data was not shared by the site immunization officers, and we could collect the data of 11 serious adverse events. The summary of serious adverse events is given in **Table 4**.

Table 2: Summary of Adverse Events of Enrolled Beneficiaries (Available data)

| S. No | Parameter | Total |
|-------|--|-------|
| 1 | Number of Beneficiaries with AEFI in less than 30 mins | 914 |
| 2 | Number of Beneficiaries with AEFI in 7 days | 6835 |
| 3 | Number of Beneficiaries with AEFI in 28 days | 400 |
| 4 | Beneficiaries Hospitalised Due to SAE | 20 |
| 5 | SAE Death | 0 |

*AEFI-Adverse Event following immunization.

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Table 3: State-wise Call-logs of Enrolled Beneficiaries (Available data)

| S.No. | District / State | AEFI In less than 30 Minutes | AEFI Within 7 Days | AEFI Within 28 Days | SAE (Death) |
|--------------|------------------|------------------------------|--------------------|---------------------|-------------|
| 1 | Delhi | 112 | 1366 | 40 | 0 |
| 2 | Rajasthan | 44 | 202 | 18 | 0 |
| 3 | Tamil Nadu | 51 | 1366 | 285 | 0 |
| 4 | Assam | 0 | 595 | 0 | 0 |
| 5 | Orrisa | 0 | 446 | 0 | 0 |
| 6 | West Bengal | 0 | 77 | 0 | 0 |
| 7 | UP | 0 | 431 | 0 | 0 |
| 8 | Bihar | 0 | 445 | 0 | 0 |
| 9 | Jharkhand | 0 | 197 | 0 | 0 |
| 10 | Andhra Pradesh | 0 | 0 | 0 | 0 |
| 11 | Telangana | 1 | 0 | 0 | 0 |
| 12 | Karnataka | 0 | 259 | 21 | 0 |
| 13 | Kerala | 0 | 0 | 0 | 0 |
| 14 | Gujarat | 0 | 82 | 0 | 0 |
| 15 | Maharashtra | 706 | 732 | 36 | 0 |
| 16 | Haryana | 0 | 637 | 0 | 0 |
| 17 | Madhya Pradesh | 0 | 0 | 0 | 0 |
| Total | | 914 | 6835 | 400 | 0 |

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6. SUMMARY OF ADVERSE EVENTS REPORTED (Available data):

- A total of 914 beneficiaries had Adverse event Following immunization within 30 mins.
- A total of 6835 beneficiaries had Adverse event Following immunization within 7 days
- A total of 400 beneficiaries had Adverse event Following immunization within 28 days.
- A total of 20 beneficiaries were hospitalized due to SAEs.

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Table 4: Summary of Serious Adverse Events (Available data)

| S. No | Place of vaccination | Date of administration | Date of occurrence of SAE | Seriousness Criteria | Brief description about the Serious Adverse Event (SAE) | Outcome of the Event | Date of Submission of Initial Report to CDSCO, EC, and Sponsor by the PI | Date of submission report to DSMB |
|-------|----------------------|--------------------------------------|---------------------------|----------------------|---|------------------------------|--|-----------------------------------|
| 1. | New Delhi | 16/01/2021 (1 st Dose) | 19/01/2021 | Hospitalization | A male vaccine recipient of age 42 years was administered with the first-dose of COVAXIN on 16 th January 2021. During the Day 7 follow-up, we came to know that a vaccine recipient who took COVAXIN at ESI Hospital, Basaidarapur, New Delhi has been admitted to the hospital with complaints of weakness on one side of the body (hemiparesis on one side of the body from the 4 th Day onwards) as per the information written on the Adverse Event Form filled by the vaccine recipient. No immediate adverse event(s) was reported within 30 minutes after vaccination. On further telephonic follow-up with the concerned doctor of the hospital, he informed that the power in the limbs are 5/5 and it may not be hemiparesis, but the person has weakness on one side of the body. The details of the hospital records, laboratory reports, and treatment are still awaited from the vaccination centre. | Discharged from the hospital | 25-01-2021 | 25-01-2021 |
| 2. | Tamil Nadu | 09/02/2021 (1 st Dose) | 09/02/2021 | Hospitalization | A female vaccine recipient of age 23 years was administered with the first dose of COVAXIN on 9 th Feb 2021. She was admitted to the hospital within 30 minutes after vaccination with complaints of itching and rashes, treated accordingly, recovered and was discharged from the hospital on 11 th Feb 2021. The details of the events are still awaited from the vaccination center. | Recovered on 11-02-2021 | 18-02-2021 | 18-02-2021 |

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| | | | | | | | | |
|----|------------|--------------------------------------|------------|-----------------|---|---|------------|------------|
| 3. | Tamil Nadu | 17/02/2021 (1 st Dose) | 13/02/2021 | Hospitalization | A female vaccine recipient of age 59 years was vaccinated with the first-dose of COVAXIN on 17 th Jan 2021. She developed fever, and was tested positive for COVID-19 and was admitted to the hospital from 13 th Feb 2021. The details of the events are still awaited from the vaccination center. | Details awaited from the vaccination centre | 22-02-2021 | 22-02-2021 |
| 4. | Gujarat | 13/02/2021 (1 st Dose) | 15/02/2021 | Hospitalization | A male vaccine recipient of age 48 years was administered with the first-dose of COVAXIN on 13 th Feb 2021. He had no immediate adverse events within 30 minutes after vaccination. He was admitted to the hospital from 3 rd day of vaccination with complaints of fever, and diarrhoea, and is being treated in the hospital. The details of the events are still awaited from the vaccination center. | Details awaited from the vaccination centre | 22-02-2021 | 22-02-2021 |
| 5. | Tamil Nadu | 20/02/2021 | 29/02/2021 | Hospitalization | A male vaccine recipient of age 55 years was administered with the first-dose of COVAXIN on 20 Feb 2021. She had no immediate adverse events within 30 minutes after vaccination. He was admitted to the hospital with complaints of Pain for 2days, Upper respiratory tract infection for 3days, Sugar level increased, admitted for COVID positive on 29-01-2021 and discharged on 02-02-2021. The details of the events are still awaited from the vaccination center. | Details awaited from the vaccination centre | 25-02-2021 | 25-02-2021 |
| 6. | Delhi | 01/02/2021 (1 st Dose) | 01/02/2021 | Hospitalization | A Female vaccine recipient was administered with the first dose of COVAXIN on 1 th Feb 2021. She was admitted to the hospital after vaccination with complaints of shivering, unconscious and was discharged within 4 hours from the hospital on 1 st Feb 2021. | Discharged within 4 hours | 05-03-2021 | 05-03-2021 |
| 7. | Delhi | 01/01/2021 (1 st dose) | 20/01/2021 | Hospitalization | A male vaccine recipient was administered with the first dose of COVAXIN on 18 th Jan 2021. He was admitted to the hospital on 20 th Jan 2021 with complaints of precipitation of | Details awaited from the vaccination | 05-03-2021 | 05-03-2021 |

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| | | | | | | | | |
|-----|---------|--------------------------------------|------------|-----------------|---|---|------------|------------|
| | | | | | liver disease for hepatic encephalopathy and Shifted to ICU 25 th Jan 2021. | centre | | |
| 8. | Delhi | 12/02/2021 (1 st dose) | 17/02/2021 | Hospitalization | A male vaccine recipient was administered with the first dose of COVAXIN on 12 Feb 2021. He was admitted to the hospital on 17 Feb 2021 after vaccination with complaints of low BP, Rashes, Fever, Itching Redness of Skin, Weakness, Vertigo, from the hospital on 22 nd Feb 2021. | Details awaited from the vaccination centre | 05-03-2021 | 05-03-2021 |
| 9. | Chennai | 25/02/2021 | 05/03/2021 | Hospitalization | A female vaccine recipient was administered with the first dose of COVAXIN on 25 th Feb 2021. She was admitted to the hospital after vaccination on 5 th Mar 2021 with complaints of pain, fever, body ache and malaise. | Details awaited from the vaccination centre | 05-03-2021 | 05-03-2021 |
| 10. | Delhi | 16/01/2021 | 16/01/2021 | Hospitalization | A 21 year old Male vaccine recipient from Delhi was administered with the first dose of COVAXIN on 16 th Jan 2021. The subject developed an anaphylactic reaction following on 16 th Jan 2021 .Thereafter the subject presented with complaints of rash with predominance on chest and upper back associated with itching. A diagnosis of post vaccination allergic reaction was kept. Steroids were administered along with antihistamines. The subject is now symptomatically better at the time of discharge | Recovered & Discharged | 05-03-2021 | 05-03-2021 |
| 11. | Delhi | 25/01/2021 | 25/01/2021 | Hospitalization | A 41 year female vaccine recipient was administered with the first dose of COVAXIN on 25 th Jan 2021. She had no immediate adverse events within 30 minutes after vaccination. From day 3 onwards developed difficulty in breathing and chest pain admitted to the hospital on 29 th Jan 2021 and discharged on 3 rd Feb 2021. | Recovered & Discharged On 3 rd Feb 2021. | 05-03-2021 | 05-03-2021 |

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7. CONCLUSIONS:

The Restricted use of COVAXIN[®] under clinical trial mode was initiated on 16th Jan 2021. Under this program, a total of more than 13 lakh beneficiaries have been vaccinated with COVAXIN[®].

Despite numerous attempts by BBIL and ICMR, data was not shared in a timely manner by the site immunization officers. A total of 8149 beneficiaries have reported adverse events following immunization. No death cases were reported in the restricted use of COVAXIN[®] under clinical trial mode. In conclusion, the COVAXIN[®] can be considered as a safe vaccine.

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ANNEXURE-5

Neutralization of UK-variant VUI-202012/01 with COVAXIN vaccinated human serum

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Abstract

We performed the plaque reduction neutralization test (PRNT₅₀) using sera collected from the 26 recipients of BBV152/COVAXIN™ against hCoV-19/India/20203522 (UK-variant) and hCoV27 19/India/2020Q111 (heterologous strain). A comparable neutralization activity of the vaccinated individuals sera showed against UK-variant and the heterologous strain with similar efficiency, dispel the uncertainty of possible neutralization escape.

Main text

The rapid surge in SARS-CoV-2 cases due to the Variant of Concern (VOC) 202012/01, also known as lineage B.1.1.7 or 20B/501Y.V1, in the United Kingdom (UK)¹ raised concerns in several countries. Many of these countries had direct flights to and from UK and the variant was associated with high transmissibility. Identification of other variants from South Africa² also initiated a global discussion on the challenges that these new variants could pose to the current vaccine candidates. The genome of the UK-variant has seventeen mutations, eight of which were found in spike receptor-binding domain (RBD) mediating the attachment of the virus to the angiotensin converting enzyme 2 (ACE2) receptor on the surface of human cells.² Therefore, it appeared that the majority of the vaccine candidates, being either recombinant or specifically targeting the single epitope of original D614G ancestral spike sequence, might not be able to generate an efficient immune response against the new variants. Here, we successfully isolated and characterized the hCoV-19/India/20203522 SARS-CoV-2 (VOC) 202012/01 from UK-returnees in India with all signature mutations of the UK-variant.³ Earlier, we have reported development of an inactivated whole-virion SARS-CoV-2 vaccine BBV152 (COVAXIN™), which elicited remarkable neutralizing antibody response in phase I clinical trial against hCoV-19/India/2020770 (homologous), and two heterologous strains from the unclassified cluster namely hCoV-19/India/2020Q111 and hCoV-19/India/2020Q100.⁴ In phase II clinical trial, the vaccine candidate showed noteworthy results with plaque reduction neutralization test (PRNT₅₀). The sero-conversion rate with neutralizing antibodies (NAb) following vaccination with BBV152 was 99.6%.⁵ Here, we present the NAb titers (PRNT₅₀) to underline the efficacy of BBV152 vaccine candidate against SARS-CoV-2 UK-variant and one of the heterologous strains hCoV-19/India/2020Q111 (unclassified cluster)⁶. Sera collected from 38 vaccine

recipients, who received BBV152 vaccine-candidate in phase-II trial⁴ had equivalent NAb titers to hCoV-19/India/2020770 homologous strain and two heterologous strains with the characteristic N501Y substitution of the UK-variant; hCoV-19/India/20203522 (UK strain) as well as hCoV-19/India/2020Q111 (Figure 1 A and B). The median ratio of 50% neutralization of sera was found to be 0.8 when compared with hCoV-19/India/2020770 against mutant hCoV19/India/20203522 (UK strain), and 0.9 while compared with hCoV-19/India/2020Q111. Non parametric Kruskal-Wallis test for the comparison of the PRNT₅₀ values from different groups revealed non-significant difference ($p > 0.05$; Figure1). Andreano E *et al.* reported an escape of the UK-variant with E484K substitution, which was followed by an 11-amino-acid insertion in the NTD N5 loop (248aKTRNKSTSRRE248k) from high NAb in convalescent plasma, which was a serious concern pertaining to the potential efficacy of the vaccines.⁷ Our study evidently highlighted comparable neutralization activity of vaccinated individuals sera against variant as well as heterologous SARS-CoV-2 strains. Importantly, sera from the vaccine recipients could neutralise the UK-variant strains discounting the uncertainty around potential escape. It was reassuring from the PRNT₅₀ data generated in our laboratory that the indigenous BBV152/ COVAXIN™, following its roll out in vaccination program, could be expected to work against the new UK-variant. It is unlikely that the mutation 501Y would be able to dampen the potential benefits of the vaccine in concern.

Acknowledgement

We thank the scientific staff of Maximum Containment Facility, ICMR-NIV, Pune Dr. Dimpal A. Nyayanit, Scientist C and Dr. Deepak Y. Patil, Scientist-B for providing excellent support. Also, authors are thankful to Darpan Phagiwala, Technician C, Prasad Gomade, Data Entry Operator, Diagnostic Virology Group, ICMR-NIV, Pune for excellent technical support.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Author Contributions

PDY and GNS contributed to study design, data collection, data analysis, interpretation, writing and critical review. GRD and RE contributed to data analysis and interpretation, writing and critical review. RRS, NG, VKM and SP contributed to data collection, writing and critical review. PA and BB contributed to writing and critical review of the manuscript.

Conflicts of Interest

The authors declared no competing interest

Financial support

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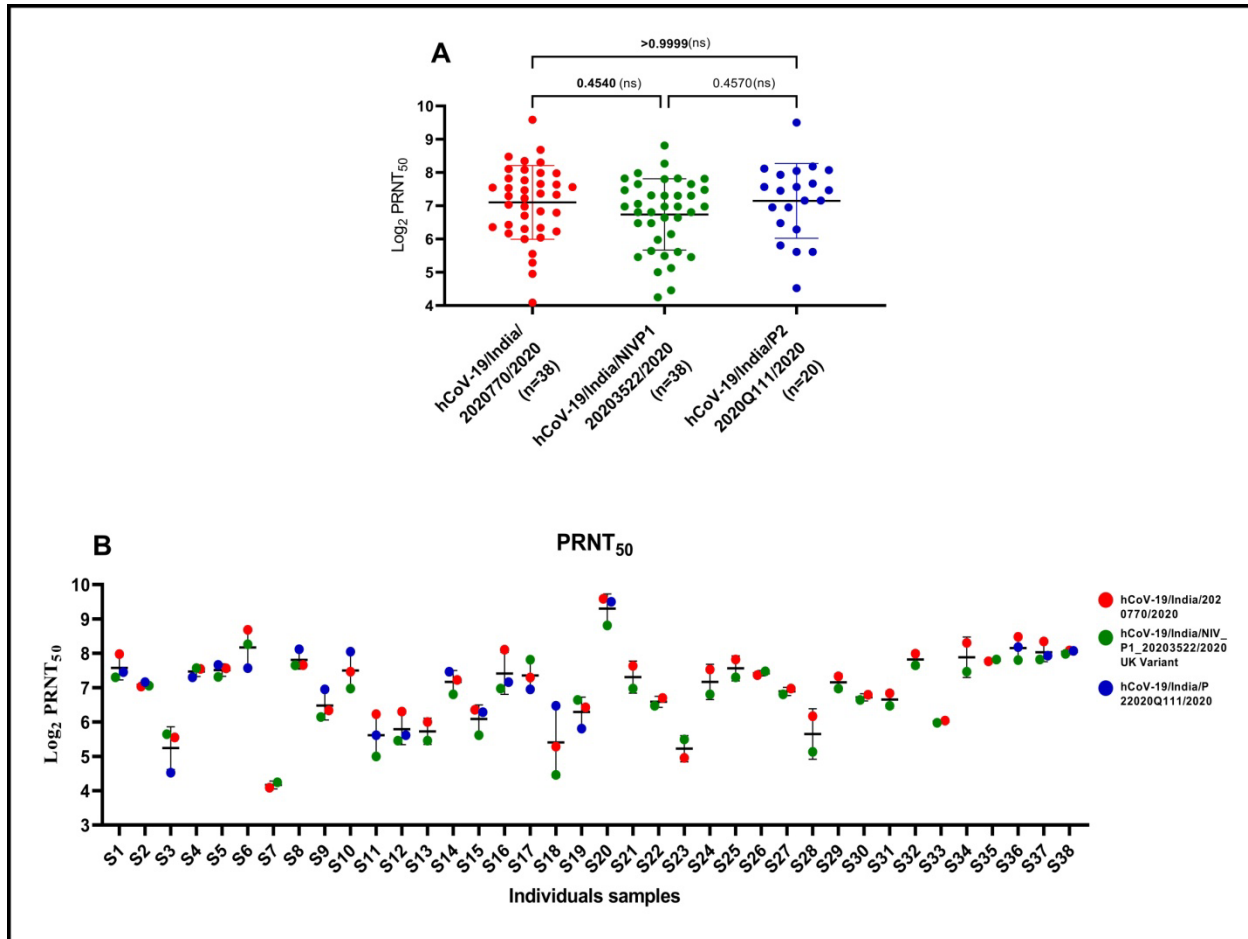


Figure 1: (A) Neutralising antibody response of BBV152/COVAXINTM vaccinated sera against SARS CoV-2 strains: Neutralizing antibody titers (PRNT_{50}) of vaccine's sera against hCoV-19/India/2020770 (homologous), hCoV-19/India/20203522 (heterologous UK strain) and hCoV-19/India/2020Q111 (heterologous unclassified cluster). The bar represents the geometric mean and standard deviation of the respective group titers. Non-parametric Kruskal-Wallis test was used for the comparison of the PRNT_{50} values from different groups. The p-values above 0.05 were considered non-significant and are marked on the figure (ns-non-significant). **(B) Comparison of PRNT_{50} value of each vaccine recipient's sera with three strains of SARS CoV-2:** Neutralizing antibody titers (PRNT_{50}) of each vaccinees' sera against hCoV-19/India/2020770 (homologous), hCoV-19/India/20203522 (heterologous UK strain) and hCoV-

19/India/2020Q111 (heterologous unclassified cluster). The bar represents the mean and standard deviation of the respective sera.

INTEGRATED CLINICAL AND STATISTICAL REPORT

| | |
|--|---|
| Title: | An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age. |
| Protocol Number: | BBIL/BBV152-C/2020 |
| Design: | This is a randomized, double-blind, phase 3 study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above. |
| Phase: | III |
| Version: | 1.0 |
| Sponsor: | Bharat Biotech International Limited (BBIL), Genome Valley, Shameerpet, Hyderabad, Telangana, India. & Indian Council of Medical Research (ICMR), New-Delhi, India |
| Study Initiation Date: | 16 th November 2020 |
| Study Completion Date: | Ongoing |
| Co-ordination Unit (Responsible for Preparation of the Report) Clinical Operations Management Unit | IQVIA & BHARAT BIOTECH INTERNATIONAL LIMITED |

Sponsor Representative: Dr. V. Krishna Mohan
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Tel: +91-11-26589397
Email: guptanivedita.hq@icmr.gov.in

GCP Statement: The trial is being conducted in compliance with the protocol, GCP, Schedule Y (Drugs and Cosmetics Act, 2005) and Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research, 2006)

Date of Report: 05th March 2021

Prepared by: Medical Affairs Department
Bharat Biotech International Limited

Study period (years): 1 Year

Date of 1st Dose 1st Subject: November 16, 2020

Date of 1st Dose last subject: January 8, 2021

Trial Registration: CTRI/2020/11/028976

Signature Page:

Study Title: An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age.

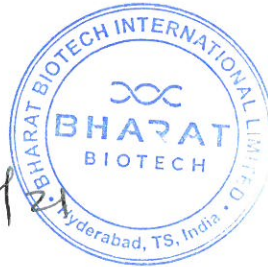
Review and approval of the Integrated Clinical and Statistical report.

We have read this report and confirm that, to the best of our knowledge, it accurately describes the conduct and results of the trial.

Signature & Date



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Title: An Event-Driven, Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Immunogenicity, and Lot-to-Lot consistency of BBV152, a Whole-virion Inactivated SARS-CoV-2 Vaccine in Adults ≥ 18 Years of Age.

Protocol No.: BBIL/BBV152-C/2020

Investigational Vaccine: Whole-Virion Inactivated SARS-CoV-2 vaccine (BBV152B).

Study Population: A total sample size of 25,800 volunteers ages 18 years and above were recruited and administered with vaccine and placebo in 1:1 ratio.

The study was conducted in 25 sites all zone of India.

Study Centres and Investigators:

| S No. | Site Codes | Site Name & Location | Zone |
|-------|------------|---|---------|
| 1 | 308 | MG Medical College, Sri Balaji Vidyapeeth - Dr. PajanivelRanganadin (Pondicherry) | South |
| 2 | 311 | Vydehi institute of medical sciences – Dr. Akshata (Bangalore) | South |
| 3 | 312 | Director of Public Health & Preventive Medicine – Dr. SelvaVinayagam - (Chennai) | South |
| 4 | 317 | Government Fever Hospital, Guntur - Dr. Laxmi Kumari (Guntur) | South |
| 5 | 320 | Nizam's institute of Medical Sciences -Dr. Prabhakar Reddy (Hyderabad) | South |
| 6 | 325 | SRM Hospital & Research Center - Dr. Satyajit Mohapatra (Chennai) | South |
| 7 | 326 | Jeevan Rekha Hospital - Dr Amit Bhate, (Belgaum) | South |
| 8 | 309 | People's University - Dr. Raghavendra Gumashta (Bhopal) | Central |
| 9 | 302 | All India Institute of Medical Sciences – Dr. Chadramani Singh (Patna) | East |
| 10 | 305 | ICMR-National Institute of Cholera and Enteric Diseases - Dr. Suman Kanungo (Kolkata) | East |
| 11 | 318 | (IMS) & SUM Hospital - Dr. E Venkata Rao (Bhubaneswar) | East |
| 12 | 301 | All India Institute of Medical Sciences – Dr. Sanjay Rai (New Delhi) | North |
| 13 | 303 | ESIC Medical College and Hospital – Dr. Anil Pandey (Faridabad) | North |
| 14 | 313 | Aligarh Muslim University - Dr. Md. Shameem (Uttar Pradesh) | North |
| 15 | 321 | PGIMS - Dr. Savita Verma (Rohtak) | North |
| 16 | 323 | Gangaram - Dr Anupam Sachdeva (New Delhi) | North |
| 17 | 324 | Prakhar Hospital – Dr. Jitendra Kushwaha, Kanpur | North |
| 18 | 307 | Lokmanya Tilak Municipal General Hospital-Dr. N.T. Awad (Mumbai) | West |
| 19 | 310 | Rahate Surgical Hospital & ICU - Dr. Manish Multani (Nagpur) | West |
| 20 | 315 | GMERS Medical College and Civil Hospital - Dr. Parul Bhatt (Ahmedabad) | West |
| 21 | 316 | Sir J.J. Group of Hospitals - Dr. PritiMeshram (Mumbai) | West |
| 22 | 322 | Redkar Hospital and Research Centre - Dr. Sagar Redkar (Goa) | West |
| 23 | 327 | Maharaja Agrasen Multi speciality Hospital – Dr. Manish Kumar Jain - (Jaipur) | West |
| 24 | 328 | RCSMGMC & CPR Hospital – Dr. Sunita Jaiprakash Ramanand (Kolhapur) | West |
| 25 | 329 | Prakash Institute of Medical Science & Research – Dr. Vijaykumar Patil (Sangli) | West |

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1. INTRODUCTION

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) has, as on March 05th, 2021, spread to over 216 countries across the globe, with a total of ~115 Million confirmed cases and ~ 2.5 Million deaths. The number of reported SARS-CoV-2 cases in India is also on an increase with ~11 Million confirmed cases and ~157000 deaths(1). Coronaviruses are a severe threat to the humans and other animals, earlier other members of the same family coronaviridae, SARS-CoV infected ~8000 people with a death rate of 10% and another member Middle East Respiratory Syndrome (MERS) virus was outbreaked in the Middle East region and infected ~2000 people with 35% fatality rate(2). Porcine epidemic diarrhea coronavirus (PEDV) has swept throughout the United States of America, causing an almost 100% fatality rate in piglets and wiping out more than 10% of America's pig population in less than a year(2).

Coronaviruses are the enveloped positive-stranded RNA viruses which have the largest genome among all RNA viruses with approximately 27 to 32 kb2. The viral genome is packed inside a helical capsid formed by the nucleocapsid protein (N) which is surrounded by an envelope. SARS-CoV viral envelope is associated with at least three structural proteins: The membrane protein (M) and the envelope protein (E) are involved in virus assembly, whereas the spike protein (S) mediates virus entry into host cells. Among these structural proteins, the spike forms large protrusions from the virus surface, giving coronaviruses the appearance of having crowns(2).

The SARS-CoV-2 virus transmits from person to person mainly through respiratory droplets(3).

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV(4,5). There is local propagation of the virus but a limited innate immune response. At this stage, the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response(6). The symptoms of SARS-CoV-2 infection appear after an incubation period of ~5 days(7). The period from the onset of SARS-CoV-2 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and the status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70(8). The most common symptoms at the onset of SARS-CoV-2 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnoea, and lymphopenia(9).

Till date, no specific treatment was recommended for SARS-CoV-2 infection hence, vaccines are a critical new tool in the battle against COVID-19. Various types of COVID-19 vaccines, such as DNA, RNA- based formulations, Recombinant subunit vaccines containing the viral protein (Spike) epitopes, vector based formulations (eg: Adeno virus) and traditional inactivated vaccines were developed(10-12). Bharat Biotech Int. Ltd., India has developed a whole-virion inactivated Covid-19 vaccine and evaluated for its safety and immunogenicity in a Phase 1 followed by phase 2 study and found that vaccine is safe and immunogenic(13,14). Bharat Biotech has been conducting a phase 3 efficacy study in 25,800 participants to evaluate the efficacy of the vaccine.

2. STUDY DESIGN

The study is an endpoint-driven randomized, double-blind, phase 3 study to evaluate the Efficacy, Safety, and Immunogenicity of BBV152B, a Whole-Virion Inactivated SARS-CoV-2 Vaccine in Volunteers aged 18 years and above.

A total of 25,800 subjects were enrolled across India in 25 sites (3 Categories) and randomized in a 1:1 ratio to receive BBV152B vaccine and control. All participants will be assessed for efficacy and safety endpoints and provide a NP swab and blood sample before the first dose of IP. The NP swab and blood collected will be subject to RT-PCR and Anti-SARS-CoV-2 IgG antibodies. The results of this will not affect enrolment of the participant. Participants who are found to be positive for either RT-PCR or Anti-SARS-CoV-2 IgG antibodies will be excluded from the primary efficacy analysis.

The purpose of this Phase 3 study is to evaluate the protective efficacy, safety, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine, BBV152B. The Phase 3 study will follow randomized study participants for efficacy until virologically confirmed (RT-PCR positive) symptomatic COVID-19 participants will be eligible for the primary efficacy analysis. After reaching the target number (n=130) of symptomatic COVID-19 cases, the study will continue to assess safety until the completion of the study duration.

Case Definition of symptomatic COVID-19

The study is designed to accrue 130 symptomatic COVID-19 cases. This includes any participant who meets any of the two below following criteria:

- Case Definition for Primary Efficacy Symptomatic Endpoint
- Case Definition for Severe Symptomatic COVID-19

Any one of the below mentioned criteria (A or B) must be met, along with a positive SARS-CoV-2 RT-PCR confirmation to be a confirmed symptomatic case

| Criteria A: One or More | | Criteria B: Two or More |
|---|-----|--|
| 1. Shortness of Breath/Difficulty in Breathing 2. New onset Anosmia/Aguesia 3. Oxygen saturation of <94% or escalation by requiring supplemental Oxygen. 4. Pneumonia: diagnosed by chest X ray or CT scan 5. Evidence of Shock 6. ICU Admission/Death | or | 1. Fever 2. Chills 3. New cough 4. Myalgia/Fatigue 5. Headache 6. Sore throat 7. Nausea/Vomiting 8. Diarrhea 9. Congestion/ Runny Nose |
| | AND | |
| Positive SARS-CoV-2 RT-PCR test | | |

SITE CATEGORIES:

Category 1 (Symptomatic): In addition to administering the IP, a series of post-dose telephonic follow-up visits will be scheduled to detect suspect symptomatic COVID-19 infections. If a suspect is identified, a nasopharyngeal sample will be collected from the participant for detecting the presence of COVID-19 infection. Telephonic follow-up will occur at 15 day intervals.

Category 2 (Symptomatic/Asymptomatic): In addition to administering the IP, a series of post-dose Nasopharyngeal samples for detecting incidence of Asymptomatic COVID-19 infection at 1-Month intervals will be collected.

Category 3 (Symptomatic/Asymptomatic+Immunogenicity): In addition to administering the IP, repeated NP swabs for asymptomatic, a series of blood samples will be collected for analyzing serum for immunological assessments.

3. STUDY POPULATION

As per the approved protocol, a total of 25,800 subjects were enrolled and received either vaccine or placebo in 1:1 ratio. Among these 25,800 participants 24,455 were received second dose and detailed site wise enrolled participants, second dose recipients and the participants who were followed up till Day 42 were listed in the Table 1.

TABLE 1: SUMMARY OF ENROLLED SUBJECTS AT EACH SITE

| S No. | Site Name and Location | Subjects completed 1 st dose | Subjects completed 2 nd dose | Subjects Completed follow up (Day 42) |
|--------------------------|---|---|---|---------------------------------------|
| Category 1: Sites | | | | |
| 1 | All India Institute of Medical Sciences - (New Delhi) | 659 | 629 | 629 |
| 2 | All India Institute of Medical Sciences - (Patna) | 1216 | 1137 | 1129 |
| 3 | ESIC Medical College and Hospital - (Faridabad) | 1126 | 1002 | 997 |
| 4 | ICMR-National Institute of Cholera and Enteric Diseases - (Kolkata) | 988 | 969 | 967 |
| 5 | Lokmanya Tilak Municipal General Hospital - (Mumbai) | 197 | 191 | 191 |
| 6 | MG Medical College, Sri Balaji Vidyapeeth - (Pondicherry) | 901 | 868 | 831 |
| 7 | People's University - (Bhopal) | 1725 | 1426 | 1424 |
| 8 | Rahate Surgical Hospital & ICU - (Nagpur) | 1670 | 1594 | 1579 |
| 9 | Vydehi institute of Medical Sciences - (Bangalore) | 496 | 476 | 429 |
| 10 | Director of Public Health & Preventive Medicine - (Chennai) | 29 | 27 | 27 |
| 11 | Gangaram - (New Delhi) | 318 | 276 | 276 |
| 12 | Prakhar Hospital – (Kanpur) | 2250 | 2244 | 2243 |
| 13 | Jeevan Rekha – (Karnataka) | 2227 | 2216 | 2216 |
| 14 | Maharaja Agrasen Multi speciality Hospital - (Jaipur) | 1494 | 1431 | 1124 |
| 15 | Sunita Jaiprakash Ramanand - RCSMGMC & CPR Hospital - (Kolhapur) | 887 | 882 | 737 |
| 16 | Vijaykumar Patil - Prakash Institute of Medical Science & Research - (Sangli) | 611 | 594 | 409 |
| Category 2: Sites | | | | |
| 17 | Aligarh Muslim University - (Uttar Pradesh) | 1008 | 938 | 937 |

| | | | | |
|--------------------------|--|--------------|--------------|--------------|
| 18 | Gmers Medical College and Civil Hospital - (Ahmedabad) | 1081 | 1018 | 1018 |
| 19 | Sir J.J. Group of Hospitals - (Mumbai) | 438 | 379 | 378 |
| 20 | Government Fever Hospital - (Guntur) | 1358 | 1351 | 1350 |
| 21 | (IMS) & SUM Hospital - (Bhubaneswar) | 510 | 495 | 494 |
| 22 | SRM Hospital & Research Center – (Chennai) | 603 | 446 | 404 |
| Category 3: Sites | | | | |
| 23 | Nizam's institute of Medical Sciences - (Hyderabad) | 1998 | 1888 | 1883 |
| 24 | PGIMS - (Rohtak) | 456 | 433 | 433 |
| 25 | Redkar Hospital and Research Centre - (Goa) | 1554 | 1544 | 1544 |
| | Total | 25800 | 24454 | 23649 |

3.1 AT-RISK POPULATION

In this study both healthy volunteers and participants with high risk for Covid-19 who is, either ≥ 60 years of age or < 60 years of age with co-morbid conditions, and HCPs were recruited.

Participants who are < 60 years old will be categorized as at risk for severe COVID-19 illness if they have at least 1 of the following risk factors at Screening:

- Stable chronic lung disease (eg, emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or mild to moderate asthma.
- Stable cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, hypertension, and pulmonary hypertension).
- Severe obesity (body mass index ≥ 35 kg/m²).
- Controlled Diabetes (Type 1, Type 2).
- Stable Liver disease.

Participants who has high risk for Covid-19 were summarized in the Table 2 (>60 Years) and Table 3 (< 60 with Co-morbid condition).

TABLE 2: SUMMARY OF AT RISK PARTICIPANTS

| Description | Treatment Arm | | Total (N = 25,800) n (%) |
|---|---------------------------------|----------------------------------|--------------------------------|
| | BBV152 (N = 12,900) n (%) | Placebo (N= 12, 900) n (%) | |
| At Risk Participants at baseline, Age ≥ 60 years | | | |
| Stable chronic heart disease | 158 (1.22) | 142 (1.10) | 300 (1.16) |
| Stable chronic lung disease | 12 (0.09) | 16 (0.12) | 28 (0.11) |
| Controlled Diabetic | 101 (0.78) | 107 (0.83) | 208 (0.81) |
| Stable Liver Disease | 4 (0.03) | 8 (0.06) | 12 (0.05) |
| Severe obesity (BMI >35) | 2 (0.02) | 2 (0.02) | 4 (0.02) |
| Other stable co-morbid condition | 129 (1.00) | 142 (1.10) | 271 (1.05) |
| None of the above | 32 (0.25) | 28 (0.22) | 60 (0.23) |
| Multiple risk categories* | 245 (1.90) | 296 (2.29) | 541 (2.10) |

* Multiple risk categories count contain for subject selected multiple categories (i.e. more than one)

TABLE 3: SUMMARY OF AT RISK PARTICIPANTS

| Description | Treatment Arm | | Total (N = 25,800) n (%) |
|--|------------------------------|-------------------------------|--------------------------------|
| | BBV152 (N = 12,900) n (%) | Placebo (N= 12, 900) n (%) | |
| At Risk Participants at baseline, Age < 60 years | | | |
| Stable chronic heart disease | 370 (2.87) | 357 (2.77) | 727 (2.82) |
| Stable chronic lung disease | 108 (0.84) | 148 (1.15) | 256 (0.99) |
| Controlled Diabetic | 593 (4.60) | 613 (4.75) | 1206 (4.67) |
| Stable Liver Disease | 17 (0.13) | 17 (0.13) | 34 (0.13) |
| Severe obesity (BMI >35) | 53 (0.41) | 90 (0.70) | 143 (0.55) |
| Other stable co-morbid condition | 613 (4.75) | 676 (5.24) | 1289 (5.00) |
| None of the above | 125 (0.97) | 118 (0.91) | 243 (0.94) |
| Multiple risk categories* | 209 (1.62) | 200 (1.55) | 409 (1.59) |

* Multiple risk categories count contain for subject selected multiple categories (i.e. more than one)

3.2 GENDER AND AGEWISE CLASSIFICATION OF THE PARTICIPANTS:

In the study both the genders were recruited, among 25800 participants 17332 (67.2%) were male and 8468 (32.8%) were female participants. Detailed description of the participants categorized by their age and gender was depicted in the Table 4.

TABLE 4: GENDER AND AGE WISE CLASSIFICATION OF THE PARTICIPANTS

| Gender | ≥18 to ≤50 | ≥51 to ≤60 | ≥61 to above |
|--------|-------------------|-----------------|-----------------|
| Male | 13790 (53.45%) | 2085 (8.08%) | 1457 (5.65%) |
| Female | 6242 (24.19%) | 1250 (4.84%) | 976 (3.78%) |

3.3 INFECTION RATE & SEROPREVALENCE

As per the protocol, all the participants were examined for their status on the Covid-19 infection and seroprevalence at baseline. Nasopharyngeal swab and serum were collected from all the participants and estimated the COVID-19 infection rate and seroprevalence among all the sites across India. The results were reported that 0.82% infection rate and 34.33% of the seroprevalence across the India. Site wise and zone wise seroprevalence and infection rate is depicted in the Table 5.

TABLE 5: INFECTION RATE AND SEROPREVALENCE OF THE COVID-19

| Site Code | Site | RTPCR Tested | RTPCR Positive | Infection Rate (%) | ELISA Samples | Positive | Seroprevalence (%) |
|----------------|----------------------------|--------------|----------------|--------------------|---------------|----------|--------------------|
| NORTH | | | | | | | |
| 301 | AIIMS, Delhi | 658 | 3 | 0.46 | 658 | 293 | 44.53 |
| 303 | ESIC, Faridabad | 1126 | 8 | 0.71 | 1126 | 290 | 25.75 |
| 313 | AMU, Aligarh | 1008 | 20 | 1.98 | 1002 | 311 | 31.04 |
| 321 | PGIMS, Rohtak | 456 | 14 | 3.07 | 456 | 72 | 15.79 |
| 323 | Gangaram, New-Delhi | 319 | 2 | 0.63 | 319 | 107 | 33.54 |
| 324 | PRAKHAR, Kanpur | 2250 | 5 | 0.22 | 2250 | 1031 | 45.82 |
| | | | | 1.18 | | | 32.75 |
| EAST | | | | | | | |
| 302 | AIIMS, Patna | 1216 | 20 | 1.64 | 1216 | 801 | 65.87 |
| 305 | NICED, Kolkata | 989 | 8 | 0.81 | 989 | 264 | 26.69 |
| 318 | IMS, Odisha | 510 | 3 | 0.59 | 510 | 123 | 24.12 |
| | | | | 1.01 | | | 38.89 |
| WEST | | | | | | | |
| 307 | Sion Hospital, Mumbai | 202 | 3 | 1.49 | 197 | 105 | 53.30 |
| 310 | RAHATE, Nagpur | 1672 | 11 | 0.66 | 1672 | 192 | 11.48 |
| 315 | GMERS, Ahmadabad | 1081 | 25 | 2.31 | 1081 | 387 | 35.80 |
| 316 | JJ Hospital, Mumbai | 437 | 5 | 1.14 | 437 | 200 | 45.77 |
| 322 | REDKAR, Goa | 1554 | 1 | 0.06 | 1554 | 497 | 31.98 |
| 326 | Jeevan Rekha, Belgavi | 2227 | 4 | 0.18 | 2227 | 936 | 42.03 |
| 327 | MAMSH, Jaipur | 1494 | 12 | 0.80 | 1494 | 698 | 46.72 |
| 328 | RCSMGMC & CPR, Kolhapur | 887 | 0 | 0.00 | 887 | 248 | 27.96 |
| 329 | PIMSR, Sangli, MH | 611 | 0 | 0.00 | 611 | 198 | 32.41 |
| | | | | 0.74 | | | 36.38 |
| SOUTH | | | | | | | |
| 308 | MGMCR, Pondicherry | 901 | 3 | 0.33 | 901 | 433 | 48.06 |
| 311 | VIMS, Bangalore | 496 | 2 | 0.40 | 496 | 172 | 34.68 |
| 312 | DPH, Chennai | 29 | 1 | 3.45 | 29 | 13 | 44.83 |
| 317 | Guntur, AP | 1358 | 5 | 0.37 | 1358 | 380 | 27.98 |
| 320 | NIMS, Hyderabad | 1998 | 31 | 1.55 | 1998 | 423 | 21.17 |
| 325 | SRM, Chennai | 605 | 0 | 0.00 | 605 | 453 | 74.88 |
| | | | | 1.02 | | | 41.93 |
| CENTRAL | | | | | | | |
| 309 | Peoples University, Bhopal | 1746 | 26 | 1.49 | 1736 | 234 | 13.48 |
| TOTAL | | | | 0.82 | | | 34.33 |

4. SAFETY

There are 25,800 participants were recruited in the study. It is decided to consider all AEs reported till 11 am (IST) March 1, 2021 for first 8000 enrolled participants. All the participants were followed up telephonically for 7 days after each dose of vaccination and reported all the solicited AEs. Unsolicited AEs from all the participants were reported throughout follow-up period (Till Day 42). A total of 655 adverse events were reported and equally distributed in both vaccine and placebo groups. Among these 655 AEs 605 were mild, 34 were moderate and 16 were severe and the severity of the AEs is similar in both the groups. All the AEs except 20 were resolved without sequelae. Detailed AEs list is summarized in the Table 6.

TABLE 6: SUMMARY OF ADVERSE EVENTS

| Description | Treatment Arm | | Total (N=7,865) n (%) |
|---|------------------------------|-------------------------------|-----------------------------|
| | BBV152 (N=4,061) n (%) | Placebo (N=3,804) n (%) | |
| No of Subject with at least one Adverse Event | 335 (8.25) | 300 (7.89) | 635 (8.07) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 99 (2.44) | 94 (2.47) | 193 (2.45) |
| No of Subjects with at least one Local Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 55 (1.35) | 39 (1.03) | 94 (1.20) |
| No of Subjects with at least one Systemic Solicited AE within 7 days after Day 0 Vaccination (1 event not resolved) | 94 (2.31) | 55 (1.45) | 149 (1.89) |
| No of subjects with at least one Systemic Solicited AE within 7 days after Day 28 Vaccination (1 event not resolved) | 30 (0.74) | 23 (0.60) | 53 (No 0.67) |
| No of subjects with at least one Unsolicited Adverse Events | 50(1.23) | 67(1.76) | 117 (1.49) |
| All Ongoing Adverse Events | 9 (0.22) | 11 (0.29) | 20 (0.25) |
| Severity | | | |
| Mild | 317 (7.81) | 288 (7.57) | 605 (7.69) |
| Moderate | 17 (0.42) | 17 (0.45) | 34 (0.43) |
| Severe | 9 (0.22) | 7 (0.18) | 16 (0.20) |

4.1 SERIOUS ADVERSE EVENTS

All the participants (25800) were followed up for serious adverse events (SAEs) and 43 SAEs were reported till date and among those cases 33 were resolved, 3 cases are ongoing and 7 deaths were reported. All the SAEs were not related to the vaccine and distributed equally among the two treatment groups. Detailed description of the SAEs is given in the Table 7.

TABLE 7: SAEs Line Listing

| S. No | Study site (Screening Number) | Date of administration | Date of occurrence of SAE | Seriousness Criteria | Diagnosis of the Event | Causality Assessment by PI | Causality Assessment by Sponsor | Outcome of the Event |
|-------|---|--|---------------------------|----------------------|--|----------------------------|---------------------------------|---|
| 1 | NIMS, Hyderabad (32000107) | 19-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 20-11-2020 | Hospitalization | Road traffic accident (RTA)- Crush Injury left foot and Fracture neck of 2 nd 3 rd and 4 th metatarsal. | Unrelated | Unrelated | Recovered and discharged from hospital on 23 rd Nov 2020. |
| 2 | NIMS, Hyderabad (32000073) | 18-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 29-11-2020 | Hospitalization | Uncontrolled Type-2 Diabetes mellitus with Diabetic ketoacidosis and dyselectrolytemia | Unlikely | Unrelated | Recovered and discharged from hospital on 12 th Dec 2020 |
| 3 | PGIMS, Rohtak (32100001) | 20-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from hospital 30 th Dec 2020 in stable condition |
| 4 | NIMS, Hyderabad (32000428) | 28-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 05-12-2020 | Hospitalization | Shortness of breath, pedal edema and fever (3 days). | Unlikely | Unrelated | Recovered and discharged from hospital 6 th Dec 2020 in stable condition |
| 5 | NIMS, Hyderabad (32000272) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 11 th Dec 2020 in stable condition |
| 6 | NIMS, Hyderabad (32000242) | 25-11-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 10-12-2020 | Hospitalization | COVID-19 | Unlikely | Unrelated | Recovered and discharged from hospital 15 th Dec 2020 in stable condition |
| 7 | Grant Medical College & JJ Hospital, Mumbai (31600192) | 08-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 12-12-2020 | Hospitalization | Homocysteine | Unrelated | Unrelated | Recovered and discharged from hospital in stable condition on 26 th Dec 2020 |
| 8 | SRM Medical College & Hospital, Chennai (32500018) | 07-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 15-12-2020 | Hospitalization | Clinical enteric fever with dehydration. | Unrelated | Unrelated | Recovered and discharged from hospital on 17 th Dec 2020 |
| 9 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900546) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 17-12-2020 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from hospital on 18 th Dec 2020 with advice to follow up for further treatment plan |
| 10 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900809) | 12-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 21-12-2020 | Death | Death | Unrelated | Unrelated | Fatal |
| 11 | MGMCRI-SBV, Puducherry (30800390) | 26-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) | 01-01-2020 | Hospitalization | "Hollow viscus perforation with Acute Kidney Injury -? Cause" | Unrelated | Unrelated | Recovered |

| | | | | | | | | |
|----|---|--|--|-----------------|---|-----------|-----------|--|
| | | 2 nd dose was not administered | | | | | | |
| 12 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30900578) | 10-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 06-01-2021 | Hospitalization | Liver abscess | Unrelated | Unrelated | Recovered and discharged from hospital on 15 th Jan 2021 |
| 13 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore. (31100060) | 09-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-12-2020 (Date of awareness of SAE:06-01-2021) | Hospitalization | Left lung opacity-LRTI | Unrelated | Unrelated | Recovered and discharged from Hospital on 23 rd December 2020 |
| 14 | People's College of medical research center, Bhopal, Madhya Pradesh (30900546) | 10/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 07-01-2021 | Hospitalization | Left non-functioning hydronephrotic kidney | Unrelated | Unrelated | Recovered and discharged from Hospital on 21 st Jan 2021. |
| 15 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901496) | 18-12-2020 (1 st Dose) (Vaccine/Placebo; blinded) 2 nd dose was not administered | 08-01-2021 | Hospitalization | Injury in both the lower limbs (ankle) | Unrelated | Unrelated | Recovered and discharged from Hospital on 19 th Feb 2021. |
| 16 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901257) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 30-12-2020 (Date of awareness of SAE:13/01/2021) | Hospitalization | Mature cataract | Unrelated | Unrelated | Recovered and discharged from hospital on 1 st Jan 2021. |
| 17 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901279) | 16/12/2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 03/01/2021 (Date of awareness of SAE: 13/01/2021) | Hospitalization | CAD with hypertension with B/L Pneumonitis /ACS/TVD. She was also positive with COVID-19. | Unrelated | Unrelated | Recovered and discharged from hospital on 6 th Jan 2021. |
| 18 | People's College of Medical Sciences & Research Centre, Bhopal, Madhya Pradesh (30901436) | 17/12/2020 (1 st Dose) 14/01/2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 15/01/2021 | Hospitalization | Acute cholecystitis and cholelithiasis. | Unrelated | Unrelated | Recovered and discharged from the hospital on 22 -01-2021 |
| 19 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901004) | 14-12-2020 (1 st Dose) 11-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 18-01-2021 | Hospitalization | Renal Calculi with Hepatomegaly. | Unrelated | Unrelated | Recovered and discharged from the hospital on 19-01-2021 |
| 20 | NIMS, Hyderabad (32001145) | 21-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 16-01-2021 (Date of awareness of the SAE:21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 21 | Jawaharlal Nehru Medical college and Hospital, AMU, Aligarh (31300207) | 25-11-2020 (1 st Dose) 24-12-2020 (2 nd dose) (Vaccine/Placebo; Blinded) | 10-01-2021 (Date of awareness of the SAE- 21-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |

| | | | | | | | | |
|----|---|--|--|-----------------|---|-----------|-----------|--|
| 22 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100290) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 11-01-2021 (Date of awareness of the SAE: 14-01-2021) | Hospitalization | Atypical viral pneumonia | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-01-2021 |
| 23 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30901512) | 18-12-2020 (1 st Dose) 20-01-2021 (2 nd dose) (Vaccine/Placebo; Blinded) | 21-01-2021 | Hospitalization | Generalised body pain | Unrelated | Unrelated | Recovered and discharged from the hospital on 25-01-2021 |
| 24 | AIIMS, New Delhi (30100090) | 5-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 22-01-2021 (Date of SAE Awareness: 24-01-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 25 | GMERS Medical College and Civil Hospital, Sola, Ahmedabad (31500928) | 28-12-2020 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 08-01-2021 (Date of awareness of SAE: 27-01-2021) | Death | Death | Unlikely | Unlikely | Fatal |
| 26 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900901) | 13-12-2020 (1 st Dose) 10-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-02-2021 | Hospitalization | Right eye mature cataract and left eye pseudophakia | Unrelated | Unrelated | Recovered and discharged from Hospital on 12 th Feb 2021. |
| 27 | SRM Medical College Hospital & Research Centre, Kanchipuram, Tamil Nadu (32500447) | 28-12-2020 (1 st Dose) 25-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 31-01-2021 (Date of awareness by Sponsor: 01-02-2021) | Death | Death | Unrelated | Unrelated | Fatal |
| 28 | SRM Medical College Hospital & Research Centre Kanchipuram, Tamil Nadu (32500303) | 23-12-2021 (1 st Dose) (Vaccine/Placebo; Blinded) 2 nd dose was not administered | 27-01-2021 (Date of awareness-02-02-2021) | Hospitalization | Viral pneumonia due to COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 9 th Feb 2021 in stable condition |
| 29 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900770) | 12-12-2020 (1 st Dose) 09-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Chronic Otitis media | Unrelated | Unrelated | Recovered and discharged from the hospital on 18-02-2021 |
| 30 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 02-02-2021 | Hospitalization | Bronchial asthma | Unrelated | Unrelated | Recovered and discharged from the hospital on 15-02-2021 |
| 31 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700845) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |
| 32 | Maharaja Agrasen Super speciality Hospital, Jaipur (32700848) | 27-12-2020 (1 st Dose) 24-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 04-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 04-02-2021 |

| | | | | | | | | |
|----|---|--|---|-----------------|----------------------------------|---------------------------------------|------------------|---|
| 33 | AIIMS, New Delhi (30100013) | 27-11-2020 (1 st Dose) 26-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-02-2021 (Date of awareness-06-02-2021) | Hospitalization | Immune Thrombocytopenia Purpura. | Could be associated with the vaccine. | Under Evaluation | Recovered and discharged from the hospital on 08-02-2021 |
| 34 | Director of Public Health & Medicine study site, Chennai (31200001) | 09-12-2020 (1 st Dose) 06-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | COVID-19 | Unrelated | Unrelated | Recovered and discharged from the hospital on 16-02-2021 |
| 35 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900391) | 07-12-2020 (1 st Dose) 05-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 12-02-2021 | Hospitalization | Chronic otitis media | Unrelated | Unrelated | Recovered and discharged from the hospital on 22-02-2021 |
| 36 | Prakash Institute of Medical Science & Research, Sangli, Maharashtra (32900012) | 30-12-2020 (1 st Dose) 26-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 13-02-2021 | Hospitalization | Fever, headache, and cough | Unrelated | Unrelated | Recovered and discharged from the hospital on 14-02-2021 |
| 37 | AIIMS, New Delhi (30100044) | 02-12-2020 (1 st Dose) 30-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 19-02-2021 | Hospitalization | Myocardial infarction (MI) | Unlikely | Unrelated | Recovered and discharged from the hospital on 01-03-2021 |
| 38 | NIMS, Hyderabad (32001185) | 22-12-2020 (1 st Dose) 19-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | COVID-19 | Unlikely | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 39 | Sir Ganga Ram Hospital Marg, Rajinder Nagar, New Delhi (32300066) | 19-12-2020 (1 st Dose) 20-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 25-02-2021) | Hospitalization | Fever and body ache | Under Evaluation | Under Evaluation | Ongoing at the time of submission of the report by the investigator |
| 40 | Aligarh Muslim University, Aligarh (31300560) | 30-11-2020 (1 st Dose) 31-12-2020 (2 nd Dose) (Vaccine/Placebo; Blinded) | 24-02-2021 (Date of awareness: 27-02-2021) | Hospitalization | Epistaxis | Unrelated | Under Evaluation | Recovered and discharged from the hospital on 27-02-2021 |
| 41 | People's College of medical sciences and Research centre, Bhopal, Madhya Pradesh (30900606) | 10-12-2020 (1 st Dose) 07-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 03-03-2021) | Hospitalization | Acute exacerbation of COPD | Unrelated | Under Evaluation | Ongoing |
| 42 | AIIMS, New Delhi (30100314) | 26-12-2020 (1 st Dose) 23-01-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 01-03-2021 (Date of awareness: 05-03-2021) | Hospitalization | Cholecystitis | Unlikely | Under Evaluation | Recovered and discharged from the hospital on 02-03-2021 |
| 43 | Vydehi Institute of Nursing Sciences and Research Centre, Bangalore (31100476) | 06-01-2021 (1 st Dose) 03-02-2021 (2 nd Dose) (Vaccine/Placebo; Blinded) | 03-03-2021 (Date of Awareness: 05-03-2021) | Death | Death | Under Evaluation | Under Evaluation | Fatal |

5. IMMUNOGENICITY

The Immunogenicity assessment was planned on the subset of the 600 participants who were recruited in the category 3 sites. All the blood samples from these participants were collected on Day 0, Day 28, Day 56 and these samples are being analysed. The immunogenicity data in terms geometric mean titers (GMTs) by neutralizing antibody, S-protein, and RBD specific anti-IgG binding titer will be submitted to CDSCO.

6. EFFICACY (INTERIM ANALYSIS)

We are considering first 43 RT-PCR (1/3 of 130 as proposed in 1st interim analysis) positive events and analysis has been done by taking data confirmed by sites. Participants who received two doses and not having PD (protocol deviation) are considered in efficacy population. The first interim analysis is based on 43 cases, of which 36 cases of COVID-19 were observed in the placebo group versus 7 cases observed in the BBV152 (COVAXIN[®]) group, resulting in a point estimate of vaccine efficacy of 80.6%.

TABLE 7: EFFICACY of BBV152

| Description | Treatment Arm | | Total (N =24417) |
|---|-----------------------|-----------------------|---------------------|
| | BBV152 (N = 12218) | Placebo (N=12199) | |
| First occurrence of Virologically confirmed (RT-PCR) n (%) | 7(0.057) | 36(0.295) | 43(0.176) |
| VE (%) | 80.6 | | |
| 95% CI | [78.1, 82.7] | | |
| p value | <0.0001 | | |

7. CONCLUSIONS

Phase 3 study is conducted to evaluate the efficacy and safety of the COVAXIN[®] vaccine. A total of 25800 participants were recruited, among these 67.2% were males and 32.8% were females. At-risk population, ages > 60 years (9.4%), participants (<60 Years) with co-morbid conditions (16.7%) were enrolled. COVID-19 seroprevalence was assessed among these 25800 participants at baseline and results reported that 34.3% of the participants were Seropositive.

All the participants were followed up for their safety, 43 SAEs were reported and among these 33 were resolved, 3 were ongoing and 7 deaths were reported. Among 25800 participants first 8000 enrolled participants AEs were recorded. A total of 655 AEs were reported and most of them were mild in severity. All the reported SAEs were not related to the vaccine.

COVAXIN[®] vaccine efficacy was assessed based on the 43 accrued COVID-19 cases and reported that the vaccine efficacy is 81%.

8. REFERENCES

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DECLARAÇÃO

Importação de vacina contra Covid-19 nos termos da Lei 14.124/21 e RDC/ANVISA 476, de 10 de março de 2021 artigo 12 inciso I

A **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA.**, pessoa jurídica de direito privado, com endereço na Avenida Portugal, n.º 1100, Rua 5, parte A-14, Bairro Itaquí, Cidade de Itapevi, Estado de São Paulo, CEP 06696-060, CNPJ 03.394.819/0005-00, neste ato representada por **Emanuela Batista de Souza Medrades**, brasileira, farmacêutica, portador do RG 35.435.759-1- SSP-SP e CPF 330.976.208-42, considerando o disposto na Resolução de Diretoria Colegiada - RDC nº 476, de 10 de março de 2021, **DECLARA**, sob as penas da lei, **que trata-se de importação de vacina contra a Covid-19 nos termos da Lei 14.124/21 e RDC/ANVISA 476, de 10 de março de 2021, conforme art. 12 inciso I.**


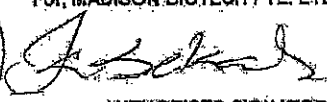
Por ser expressão da verdade, firmamos a presente para que surta os seus efeitos legais.

Brasília/DF, 17 de março de 2021.

EMANUELA BATISTA DE SOUZA MEDRADES
CPF 330.976.208-42
Representante Legal/Técnica

MADISON

Biotech PTE Ltd

| PROFORMA INVOICE | | | | | |
|---|---|---|----------|---|---------------|
| EXPORTER MADISON BIOTECH PTE LIMITED 31 Cantonment Road Singapore -089747 Company Registration No: 202005277E | | No & Date No: MAD/HM/2021/07 19 March 2021 | | Exporter's Ref | |
| | | Buyer's Order No : | | | |
| | | Other Reference(s) | | | |
| CONSIGNEE HEALTH'S MINISTRY (ATN.: DEPTO DE LOGÍSTICA EM SAÚDE – DLOG SADM – SERVIÇO DE ARMAZENAMENTO E DISTRIBUIÇÃO DE MEDICAMENTOS RUA JAMIL JOÃO ZARIF, 684, JARDIM SANTA VICÊNCIA, UNIDADES 11 A 17 E 18A. CEP: 07143-000- MUNICÍPIO DE GUARULHOS | | BUYER HEALTH'S MINISTRY (ATN.: DEPTO DE LOGÍSTICA EM SAÚDE – DLOG SADM – SERVIÇO DE ARMAZENAMENTO E DISTRIBUIÇÃO DE MEDICAMENTOS RUA JAMIL JOÃO ZARIF, 684, JARDIM SANTA VICÊNCIA, UNIDADES 11 A 17 E 18A. CEP: 07143-000- MUNICÍPIO DE GUARULHOS | | | |
| Pre Carriage By | | Place of Receipt By Pre-Carrier | | Country of Origin of Goods INDIA | |
| Vessel / Flight No | | Port of Loading HYDERABAD, INDIA | | Country of Final Destination BRAZIL | |
| Port of Discharge | | Final Destination | | Terms Payment : 100% Advance payment Dispatched by : FCA Hyderabad Dispatch : In the month of April 2021 | |
| | | Currency USD | | | |
| No | PRODUCT | PACK SIZE | Quantity | Unit Price USD | Amount USD |
| 1 | COVAXIN (Whole Virus Inactivated Corona Virus Vaccine) | 5.0ml | 300,000 | 150.00 | 45,000,000.00 |
| | | | | Total: CIF | 45,000,000.00 |
| Amount in Words: USD FORTY FIVE MILLION ONLY. | | | | | |
| Bank name DBS Bank. Address: 12 Marina Boulevard, DBS Asia Central, Marina Bay Financial Centre Tower 3, Singapore 018982. Account number: 0720224590 IFSC Code: DBSSDIN0811 SWIFT Code: DBSSSGSG | | | | | |
| Declaration: We declare that this invoice shows the actual price of the goods described and that all particulars are true and correct | | | | | |
| Accepted For, HEALTH'S MINISTRY | | For, MADISON BIOTECH PTE. LTD. | | | |
| AUTHORISED SIGNATORY | |   AUTHORISED SIGNATORY | | | |

31 Cantonment Road , Singapore - 089747

Recibo Eletrônico de Protocolo - 1379496

Usuário Externo (signatário): William Amorim Santana
IP utilizado: 189.28.128.242
Data e Horário: 22/03/2021 15:22:54
Tipo de Peticionamento: Processo Novo
Número do Processo: 25351.908110/2021-03
Interessados:

MINISTERIO DA SAUDE/DEPARTAMENTO DE LOGISTICA EM SAUDE-DLOG/CGLOG/DIIMP

Protocolos dos Documentos (Número SEI):

- Documento Principal:
- Ofício 62/2021/DLOG/SE/MS 1379489

- Documentos Complementares:
- Estudo Eficácia 1379495
- Documento INVOICE 1379494
- Registro Índia 1379493
- Declaração Empresa Precisa Medicamentos 2 1379492
- Declaração Empresa Precisa Medicamentos 1379491
- Estudo Fase 03 1379490

O Usuário Externo acima identificado foi previamente avisado que o peticionamento importa na aceitação dos termos e condições que regem o processo eletrônico, além do disposto no credenciamento prévio, e na assinatura dos documentos nato-digitais e declaração de que são autênticos os digitalizados, sendo responsável civil, penal e administrativamente pelo uso indevido. Ainda, foi avisado que os níveis de acesso indicados para os documentos estariam condicionados à análise por servidor público, que poderá alterá-los a qualquer momento sem necessidade de prévio aviso, e de que são de sua exclusiva responsabilidade:

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- a observância de que os atos processuais se consideram realizados no dia e hora do recebimento pelo SEI, considerando-se tempestivos os praticados até as 23h59min59s do último dia do prazo, considerado sempre o horário oficial de Brasília, independente do fuso horário em que se encontre;
- a consulta periódica ao SEI, a fim de verificar o recebimento de intimações eletrônicas.

A existência deste Recibo, do processo e dos documentos acima indicados pode ser conferida no Portal na Internet do(a) Agência Nacional de Vigilância Sanitária.

Genome Valley, Turkapally, Shameerpet
Hyderabad-500078, INDIA

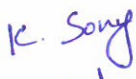

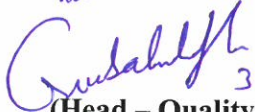
Department: Quality Control

CERTIFICATE OF ANALYSIS

Product : **WHOLE VIRION, INACTIVATED CORONA VIRUS BULK**
Batch Number : 37620001A **A.R. Number** : IP-37-20-047
Batch size : NLT 10 L **Date of Receipt** : 27/10/2020
Mfg. Date : 10/20 **Qty. Sampled** : 102 mL
Exp. Date : To be established **Batch Release Date** : 30/12/2020
Specification No. : FPS306

| TESTS | SPECIFICATIONS | RESULTS |
|--|--|--|
| Identity test for vaccine virus (In-vitro) | ELISA test and SDS PAGE serve as an identity test | Complies |
| Description | Clear colourless, translucent liquid, free from particulate matter | Clear colourless, translucent liquid, free from particulate matter |
| pH | 7.00 - 8.00 | 7.20 |
| Sterility | No growth should be observed (Sterile) | No growth observed |
| Total Protein content (Lowry et al) | NLT 15.00 µg/mL | 154.88 µg/mL |
| Corona virus amplification test | No residual live virus should be observed in Corona virus Amplification test | No residual live virus observed |
| Corona virus inactivation test | No CPE should be observed | No CPE observed |
| Residual cellular DNA Content | NMT 10.00 ng/SHD | 0.02 ng/SHD |
| Residual Bovine serum Albumin content | NMT 50.00 ng/SHD | 2.16 ng/SHD |
| Antigenic purity by SDS-PAGE | Should show only Corona virus specific bands | Complies |
| Bacterial Endotoxin | Less than 25 international Units (IU) per mL | <12.5 IU per mL |
| Residual BPL Content | No Residual BPL Content should be present | No Residual BPL Content present |
| Residual trypsin content by ELISA method | For information only | 0 ng/mL |

OPINION: Sample ~~DOES NOT COMPLY~~ [✓]COMPLIES as per specification No.: FPS306

| | | |
|--|---|--|
| Prepared By:  30/12/2020 | Checked By:  30/12/2020 | Approved By: ^{for}  30/12/2020 (Head - Quality Control) |
|--|---|--|

Genome Valley, Turkapally, Shameerpet
Hyderabad-500078, INDIA

Department: Quality Control

CERTIFICATE OF ANALYSIS

Product : WHOLE VIRION, INACTIVATED CORONA VIRUS BULK

Batch Number : 37620003A

A.R. Number : IP-37-20-049

Batch size : NLT 10 L

Date of Receipt : 28/11/2020

Mfg. Date : 11/20

Qty. Sampled : 102 mL

Exp. Date : To be established

Batch Release Date : 30/12/2020

Specification No. : FPS306

| TESTS | SPECIFICATIONS | RESULTS |
|--|--|--|
| Identity test for vaccine virus (In-vitro) | ELISA test and SDS PAGE serve as an identity test | Complies |
| Description | Clear colourless, translucent liquid, free from particulate matter | Clear colourless, translucent liquid, free from particulate matter |
| pH | 7.00 - 8.00 | 7.41 |
| Sterility | No growth should be observed (Sterile) | No growth observed |
| Total Protein content (Lowry et al) | NLT 15.00 µg/mL | 106.13 µg/mL |
| Corona virus amplification test | No residual live virus should be observed in Corona virus Amplification test | No residual live virus observed |
| Corona virus inactivation test | No CPE should be observed | No CPE observed |
| Residual cellular DNA Content | NMT 10.00 ng/SHD | 0.41 ng/SHD |
| Residual Bovine serum Albumin content | NMT 50.00 ng/SHD | 13.56 ng/SHD |
| Antigenic purity by SDS-PAGE | Should show only Corona virus specific bands | Complies |
| Bacterial Endotoxin | Less than 25 international Units (IU) per mL | <12.5 IU per mL |
| Residual BPL Content | No Residual BPL Content should be present | No Residual BPL Content present |
| Residual trypsin content by ELISA method | For information only | 0 ng/mL |

OPINION: Sample ~~COMPLIES~~ [✓] ~~DOES NOT COMPLY~~ as per specification No.: FPS306

Prepared By:

K. Sanyal
30/12/2020

Checked By:

[Signature]
30/12/2020

Approved By:

[Signature]
30/12/2020
(Head – Quality Control)

L.Dis.No. : 35698/TS/2020

Dated : 06.2020

GMP CERTIFICATE

This is to certify that M/s. Bharat Biotech International Limited, situated at Sy. No. 230, 231 & 235, Genome Valley, Turkapally, Shamirpet Mandal, Medchal-Malkajgiri District - 500 078, Telangana State, India are holding Drug Licence in Form-28D bearing No. **03/HD/AP/98/V/R, Dated:14.10.1998 valid up to 31.12.2021** for the manufacture for sale or distribution of the drugs approved by this Department. The firm is subject to periodical inspection by this Department.

The firm is following **GOOD MANUFACTURING PRACTICES** as stipulated under the provisions of Schedule “M” of Drugs and Cosmetics Rules, 1945.

The firm should however carry out self-inspection from time to time to ensure that the requirements of Good Manufacturing Practices are complied with.

This certificate is valid for one year from the date of issue.

Yours faithfully,



B. Venkateswarlu
Dr. B.VENKATESWARLU
Deputy Director

To,
**M/s. Bharat Biotech International Limited,
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal-Malkajgiri District – 500 078,
Telangana State, India.**

L. Dis.No. 1646/STORES/2020

Date: 28/11/2020

To
M/s. Bharat Biotech International Limited,
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal,
Medchal - Malkajgiri District-500078,
Telangana State, India.

Sir,

Sub: Drugs and Cosmetics Act, 1940 and Rules made thereunder-Issue of World Health Organization G.M.P Certificate - Regarding.

Ref: 1. Your letter dated: 17/03/2020
2. Joint Inspection report dt: 04/03/2020 to 06/03/2020 and further on 08/07/2020 to 10/07/2020.

-X-X-X-X-

With reference to your application cited, I forward herewith **WORLD HEALTH ORGANISATION GOOD MANUFACTURING PRACTICE** Certificate for the products mentioned in the joint Inspection Report of the officers of Drugs Control Administration, Telangana State and CDSO, ZONAL Office, Hyderabad vide reference 2nd cited.

This Certificate is valid for a period of Three years from the date of issue.



Yours faithfully,



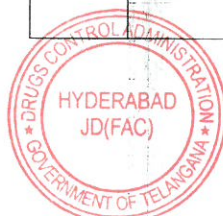
Dr. Y. Naveen Kumar
Joint Director (FAC) & Licensing Authority

L. Dis.No. 1646/STORES/2020

Date: 28/11/2020

**LIST OF PRODUCTS APPROVED UNDER WHO-GMP
CERTIFICATION SCHEME FOR EXPORT PURPOSE**

| | | |
|----------------------------|---|--|
| 1. | Purified Rabies Final Bulk Vaccine BP (For Export Purpose) | |
| | Presentation : 10 L & 20 L Bottles | |
| | Composition: Each 1 mL contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | NLT 4.0 I.U. |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | up to 1 immunizing dose |
| | Human Albumin BP | up to 1 immunizing dose |
| 2. | Typhoid Polysaccharide Final Bulk Vaccine BP (For Export Purpose) | |
| | Presentation : 1 L, 5 L, & 10 L, 20 L Bottles | |
| | Composition: Each 1 mL contains: | |
| | Purified Vi Capsular Polysaccharide of <i>Salmonella typhi</i> Ty2 | 50 µg |
| | Phenol BP | NMT 0.25% w/v |
| | Phosphate Buffered Saline | q.s to 1.0 mL |
| 3. | Poliomyelitis Vaccine, Live (Oral) BP (For Export Purpose) | |
| | Brand Name: BIOPOLIO | |
| | Presentation: 1.0 mL (10-dose) vial & 2.0 mL (20-dose) vial | |
| | Route of Administration: Oral | |
| | Composition: 1 dose = 0.1mL (2 Drops) contains: | |
| | Primary Monkey Kidney Cell Culture-derived | |
| | Poliovirus Type 1 (Sabin) | NLT 10 ^{6.0} CCID ₅₀ |
| | Poliovirus Type 2 (Sabin) | NLT 10 ^{5.0} CCID ₅₀ |
| | Poliovirus Type 3 (Sabin) | NLT 10 ^{5.5} CCID ₅₀ |
| | Stabilized with Magnesium Chloride (MgCl ₂ 1M) | |
| Neomycin Sulphate BP | 15 µg | |
| Kanamycin Acid Sulphate BP | 15 µg | |
| 4. | Monovalent Poliomyelitis Vaccine Type 1 Live (Oral) (For Export Purpose) | |
| | Brand Name : BIOPOLIO M1 | |
| | Presentation: 1.0 mL (10- dose) vial & 2.0 mL (20- dose) vial | |
| | Route of Administration: Oral | |
| | Composition: 1 dose = 0.1 mL (2 Drops) contains: | |
| | Primary Monkey Kidney Cell Culture-derived | |
| | Poliovirus Type 1 (Sabin) | NLT 10 ^{6.0} CCID ₅₀ |
| | Stabilized with Magnesium Chloride (MgCl ₂ 1M) | |
| | Neomycin Sulphate BP | 15 µg |
| Kanamycin Acid Sulphate BP | 15 µg | |
| | Water for Injections BP | q.s to 0.1 mL |



Handwritten signature and date: 28/11/2020

L. Dis.No. 1646/STORES/2020

Date: 28/11/2020

| | | | |
|--|---|----------------------------|--|
| 5. | Poliomyelitis Vaccine Live (ORAL) BP (For Export Purpose) | | |
| | Brand Name : BIOPOLIO | | |
| | Presentation: 1.0 mL (10-dose) vial & 2.0 mL (20-dose) vial | | |
| | Route of Administration: Oral | | |
| | Composition: 1 dose = 0.1mL (2 Drops) contains: | | |
| | MRC-5 Cell Line -derived | | |
| | | Poliovirus Type 1 (Sabin) | NLT 10 ^{6.0} CCID ₅₀ |
| | | Poliovirus Type 2 (Sabin) | NLT 10 ^{5.0} CCID ₅₀ |
| | | Poliovirus Type 3 (Sabin) | NLT 10 ^{5.5} CCID ₅₀ |
| | Stabilized with Magnesium Chloride (MgCl ₂ 1M) | | |
| | | Neomycin Sulphate BP | 15 µg |
| | | Kanamycin Acid Sulphate BP | 15 µg |
| | Water for Injections BP | q.s. to 0.1 mL | |
| 6. | Rabies Vaccine BP (For Export Purpose) | | |
| | Brand Names : INDIRAB & CELLRAB | | |
| | Presentation: Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | | |
| | Route of Administration: Intramuscular | | |
| | Composition: Each dose (0.5mL) of reconstituted vaccine contains: | | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | | |
| | | Potency | ≥ 2.5 IU |
| | | Thiomersal BP | NMT 0.01% w/v |
| | | Maltose NF | upto 1 immunizing dose |
| | | Human Albumin BP | upto 1 immunizing dose |
| 7. | Rabies Vaccine BP (For Export Purpose) | | |
| | Brand Names : INDIRAB & CELLRAB | | |
| | Presentation : Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | | |
| | Route of Administration : Intradermal Injection of 0.1 mL per site & Intramuscular Injection of 0.5 mL | | |
| | Composition: Each dose (0.5mL) of reconstituted vaccine contains: | | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | | |
| | | Potency | ≥ 2.5 IU |
| | | Thiomersal BP | NMT 0.01% w/v |
| | | Maltose NF | upto 1 immunizing dose |
| | | Human Albumin BP | upto 1 immunizing dose |
| Each 0.5 mL Diluent ampoule contains: | | | |
| | Sodium Chloride IP/BP | 1.5 mg | |
| | Water for Injections IP/BP | q.s to 0.5 mL | |

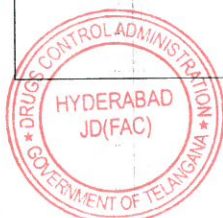


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| 8. | Rabies Vaccine BP (For Export Purpose) | |
| | Presentation : Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | |
| | Route of Administration : Intradermal Injection of 0.1 mL per site & Intramuscular Injection of 0.5 mL | |
| | Composition: Each dose (0.5mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Each 0.5 mL Diluent ampoule contains: | |
| Sodium Chloride IP/BP | 1.5 mg | |
| Water for Injections IP/BP | q.s to 0.5 mL | |
| 9. | Rabies Vaccine BP (For Export Purpose) | |
| | Brand Names : INDIRAB & CELLRAB | |
| | Presentation : Lyophilized Vaccine vial supplied along with 1.0 mL diluent ampoule | |
| | Route of Administration : Intradermal Injection of 0.1 mL per site | |
| | Composition: Each dose (1.0 mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| Each 1.0 mL Diluent ampoule contains: | | |
| Sodium Chloride IP/BP | 3 mg | |
| Water for Injections IP/BP | q.s to 1.0 mL | |
| 10. | Rabies Vaccine BP (For Export Purpose) | |
| | Brand Names : INDIRAB & CELLRAB | |
| | Presentation: Lyophilized Vaccine vial supplied along with 1.0 mL diluent ampoule | |
| | Route of administration: Intramuscular Injection of 1.0 mL per dose or Intradermal Injection of 0.1 mL per site | |
| | Composition: Each dose (1.0 mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| Each 1.0 mL Diluent ampoule contains: | | |
| Sodium Chloride IP/BP | 3 mg | |
| Water for Injections IP/BP | q.s to 1.0 mL | |

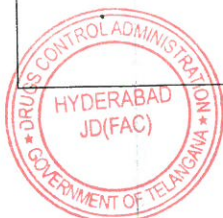


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| 11. | Rabies Vaccine BP (For Export Purpose) | |
| | Brand Name : INDIRAB & CELLRAB | |
| | Presentation: Lyophilized Vaccine vial supplied along with 1.0 mL diluent ampoule | |
| | Route of administration: Intramuscular | |
| | Composition: Each dose (1.0 mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Each 1.0 mL diluent ampoule contains: | |
| Sodium Chloride IP/BP | 3 mg | |
| Water for Injections IP/BP | q.s to 1.0 mL | |
| 12. | Rabies Vaccine BP (Thiomersal-free) (For Export Purpose) | |
| | Brand Name : INDIRAB | |
| | Presentation : Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | |
| | Route of Administration: Intramuscular | |
| | Composition: Each dose (0.5 mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Each 0.5 mL Diluent ampoule contains: | |
| | Sodium Chloride IP/BP | 1.5 mg |
| Water for Injections IP/BP | q.s to 0.5 mL | |
| 13. | Rabies Vaccine BP (Thiomersal-free) (For Export Purpose) | |
| | Presentation : Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose (0.5 mL) of reconstituted vaccine contains: | |
| | Vero Cell derived Purified BPL Inactivated Pitman Moore strain of Rabies Virus | |
| | Potency | ≥ 2.5 IU |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Each 0.5 mL Diluent ampoule contains: | |
| | Sodium Chloride IP/BP | 1.5 mg |
| | Water for Injections IP/BP | q.s to 0.5 mL |



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| 14. | (TEN) HUMAN RABIES VACCINE BP (INDIRAB) LYOPHILIZED VIAL + (TEN) 0.5ML DILUENT + (TEN) 2 ML DISPOSABLE SYRINGE: (MULTICARTON) FOR INTRAMUSCULAR USE (For Export Purpose) | |
| | (a) (Ten) Human Rabies Vaccine BP | |
| | Composition: On Reconstitution each Vial (0.5mL) contains: | |
| | Purified BPL Inactivated Rabies Virus | |
| | Potency | ≥2.5 IU |
| | (Prepared on Vero Cells Pitman Moore strain of Rabies Virus) | |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose NF | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Dosage: 0.5mL (Intramuscular Injection) | |
| | (b) (Ten) Diluent for Reconstitution | |
| | Composition: Each 0.5 mL Diluent ampoule contains: | |
| | Sodium Chloride IP/BP | 1.5mg |
| | Water for Injections IP/BP | 0.5 mL |
| (c) (Ten) 2 mL disposable syringe with 25 gauge needle | | |
| 15. | (TEN) HUMAN RABIES VACCINE BP (INDIRAB) LYOPHILIZED VIAL + (TEN) 1 ML DILUENT + (HUNDRED) 1 ML INSULIN SYRINGE WITH 30 GAUGE NEEDLE: (MULTICARTON) FOR INTRADERMAL USE (For Export Purpose) | |
| | (a) (Ten) Human Rabies Vaccine BP | |
| | Composition: On Reconstitution each Vial (0.5mL) contains: | |
| | Purified BPL Inactivated Rabies Virus | |
| | Potency | ≥2.5 IU |
| | (Prepared on Vero Cells Pitman Moore strain of Rabies Virus) | |
| | Thiomersal BP | NMT 0.01% w/v |
| | Maltose | upto 1 immunizing dose |
| | Human Albumin BP | upto 1 immunizing dose |
| | Dosage: 0.1 mL (Intradermal Injection) | |
| | (b) (Ten) Diluent for Reconstitution | |
| | Composition: Each 1 mL Diluent ampoule contains: | |
| | Sodium Chloride IP/BP | 3.0mg |
| | Water for Injections IP/BP | 1 mL |
| (c) Hundred 1 ML Insulin Syringe with 30 Gauge Needle | | |



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| 16. | ADJUVANTED H1N1 VACCINE (For Export Purpose) | |
| | Brand Name : HN-VAC | |
| | Presentation: 0.5 mL (Single dose) vial & 5.0 mL (Multi dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | MDCK Cell-derived Hemagglutinin Antigen (HA) equivalent of Purified, Inactivated Influenza A (H1N1) Pandemic Virus Bulk [A/California/7/2009/NYMCX-179-A(H1N1) virus] | |
| | Potency | ≥15 µg |
| | Aluminium Hydroxide Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.25 mg |
| | Thiomersal BP | 0.025 mg |
| Phosphate Buffered Saline | q.s to 0.5 mL | |
| 17. | Typhoid Polysaccharide Vaccine BP (For Export Purpose) | |
| | Brand Name : TYPBAR-PFS | |
| | Presentation : 0.5mL (Single dose) in PFS | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | Purified Vi Capsular Polysaccharide of <i>Salmonella typhi</i> Ty2 | 25 µg |
| Phenol BP | NMT 0.25% w/v | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | |
| 18. | Typhoid Vi Conjugate Vaccine (For Export Purpose) | |
| | Brand Name : Typbar TCV | |
| | Presentation: 0.5 mL (Single dose) vial, 2.5 mL (Multi dose) vial & 0.5 mL (Single dose) in PFS | |
| | Route of Administration: Intramuscular | |
| | a) Composition for Single dose presentation in Vial and PFS: | |
| | Each dose of 0.5 mL contains | |
| | Purified Vi Capsular Polysaccharide of <i>Salmonella typhi</i> Ty2 conjugated to Tetanus Toxoid | 25 µg |
| | Sodium Chloride BP | 4.5 mg |
| | Water for Injections BP | q.s. to 0.5 mL |
| | b) Composition for Multi dose presentation in Vial: | |
| | Each dose of 0.5 mL contains | |
| | Purified Vi Capsular Polysaccharide of <i>Salmonella typhi</i> Ty2 conjugated to Tetanus Toxoid | 25 µg |
| Sodium Chloride BP | 4.5 mg | |
| 2-Phenoxyethanol BP | 5.0 mg | |
| Water for Injections BP | q.s. to 0.5 mL | |



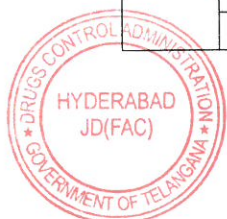
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| 19. | Haemophilus Type b Conjugate Vaccine BP (For Export Purpose) | |
| | Brand Name : BioHib | |
| | Presentation : Lyophilized Vaccine vial supplied along with 0.5 mL diluent ampoule | |
| | Route of Administration : Intramuscular | |
| | Composition : On reconstitution each dose of 0.5mL reconstituted Vaccine contains: | |
| | Purified Capsular polysaccharide of Hib [Covalently bound to 20-40 µg Tetanus Toxoid (PRP-TT)] | 10 µg |
| | Each 0.5 mL Diluent ampoule contains: | |
| Sodium Chloride IP | 4.5 mg (0.9% w/v) | |
| Water for Injections IP | q.s. to 0.5 mL | |
| 20. | Hepatitis B Vaccine (rDNA) BP (For Export Purpose) | |
| | (Pediatric dose) | |
| | Brand Names : Revac-B+ / Revac-B / Hepliv / Heptec-B / Unihep-B* | |
| | Presentation : 0.5mL (Single dose) Vial, 2.5 mL (Multi dose) vial & 5.0 mL (Multi dose) Vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each pediatric dose of 0.5 mL contains: | |
| | Hepatitis B surface Antigen (HBsAg) | ≥ 10 µg |
| Aluminium Hydroxide Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.25 mg | |
| Thiomersal BP | 0.025 mg | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | |
| 21. | Hepatitis B Vaccine (rDNA) BP (For Export Purpose) | |
| | (Adult dose) | |
| | Brand Names : Revac-B+ / Revac-B / Hepliv / Heptec-B / Unihep-B* | |
| | Presentation : 1.0 mL (Single dose) vial & 10.0 mL (Multi dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition : Each adult dose of 1.0 mL contains: | |
| | Hepatitis B surface Antigen (HBsAg) | ≥ 20 µg |
| Aluminium Hydroxide Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.5 mg | |
| Thiomersal BP | 0.05 mg | |
| Phosphate Buffered Saline | q.s to 1.0 mL | |
| 22. | Hepatitis B Vaccine (rDNA) BP (For Export Purpose) | |
| | (Pediatric Dose) (Thiomersal-Free) | |
| | Brand Name : Revac-B mcf | |
| | Presentation: 0.5 mL (Single dose) vial, 0.5 mL PFS | |
| | Route of Administration : Intramuscular | |
| | Composition: Each Pediatric dose of 0.5 mL contains: | |
| | Hepatitis B surface Antigen (HBsAg) | ≥10 µg |
| Aluminium Hydroxide Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.25 mg | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | |

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| 23. | Hepatitis B Vaccine (rDNA) BP (For Export Purpose) (Adult Dose) (Thiomersal-Free) | |
| | Brand Name : Revac-B mcf | |
| | Presentation : 1.0 mL (Single dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each adult dose of 1.0 mL contains: | |
| | Hepatitis B surface Antigen (HBsAg) | ≥ 20 µg |
| | Aluminium Hydroxide Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.5 mg |
| | Phosphate Buffered Saline | q.s. to 1.0 mL |
| 24. | Diphtheria, Tetanus and Pertussis (Whole Cell) Vaccine (Adsorbed) BP (For Export Purpose) | |
| | Brand Name : ComVac3 | |
| | Presentation : 0.5 mL (Single dose) vial, 0.5 mL PFS (Single dose), 2.5 mL (Multi dose) vial & 5.0 mL (Multi dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | Diphtheria Toxoid | ≥ 20 Lf to ≤ 30 Lf (≥30 IU) |
| | Tetanus Toxoid | ≥ 5Lf to ≤ 25Lf (≥ 60 IU) |
| | B. pertussis (Whole Cell Inactivated) | ≥ 4 IU |
| 25. | Adsorbed Diphtheria, Tetanus, Pertussis (whole Cell) and Hepatitis B(rDNA) Vaccine (For Export Purpose) | |
| | Brand Name : ComVac-4 HB | |
| | Presentation : 0.5 mL (Single dose) vial, 2.5 mL (Multi dose) vial & 5.0 mL (Multi dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | Diphtheria Toxoid | ≥ 20 Lf to ≤ 30 Lf (≥ 30 IU) |
| | Tetanus Toxoid | ≥ 5Lf to ≤ 25 Lf (≥ 60 IU) |
| | B. pertussis (Whole Cell Inactivated) | ≥ 4 IU |
| Hepatitis B surface Antigen (HBsAg) | ≥ 10 µg | |
| Aluminium Phosphate Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.3 mg | |
| Thiomersal BP | NMT 0.029 mg | |

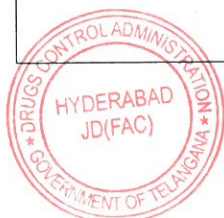


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| 26. | Diphtheria, Tetanus, Pertussis (Whole cell), Hepatitis B (rDNA) and Haemophilus influenzae Type b Conjugate vaccine (Adsorbed) (For Export Purpose) | |
| | Brand Name : Comvac 5 | |
| | Presentation : 0.5 mL (Single dose) vial, 0.5 mL PFS (Single dose), 2.5 mL (Multi dose) vial & 5.0 mL (Multi dose) vial | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | Diphtheria Toxoid | ≥ 20 Lf to ≤ 30 Lf (≥30 IU) |
| | Tetanus Toxoid | ≥ 5 Lf to ≤ 25 Lf (≥ 60 IU) |
| | B. Pertussis (Whole Cell Inactivated) | ≥ 4 IU |
| | Hepatitis B surface Antigen (HBsAg) | ≥10 µg |
| Hib PRP- TT Conjugate | ≥10µg | |
| Aluminium Phosphate Gel equivalent to Aluminium (Al ⁺⁺⁺) | 0.3 mg | |
| Thiomersal BP | NMT 0.029 mg | |
| 27. | Recombinant Human Epidermal Growth Factor Gel (For Export Purpose) | |
| | Brand Name : REGEN-D 10 | |
| | Presentation : 7.5 gm, 15 gm, 30 gm, 60 gm & 150 gm | |
| | Route of Administration : For External Use only | |
| | Composition: Each gram contains: | |
| | Purified Bulk of rh-Epidermal Growth Factor | 10 µg |
| | Sodium Methylparaben BP | 1.8 mg |
| Sodium Propylparaben BP | 0.2 mg | |
| Excipients | q.s | |
| 28. | Japanese Encephalitis Vaccine, Inactivated (Adsorbed, Human) (For Export Purpose) | |
| | Brand Name: JENVAC | |
| | Presentation : 0.5 mL (Single dose) Vial, 2.5 mL (Multi Dose) Vial and 0.5 mL in Pre-Filled Syringe (PFS) | |
| | Route of Administration : Intramuscular | |
| | Composition: Each dose of 0.5 mL contains: | |
| | Vero Cell derived Purified, Inactivated Japanese Encephalitis Virus (JEV strain 821564-XY) Protein | |
| | Potency | NLT 5µg |
| | Aluminium Hydroxide Gel equivalent to Aluminium(Al ⁺⁺⁺) | 0.25 mg |
| Thiomersal BP | 0.025 mg | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | |



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| 29. | Japanese Encephalitis Vaccine Inactivated (Adsorbed, Human) (For Export Purpose) | |
| | Brand Name : JENVAC | |
| | Presentation : 0.5 mL in Pre-Filled Syringe | |
| | Route of Administration : Intramuscular | |
| | Composition : Each dose of 0.5 mL contains: | |
| | Vero Cell derived Purified, Inactivated Japanese Encephalitis Virus (821564-XY) Protein | |
| | Potency | NLT 5.0 µg |
| | Aluminium Hydroxide Gel equivalent to Aluminium(AI ⁺⁺⁺) | 0.25 mg |
| | 2-Phenoxyethanol BP | 2.0mg to 3.0mg |
| Phosphate Buffered Saline | q.s. to 0.5 mL | |
| 30. | DTP+Hib (Combopack) (For Export Purpose) | |
| | DTP- Liquid suspension (0.5mL) | |
| | Hib- Lyophilized Powder Reconstitute Hib component with DTP Vaccine (0.5 mL) | |
| | Brand Name : ComVac 3+ BioHib | |
| | Composition: Each reconstituted dose of 0.5 mL contains: | |
| | a)Diphtheria Toxoid | ≥20 Lf to ≤30 Lf (≥30IU) |
| | Tetanus Toxoid | ≥ 5 Lf to ≤ 25 Lf (≥ 60 IU) |
| | Inactivated <i>B. pertussis</i> (w) | ≥4 IU |
| | Aluminium Phosphate Gel equivalent to Aluminium (AI ⁺⁺⁺) | 0.3 mg |
| | Thiomersal BP | NMT 0.029 mg |
| | b)Lyophilized dose of 0.5mL | |
| Purified Capsular polysaccharide of Hib | 10 µg | |
| [Covalently bound to 20-40 µg Tetanus Toxoid PRP-TT] | | |
| 31. | Typhoid Vi Conjugate Vaccine (For Export Purpose) | |
| | Brand Name : Typbar TCV | |
| | Presentation : 5.0 mL Vial (Multi Dose) | |
| | Route of Administration : Intramuscular (IM) | |
| | Composition : Each dose of 0.5 mL contains: | |
| | Purified Vi Capsular Polysaccharide of <i>S.typhi</i> Ty2 conjugated to Tetanus Toxoid | 25.0 µg |
| | Sodium Chloride BP | 4.5 mg |
| 2-Phenoxyethanol BP (as preservative) | 5.0 mg | |
| Water for Injections BP | q.s. to 0.5 mL | |



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| 32. | SILVER SULFADIAZINE, CHLORHEXIDINE GLUCONATE AND RECOMBINANT HUMAN EPIDERMAL GROWTH FACTOR CREAM (For Export Purpose) | |
| | Brand Names: SLVRGEN & SIMGEN | |
| | Pack Size : 50 gms & 100 gms | |
| | Composition : Each gram of cream contains | |
| | Recombinant Human Epidermal Growth Factor | 10 µg |
| | Silver Sulfadiazine USP | 1% w/w |
| | Chlorhexidine Gluconate USP | 0.2% w/w |
| | Sodium Methylparaben USP | 0.18% w/w |
| Sodium Propylparaben USP | 0.02% w/w | |
| Purified Water USP | q.s | |
| 33. | Rotavirus Vaccine (Live , Oral) BP (For Export Purpose) | |
| | Brand Name: ROTAVAC 5D[®] | |
| | Presentation : 0.5 mL (Single dose) vial and 2.5 mL (Multi dose) vial | |
| | Route of Administration : Oral | |
| | Composition: Each Dose of 0.5 mL (5drops) contains: | |
| | Vero Cell derived Rotavirus 116E Bulk, Live Attenuated | NLT 10 ^{5.0} FFU |
| | Neomycin Sulphate BP | 15 µg |
| | Kanamycin Acid sulphate BP | 15 µg |
| | Sucrose BP | 0.25 gms |
| | Trehalose BP | 2.5 mg |
| | Lactalbumin Hydrolysate (LAH) | 2.5 mg |
| | Human Albumin BP | 0.35 % |
| | Potassium Di hydrogen orthophosphate BP | 1.65 mg |
| Di Potassium hydrogen orthophosphate BP | 10 mg | |
| Tri Sodium Citrate Dihydrate BP | 7.75 mg | |
| Water for Injections BP | q.s | |
| 34. | Rotavirus Vaccine (Live , Oral) BP (For Export Purpose) | |
| | Brand Name: ROTAVAC 5D[®] | |
| | Presentation : 0.5 mL (Single dose) PFS | |
| | Route of Administration : Oral | |
| | Composition: Each Dose of 0.5 mL contains: | |
| | Vero Cell derived Rotavirus 116E Bulk, Live Attenuated | NLT 10 ^{5.0} FFU |
| | Neomycin Sulphate BP | 15 µg |
| | Kanamycin Acid sulphate BP | 15 µg |
| | Sucrose BP | 0.25 gms |
| | Trehalose BP | 2.5 mg |
| | Lactalbumin Hydrolysate (LAH) | 2.5 mg |
| | Human Albumin BP | 0.35 % |
| | Potassium Di hydrogen orthophosphate BP | 1.65 mg |
| Di Potassium hydrogen orthophosphate BP | 10 mg | |
| Tri Sodium Citrate Dihydrate BP | 7.75 mg | |
| Water for Injections BP | q.s | |



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| 35. | Bivalent Poliomyelitis Vaccine Type 1& 3 Live (Oral) (For Export Purpose) | |
| | Brand Name: BIOPOLIO B1/3 | |
| | Presentation: 1.0 mL (10-dose) vial & 2.0 mL (20-dose) vial | |
| | Route of Administration: Oral | |
| | Composition: 1 dose = 0.1 mL (2 Drops) contains: | |
| | Primary Monkey Kidney Cell Culture-derived | |
| | Poliovirus Type 1 (Sabin) | NLT 10 ^{6.0} CCID ₅₀ |
| | Poliovirus Type 3 (Sabin) | NLT 10 ^{5.8} CCID ₅₀ |
| | Stabilized with Magnesium Chloride (MgCl ₂ 1M) | |
| | Neomycin Sulphate BP | 15 µg |
| | Kanamycin Acid Sulphate BP | 15 µg |
| Water for Injections BP | q.s to 0.1 mL | |
| 36. | Monovalent Poliomyelitis Vaccine Type 3 Live (Oral) (For Export Purpose) | |
| | Brand Name: BIOPOLIO M3 | |
| | Presentation: 1.0 mL (10-dose) vial & 2.0 mL (20-dose) vial | |
| | Route of Administration : Oral | |
| | Composition: 1 dose = 0.1 mL (2 Drops) contains: | |
| | Primary Monkey Kidney Cell Culture-derived | |
| | Poliovirus Type 3 (Sabin) | NLT 10 ^{5.8} CCID ₅₀ |
| | Stabilized with Magnesium Chloride (MgCl ₂ 1M) | |
| | Neomycin Sulphate BP | 15 µg |
| | Kanamycin Acid Sulphate BP | 15 µg |
| Water for Injections BP | q.s to 0.1 mL | |

Manufacturer : M/s. Bharat Biotech International Limited,
Sy. No. 230, 231 & 235, Genome Valley,
Turkapally, Shamirpet Mandal, Medchal-
Malkajgiri District-500078, Telangana
State, India.

When applicable : Placing the product on the market as
detailed above

It is certified that the above products had been authorized to be placed on the market for
use in the Country and exporting countries.

Drug Licence No. : 03/HD/AP/98/V/R, dated: 14/10/1998
under Form 28D valid up to 31/12/2021.

It is also certified that (a) the manufacturing plant in which the product is produced is
subject to inspection at suitable intervals.



Handwritten signature and date: 28/11/2020

L. Dis.No. 1646/STORES/2020

Date: 28/11/2020

The Unit M/s. Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Turkapally, Shamirpet Mandal, Medchal-Malkajgiri District-500078, Telangana State, India was inspected jointly by Mrs. L. Suganthi, DI, CDSCO Zonal office, Hyderabad and Mr. G. Prasad, DI, DCA, Hyderabad on 04/03/2020 to 06/03/2020 and further on 08/07/2020 to 10/07/2020.

(b) The manufacturer conforms to requirements for Good Manufacturing Practices in the manufacturer and Quality Control (As recommended by the World Health Organization) in respect of 36 (Thirty-Six) products to be sold or distributed with in the Country or origin (or to be exported).

This Certificate is valid for Three years from the date of issue.




Dr. Y. Naveen Kumar
Joint Director (FAC) & Licensing Authority

Recibo Eletrônico de Protocolo - 1380004

Usuário Externo (signatário): William Amorim Santana
IP utilizado: 189.28.128.242
Data e Horário: 22/03/2021 18:21:15
Tipo de Peticionamento: Intercorrente
Número do Processo: 25351.908110/2021-03
Interessados:

MINISTERIO DA SAUDE/DEPARTAMENTO DE LOGISTICA EM SAUDE-DLOG/CGLOG/DIIMP

Protocolos dos Documentos (Número SEI):

| | |
|--------------------------------------|---------|
| - Laudo Analítico (COA) | 1380000 |
| - Certificado de Boas Práticas | 1380001 |
| - Certificado de Vacinas | 1380002 |
| - Relatório Técnico autoridade Local | 1380003 |

O Usuário Externo acima identificado foi previamente avisado que o peticionamento importa na aceitação dos termos e condições que regem o processo eletrônico, além do disposto no credenciamento prévio, e na assinatura dos documentos nato-digitais e declaração de que são autênticos os digitalizados, sendo responsável civil, penal e administrativamente pelo uso indevido. Ainda, foi avisado que os níveis de acesso indicados para os documentos estariam condicionados à análise por servidor público, que poderá alterá-los a qualquer momento sem necessidade de prévio aviso, e de que são de sua exclusiva responsabilidade:

- a conformidade entre os dados informados e os documentos;
- a conservação dos originais em papel de documentos digitalizados até que decaia o direito de revisão dos atos praticados no processo, para que, caso solicitado, sejam apresentados para qualquer tipo de conferência;
- a realização por meio eletrônico de todos os atos e comunicações processuais com o próprio Usuário Externo ou, por seu intermédio, com a entidade porventura representada;
- a observância de que os atos processuais se consideram realizados no dia e hora do recebimento pelo SEI, considerando-se tempestivos os praticados até as 23h59min59s do último dia do prazo, considerado sempre o horário oficial de Brasília, independente do fuso horário em que se encontra;
- a consulta periódica ao SEI, a fim de verificar o recebimento de intimações eletrônicas.

A existência deste Recibo, do processo e dos documentos acima indicados pode ser conferida no Portal na Internet do(a) Agência Nacional de Vigilância Sanitária.



Gabinete do Diretor-Presidente - Chefe de Gabinete
SIA Trecho 05, Área Especial 57, Brasília/DF, CEP 71.205.05
Telefone: 0800 642 9782 - www.anvisa.gov.br

Ofício nº 643/2021/SEI/GADIP-CG/ANVISA

Ao Senhor
Antônio Elcio Franco Filho
Secretário-Executivo
Secretaria-Executiva do Ministério da Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Com cópia
Ao Senhor
Roberto Ferreira Dias
Diretor do Departamento de Logística em Saúde
Departamento de Logística em Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Assunto: Solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN

Referência: Caso responda este Ofício, indicar expressamente o Processo nº 25351.908110/2021-03.

Senhor Secretário-Executivo,

1. Em atenção ao Ofício Nº 62/2021/DLOG/SE/MS, por meio do qual o Departamento de Logística em Saúde, da Secretaria-Executiva do Ministério da Saúde solicita autorização para importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152, informo que os documentos recebidos foram analisados à luz da RDC nº 476/2021, que “Estabelece os procedimentos e requisitos para submissão de pedido de autorização excepcional e temporária para importação e distribuição de medicamentos e vacinas contra Covid19 para o enfrentamento da emergência de saúde pública de importância nacional decorrente do surto do novo coronavírus (SARS-CoV-2), nos termos da Lei nº 14.124, de 10 de março de 2021”.

2. Após verificação da instrução processual, permanecem pendentes os seguintes documentos:

I - Certificados de liberação dos lotes a serem importados (inciso IV do art. 16 da RDC 476/2021). Foram enviados apenas os laudos analíticos dos lotes 37620001A, 37620002A e 37620003A, restando pendente os certificados de liberação dos respectivos lotes emitidos pelo fabricante;

II - Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz

de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

III - Licenciamento de importação (LI) registrado no SISCOMEX (inciso VI do art. 17 da RDC 476/2021).

3. Quanto aos documentos apresentados, os seguintes esclarecimentos fazem-se necessários:

I - Declaração da Precisa – Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa – Comercialização de Medicamentos Ltda;

II - Declaração da Precisa – Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

III - No *Invoice* apresentado, o quantitativo de doses (3 milhões) não corresponde ao requisitado no Ofício nº 62/2021/DLOG/SE/MS (20 milhões);

IV - O prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. De acordo com as datas de fabricação dos lotes a serem importados, observa-se que o prazo de validade irá expirar nos meses de abril e maio/2021. Solicita-se esclarecer se é possível a utilização de todo o quantitativo previamente à data de expiração dos lotes.

4. Esclareço que, conforme Lei nº 14.124, de 10 de março de 2021, os prazos para decisão da Anvisa estão vinculados com o conteúdo das informações apresentadas. Ademais, o § 3º do art. 17 da RDC 476/2021 estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo até que sejam atendidas.

Atenciosamente,



Documento assinado eletronicamente por **Karin Schuck Hemesath Mendes, Chefe de Gabinete**, em 23/03/2021, às 21:10, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015 http://www.planalto.gov.br/ccivil_03/_Ato2015-2018/2015/Decreto/D8539.htm.



A autenticidade deste documento pode ser conferida no site <https://sei.anvisa.gov.br/autenticidade>, informando o código verificador **1381784** e o código CRC **977A092D**.

Referência: Caso responda este Ofício, indicar expressamente o Processo nº 25351.908110/2021-03

SEI nº 1381784

Daniele Araújo Silva

De: Daniele Araújo Silva
Enviado em: quarta-feira, 24 de março de 2021 12:00
Para: APOIO DA SECRETARIA-EXECUTIVA; 'administrativo.gadip@anvisa.gov.br'
Assunto: RES: Ofício nº 643/2021/SEI/GADIP-CG/ANVISA

Prezados,

Acuso recebimento de e-mail. Informo que o mesmo foi inserido no Sistema Eletrônico de Informação - SEI/MS sob o nº 25000.043170/2021-42 e encaminhado às áreas competentes para providências necessárias.

Att,

Daniele Araújo Silva

Serviço de Análise Técnica Administrativa Gabinete da Secretaria Executiva Esplanada dos Ministérios – Bloco “G”.

CEP: 70058-900 – Brasília DF

(61) 3315-2514 | daniela.araujo@saude.gov.br

-----Mensagem original-----

De: Lisiane Martins Collares <lisiane.collares@saude.gov.br> Em nome de APOIO DA SECRETARIA-EXECUTIVA
Enviada em: quarta-feira, 24 de março de 2021 11:10
Para: Daniele Araújo Silva <daniele.araujo@saude.gov.br>
Cc: APOIO DA SECRETARIA-EXECUTIVA <apoio.se@saude.gov.br>
Assunto: ENC: Ofício nº 643/2021/SEI/GADIP-CG/ANVISA

-----Mensagem original-----

De: ANVISA/Coordenação de Apoio Administrativo <administrativo.gadip@anvisa.gov.br>
Enviada em: terça-feira, 23 de março de 2021 21:17
Para: APOIO DA SECRETARIA-EXECUTIVA <apoio.se@saude.gov.br>
Assunto: Ofício nº 643/2021/SEI/GADIP-CG/ANVISA

Prezados,

Encaminha-se o Ofício nº 643/2021/SEI/GADIP-CG/ANVISA, em atenção ao Ofício Nº 62/2021/DLOG/SE/MS, com solicitação de autorização para importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152.

Por gentileza, solicita-se confirmação de recebimento da presente mensagem e seus anexos.

Atenciosamente,

Coordenação de Apoio Administrativo - Coadi Gabinete do Diretor-Presidente - Gadip Agência Nacional de Vigilância Sanitária - Anvisa
(pco)

IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA.

É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET



Ministério da Saúde
Secretaria Executiva
Gabinete da Secretaria Executiva

DESPACHO

SE/GAB/SE/MS

Brasília, 24 de março de 2021.

Assunto: Solicita autorização para importação, em caráter excepcional, de 20.000.000 (vinte milhões) de doses da vacina COVAXIN.

1. Trata-se do Ofício nº 643/2021/SEI/GADIP-CG/ANVISA (0019715346), de 23/03/2021, oriundo da Agência Nacional de Vigilância Sanitária - Anvisa, que, em atenção ao Ofício nº 62/2021/DLOG/SE/MS (0019668812), informa que, após verificação, permanecem pendentes os seguintes documentos, para avaliação da autorização de importação da vacina COVAXIN:

I - Certificados de liberação dos lotes a serem importados (inciso IV do art. 16 da RDC 476/2021). Foram enviados apenas os laudos analíticos dos lotes 37620001A, 37620002A e 37620003A, restando pendente os certificados de liberação dos respectivos lotes emitidos pelo fabricante;

II - Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

III - Licenciamento de importação (LI) registrado no SISCOMEX (inciso VI do art. 17 da RDC 476/2021).

2. Ressalta-se que, quanto aos documentos apresentados, fazem-se necessários os seguintes esclarecimentos:

I - Declaração da Precisa - Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa - Comercialização de Medicamentos Ltda;

II - Declaração da Precisa - Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

III - No *Invoice* apresentado, o quantitativo de doses (3 milhões) não corresponde ao requisitado no Ofício nº 62/2021/DLOG/SE/MS (20 milhões);

IV - O prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. De acordo com as datas de fabricação dos lotes a serem importados, observa-se que o prazo de validade irá expirar nos meses de abril e maio/2021. Solicita-se esclarecer se é possível a utilização de todo o quantitativo previamente à data de expiração dos lotes.

2. Ao Departamento de Logística em Saúde - **DLOG/SE/MS**, para

conhecimento e demais providências, tendo em vista o § 3º do art. 17 da RDC 476/2021, o qual estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo, até que sejam atendidas.

PAULO MARCOS C. R. DE OLIVEIRA
Chefe de Gabinete



Documento assinado eletronicamente por **Paulo Marcos Castro Rodopiano de Oliveira, Chefe de Gabinete da Secretaria Executiva**, em 25/03/2021, às 16:24, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



A autenticidade deste documento pode ser conferida no site http://sei.saude.gov.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0019715459** e o código CRC **6BF752C7**.

Referência: Processo nº 25000.043170/2021-42

SEI nº 0019715459

MADISON


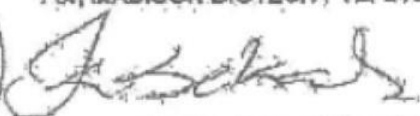
Biotech PTE Ltd

PROFORMA INVOICE

| EXPORTER - EXPORTADOR MADISON BIOTECH PTE LIMITED 31 Cantonment Road Singapore-089747 Cia Registration No 202005277E | | NONo&Date No: MAD/HM/2021/07 19 MARCH 2021 | | Exporte's Ref | |
|---|--|---|-----------------------------|---|----------------------|
| MANUFACTURER – PRODUTOR BHARAT BIOTECH INTERNACIONAL LIMITED ADDRESS: GENOME VALLEY, SHAMEERPET, HYDERABAD, 500 078, TELANGANA, INDIA | | Buyer's Order No: Other Reference(s): CT 29/2021 | | | |
| CONSIGNEE – Consignatário MINISTÉRIO DA SAÚDE DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG CNPJ: 00.394.544/0008-51 ESPLANADA DOS MINISTÉRIOS, BLOCO "G" ANEXO A, 4ª ANDAR, SALA 431 - BRASÍLIA- DF - CEP: 70.310-500 - BRASIL | | BUYER – Comprador MINISTÉRIO DA SAÚDE DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG CNPJ: 00.394.544/0008-51 ESPLANADA DOS MINISTÉRIOS, BLOCO "G" ANEXO A, 4ª ANDAR, SALA 431 - BRASÍLIA- DF - CEP: 70.310-500 - BRASIL | | | |
| Pre Carriage By TBD | Place of Receipt By Pre-Carrier TBD | Country of Origin Of Goods INDIA – AIRPORT OF HYDERABAR (HYD) | | Country of Final Destination BRAZIL – AEROPORTO DE GUARULHOS (GRU) | |
| Vessel / Flight TBD. | Port of Loading HYDERABAD, INDIA | Terms Payment : 100% Advance payment Shipment Terms : CIF GRU Airport BR Dispatch : TBD – First Week of April if LI Approval. Currency USD | | | |
| Airport of Discharge HYD airpor | Final Destination GRU Airport | | | | |
| NO | PRODUCT | PACK SIZE | Quantity <i>In doses</i> | Unit Prince <i>USD</i> | Amount <i>USD</i> |
| 1 | COVAXIN (Whole Virion Inactivated Corona Virus Vaccine) 5 ml vial doses in 300,000 boxes/secondary packages w/ 16 vials/bottles each box. Shelf life – 24 months. NCM 3002.20.29 | 5.0ml Per vial/bottle | 3.000.000 | 15,00 | 45,000,000.00 |
| Shipper Dimensions/Tertiary package with 512 bottles in 586 volumes. Gross Weight/box 28 kg Net Weight/box 16 kg | | | Air Freight | 862,367.02 | |
| | | | Insurance | 67,500.00 | |
| | | | | Total: CIP | 45,929,867.02 |
| Amount in Words: USD FORTY-FIVE MILLION AND NINE HUNDRED AND TWENTY-NINE THOUSAND AND EIGHT HUNDRED AND SIXTY-SEVEN DOLLARS AND TWO CENTS. | | | | | |

MADISON


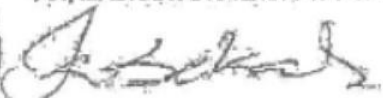
Biotech PTE Ltd

| | |
|---|--|
| <p>Bank name DBS Bank. Address: 12 Marina Boulevard, DBS Asia Central, Marina Bay Financial Centre Tower 3, Singapore 018982. Account number: 0720224590 IFSC Code: DBSSDIN0811 SWIFT Code: DBSSSGSG:</p> | |
| <p>Declaration: We declare that this invoice shows the actual price of the goods described and that all particulars are true and correct</p> | |
| <p>Accepted For, HEALTH'S MINISTRY</p> <p>AUTHORISED SIGNATORY</p> | <p>For, MADISON BIOTECH PTE. LTD.</p>   <p>AUTHORISED SIGNATORY</p> |

MADISON

Biotech PTE Ltd

PACKING LIST / DELIVERY CHALLAN

| | | | |
|--|--------------------------------------|---|--|
| EXPORTER - EXPORTADOR MADISON BIOTECH PTE LIMITED 31 Cantonment Road Singapore-089747 Cia Registration No 202005277E | | NONo&Date No: MAD/HM/2021/07 19 MARCH 2021 | |
| MANUFACTURER – PRODUTOR BHARAT BIOTECH INTERNACIONAL LIMITED ADDRESS: GENOME VALLEY, SHAMEERPET, HYDERABAD, 500 078, TELANGANA, INDIA | | Buyer's Order No: Other Reference(s): CT 29/2021 & PROFORMA INVOICE MAD/HM/2021/07 | |
| CONSIGNEE – Consignatário MINISTÉRIO DA SAÚDE DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG CNPJ: 00.394.544/0008-51 ESPLANADA DOS MINISTÉRIOS, BLOCO "G" ANEXO A, 4ª ANDAR, SALA 431 - BRASÍLIA- DF - CEP: 70.310-500 - BRASIL | | BUYER – Comprador/ Shipped to MINISTÉRIO DA SAÚDE DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG CNPJ: 00.394.544/0008-51 ESPLANADA DOS MINISTÉRIOS, BLOCO "G" ANEXO A, 4ª ANDAR, SALA 431 - BRASÍLIA- DF - CEP: 70.310-500 - BRASIL | |
| Pre Carriage By TBD | Place of Receipt By Pre-Carrier TBD | Country of Origin Of Goods INDIA – AIRPORT OF HYDERABAR (HYD) | Country of Final Destination BRAZIL – AEROPORTO DE GUARULHOS (GRU) |
| Vessel / Flight TBD. | Port of Loading HYDERABAD, INDIA | Terms Payment : 100% Advance payment Shipment Terms : CIF GRU Airport BR Dispatch : TBD – First Week of April if LI Approval. | |
| Airport of Discharge HYD Airport | Final Destination GRU Airport | | |
| COVAXIN – WHOLE VIRION INACTIVATED CORONA VIRUS VACCINE – 5 ml vial doses in 300,00 boxes/secondary packages w/ 16 vials/bottles per box. Remark TBD. | | | |
| BATCH NUMBER: 37F21004A BATCH SIZE: 300,000 VIALS MFG. 01/21. EXP DATE. 01/23. | | | |
| Accepetd For, HEALTH'S MINISTRY AUTHORISED SIGNATORY | | For, MADISON BIOTECH PTE. LTD.   AUTHORISED SIGNATORY | |

Recibo Eletrônico de Protocolo - 1379496

Usuário Externo (signatário): William Amorim Santana
IP utilizado: 189.28.128.242
Data e Horário: 22/03/2021 15:22:54
Tipo de Peticionamento: Processo Novo
Número do Processo: 25351.908110/2021-03
Interessados:

MINISTERIO DA SAUDE/DEPARTAMENTO DE LOGISTICA EM SAUDE-DLOG/CGLOG/DIIMP

Protocolos dos Documentos (Número SEI):

- Documento Principal:
- Ofício 62/2021/DLOG/SE/MS 1379489

- Documentos Complementares:
- Estudo Eficácia 1379495
- Documento INVOICE 1379494
- Registro Índia 1379493
- Declaração Empresa Precisa Medicamentos 2 1379492
- Declaração Empresa Precisa Medicamentos 1379491
- Estudo Fase 03 1379490

O Usuário Externo acima identificado foi previamente avisado que o peticionamento importa na aceitação dos termos e condições que regem o processo eletrônico, além do disposto no credenciamento prévio, e na assinatura dos documentos nato-digitais e declaração de que são autênticos os digitalizados, sendo responsável civil, penal e administrativamente pelo uso indevido. Ainda, foi avisado que os níveis de acesso indicados para os documentos estariam condicionados à análise por servidor público, que poderá alterá-los a qualquer momento sem necessidade de prévio aviso, e de que são de sua exclusiva responsabilidade:

- a conformidade entre os dados informados e os documentos;
- a conservação dos originais em papel de documentos digitalizados até que decaia o direito de revisão dos atos praticados no processo, para que, caso solicitado, sejam apresentados para qualquer tipo de conferência;
- a realização por meio eletrônico de todos os atos e comunicações processuais com o próprio Usuário Externo ou, por seu intermédio, com a entidade porventura representada;
- a observância de que os atos processuais se consideram realizados no dia e hora do recebimento pelo SEI, considerando-se tempestivos os praticados até as 23h59min59s do último dia do prazo, considerado sempre o horário oficial de Brasília, independente do fuso horário em que se encontre;
- a consulta periódica ao SEI, a fim de verificar o recebimento de intimações eletrônicas.

A existência deste Recibo, do processo e dos documentos acima indicados pode ser conferida no Portal na Internet do(a) Agência Nacional de Vigilância Sanitária.



SISCOMEX - Sistema Licenciamento de Importação

Extrato de Licença de Importação

Informações da LI

| | |
|---------------------------------|-----------------------|
| Licenciamento: | 21/0796694-1 |
| Data e Hora do Registro: | 24/03/2021 - 10:09 |
| Data e Hora da Situação: | 24/03/2021 - 10:09:18 |
| Situação: | PARA ANALISE |

Básicas

Importador

| | |
|-----------------------------|---------------------------|
| Tipo do Importador: | Pessoa Jurídica |
| Nome do Importador: | |
| CNPJ: | 00.394.544/0008-51 |
| Razão Social: | MINISTERIO DA SAUDE |
| País: | |
| Atividade Econômica: | |
| Natureza Jurídica: | PODER EXECUTIVO FEDERAL |
| Logradouro: | ESP DOS MINISTERIOS BL. G |
| Complemento: | ANEXO A SALA 420A |
| Número: | 11 |
| Bairro: | ESPL. DOS MINISTERI |
| Cidade/Distrito: | BRASILIA |
| CEP: | 70310500 |
| UF: | DF |
| Telefone: | 061 - 3152425 |

Outras Informações

| | |
|-----------------------------|--|
| País de Procedência: | INDIA |
| URF de Despacho: | AEROPORTO INTERNACIONAL DE SAO PAULO/GUARULHOS |
| URF de Entrada: | AEROPORTO INTERNACIONAL DE SAO PAULO/GUARULHOS |

Informações Complementares

REF: MADISON BIOTECH . NR MAD/HM/2021/07 . CT 29/2021 - 1 PARCELA .

Fornecedor

Exportador

Nome: MADISON BIOTECH PTE LIMITED

E-Mail:

Responsavel:

País de Aquisição: CINGAPURA

Logradouro: CANTONMENT ROAD

Número: 31

Complemento: 089747

Cidade: CINGAPURA

Estado: CINGAPURA

Fabricante/Produtor

Nome: BHARAT BIOTECH INTERNATIONA LIMITED

E-Mail:

Responsavel:

País de Origem: INDIA

Logradouro: GENOME VALLEY, SHAMEERPET

Número: 0

Complemento: 500 078

Cidade: HYDERABAD

Estado: TELANGANA

Mercadoria

Dados Gerais

NCM: 3002.20.29

Descrição da NCM: Outras

Destaque NCM:

Unidade da Medida Estatística: QUILOGRAMA LIQUIDO

NALADI/SH:

Moeda Negociada: DOLAR DOS EUA

INCOTERM: CIP - CARRIAGE AND INSURANCE PAID TO

Condição da Mercadoria

Tipo da Condição da Mercadoria: Nenhuma

Enquadramento Material Usado: Nenhuma

Tipo de Operação: Nenhuma

Detalhes da Mercadoria

Produto 1

| | |
|---|--------------------|
| Unidade Comercializada: | DOSE |
| Peso Líquido Kg: | 16,00000 |
| Qtde. na Unidade Comercializada: | 3.000.000,00000 |
| Qtde. na Medida Estatística: | 16,00000 |
| Valor do Produto no Local de Embarque: | 44.070.132,9800000 |
| Valor Unitário na Condição de Venda: | 15,0000000 |
| Valor do Produto na Condição de Venda: | 45.000.000,0000000 |

Especificação:

VACINA COVAXIN (WHOLE VIRION INACTIVATED CORONA VIRUS VACCINE - 5ml
VIAL DOSES IN 300.000 BOXES) - VACINA DE CORONA VIRUS INATIVADA
VIRION INTEIRA - DOSES DE 5ml EM FRASCO EM 300.000 CAIXAS) . TOTAL DE
3.000.000 DE DOSES . LOTE: 37F21004A . EXP: 01/2023

Totalizadores

| | |
|--|--------------------|
| Qtde.Total na Medida Estatística: | 16,00000 |
| Peso Líquido Total em Kg: | 16,00000 |
| Valor Total no Local do Embarque: | 44.070.132,9800000 |
| Valor Total na Condição de Venda: | 45.000.000,0000000 |

Negociação

Modalidade Drawback:

Acordo Tarifário:

Acordo Aladi:

Regime de Tributação: IMUNIDADE

Fundamentação: UNIÃO, ESTADOS, DF E MUNICÍPIOS; AUTARQUIAS E FUNDS. INSTITUÍDAS

Cobertura Cambial: COM COBERTURA CAMBIAL E PAGAMENTO FINAL A PRAZO DE ATÉ 180

Modalidade de pagamento: FINANCIAMENTO DO FORNECEDOR (SUPPLIER'S CREDIT) - OUTROS

Qtde. Dias Limite pagto:

Instituição Financeira:

Motivo:

LI / Anuências

Informações da LI Vinculada a DI

Declaração Vinculada:

Adição Vinculada:

Retificação:

Informações do Cancelamento/Vencimento da LI

Motivo:

CPF do Imp. que efetuou o cancelamento da LI:

Data do Cancelamento/Vencimento:

Hora do Cancelamento/Vencimento:

Andamento das Anuências

Anuência 1

| | |
|--|--------------|
| <i>Órgão Anuente:</i> | ANVISA |
| <i>Tratam. Administrativo:</i> | MERCADORIA |
| <i>Situação:</i> | PARA ANALISE |
| <i>Data da Situação:</i> | 24/03/2021 |
| <i>Hora da Situação:</i> | 10:09 |
| <i>Validade da Anuência para Embarque:</i> | |
| <i>Validade da Anuência para Despacho:</i> | |
| <i>Diagnóstico do Anuente:</i> | |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|---|--|--|--|
| 1. | <p>Media fill: The media fill activity as per protocol in the month of May 2020 in PA 1 facility. Firm raised a planned deviation (No. PR/SAS/20002) as the Media fill was postponed for the COVID-19 pandemic situation and it will be performed as per the load evaluation due to incorporation of the SARS-CoV-2 vaccine and target date is 31.10.2020. However, media fill is not performed before starting the formulation & filling of Whole Virion, Inactivated Corona Virus vaccine.</p> | <p>As stated in the previous compliance, BBIL would like to confirm that, process of SARS-CoV-2 vaccine aseptic process simulation shall be carried out.</p> | <p>Aseptic Process Simulation Summary report (No: ASR/PS2/002/20/00 dated 07.12.2020) of SARS COY -2 Inactivated purified Whole Virion Viral Vaccine Bulk (Sterilized Media Hold time study for 250 L Bio Reactor & Inactivation Vessels (1x300 L & 2x150 L MVL) is verified. Firm had simulated each stage of the manufacturing process by using SCDM media (B. no: MS220001A). At media preparation stage water quality is tested, Sterility test is verified at Bioprocess stage, Inactivation clarification stage and Sterile filtration. The sterility results comply for all the samples at all the stages. Records verified.</p> <p>Aseptic Process Simulation Interim Summary report (No: ASR/PA1/007/20/00 dated 07.12.2020) of SARS COV-2 Inactivated purified Whole Virion Viral Vaccine was verified. Firm had performed the study by adapting bracketing approach (Minimum and Maximum container closure combination for 0.5 ml single dose and 10 ml multiple dose). Firm has simulated each stage of the manufacturing process by using SCDM media (B. no: MA120001A- 50 L Batch Size & MA120002A- 250 L Batch Size) At excipient preparation stage water quality is tested, Sterility test is verified at Excipient solution preparation stage, Formulation stage, Filling and Sealing stage. The samples are under testing. Reports to be submitted by the firm.</p> | <p>Samples of aseptic process simulation of SARS COV-2 inactivated purified Whole virion viral vaccine for minimum and maximum container closure combination for 0.5 ml single dose and 10 ml multiple dose are under analysis. The results are yet to received.</p> |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|---|-----------------|---|-----------------------------|
| | <p>BBIL Response : BBIL would like to confirm that aseptic process simulation (Media fill) batches for manufacturing & filling process of Whole Virion, Inactivated Corona Virus Vaccine with minimum and maximum container closure of 0.5 mL single dose and 10 mL multiple dose are successfully completed vide Media simulation protocol No. ASP/PA1/007/20/00 . The Aseptic process simulation summary report no.ASR/PA1/007/21/00 dated 16/01/2021 is attached for your reference as Annexure-01.</p> | | | <p>Status:Closed</p> |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|--|---|---|---|
| 4. | <p>Firm verbally stated that TLR 7/8 agonist (used as an adjuvant) is received from Mr. Ramalingaswami fellow (DBT), Assistant Professor, Punjab University, Chandigarh. Firm Molecular weight: 512.33 Daltons. Firm has shown the spectrum of LC-MS/MS which is having only molecular weight of the material without any report. Upon request, firm not shown the purchase order invoice copy, quantity received & certificate of analysis from vendor for TLR 7/8 agonist.</p> | <p>BBIL would like to confirm that, we are procuring the agonist from 3 different vendors, i.e. Virovax (Innovator), Indian Institute of Chemical Technology (IICT) - Hyderabad and Punjab University. Details about these 3 vendors have been provided earlier, in terms of these organizations, professional experience etc. Material received from all the 3 vendors have been characterized by high resolution NMR and LC-MS. The details of the individual Purchase Orders, Proforma Invoice, Goods Receipt Note and CoA (LC-MS data report) are enclosed for each vendor and the same is attached as Annexure-XVIII.</p> | <p>Earlier firm purchased TLR 7/8 agonist from Dr. Deepak Salunke, Asst. Professor, Mr. Ramalingaswami fellow DBT, Punjab University, Chandigarh and he was the student of Dr. Sunil David original inventor of the molecule) is the CEO of Virovax LLC, 4940 Research Parkway KS 66047. During initial stage, firm not maintained Inventory and reconciliation records. After initial purchase, firm not procured from Dr. Deepak Salunke, Asst. Professor, Mr. Ramalingaswami fellow DBT Punjab University Chandigarh.</p> <p>After observation raised by the inspection team dated 8.7.2020 to 10.7.2020 the purchased details, Quantity received, COA, Utilization details are maintained by the firm for the purchased lots from Virovax LLC. Subsequently, firm purchased 3 lots of TLR 7/8 agonist from The Indian Institute of Chemical Technology, Hyderabad on 27.11.2020, 30.11.2020 and 13.12.2020. Materials received from the three vendors have been characterized by using high resolution NMR and LCMS and its details were submitted by the firm to the Authority as a part of Annexure-XVIII dated 02/11/2020.</p> <p>The inventory details and its reconciliation are maintained for the received lots in SAP. The verified details are tabulated in page no: 3 of this report.</p> | <p>Firm is under the process of making Quality Technical agreement with IICT, Hyderabad for supply of TLR 7/8 agonist after testing. The agreement is not submitted by the firm and also SOP QAS/021 "Vendor Qualification" needs to be updated on handling procedures in case the source material is from Government Organization.</p> |


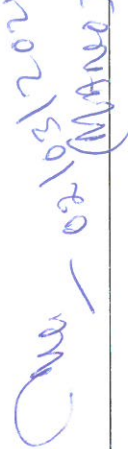
| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|--|-----------------|---|---------|
| | | | <p>Details about TLR 718 agonist vendor used in manufactured batches and batch utilization details are tabulated in page no: 3 & 4 of this inspection report.</p> <p>Based on the CAP A verification comments for inspection dated 18.11.2020, firm ensured the availability of the vendor COA along ", the consignment and upon receipt of the consignment, the inventory has been maintained by the stores department in SAP. All the received consignments had been tested by IICT Hyderabad and also as per SOP QAS/021 "Vendor Qualification" Viro Vax vendor is evaluated and approved by the firm based on Questionnaire and Virtual Audit. As per SOP, Vendor Questionnaire from Viro Vax LLC, 2029</p> <p>Becker Drive, Lawrence, KS 66047 in Form no: FMQAS/021/014.04 and Vendor Audit checklist Form no: FMQAS/0211019.02 received by the firm on 21.12.2020. Virtual Audit was carried by the firm on 22.12.2020. Paper audit and virtual audit carried by the firm found satisfactory which is declared by the firm in their cover letter. The second vendor, Indian Institute of Chemical Technology, Hyderabad is a Government organization. Firm is under the process of making the Quality Technical agreement with IICT for supply of TLR 7/8 agonist after testing.</p> | |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|-------------------------|--|--|---|---------|
| BBIL Response : | <ul style="list-style-type: none"> ➤ BBIL would like to confirm that quality technical agreement between Bharat Biotech & IICT, Hyderabad is placed with effective from 07th Jan 2021. ➤ The copy of Quality Technical agreement No. CTL/CSIR-IICT/2021 is attached as Annexure-02. ➤ BBIL would like to confirm that change control No. CC/QAS/20019 has been initiated on 10/09/2020 for the revision of SOP QAS/025 (i.e. "Approval of Contract Testing Laboratories") to include the below specified instruction applicability in case of qualification & approval of Government Organizations for testing of Quality Control samples. | <ol style="list-style-type: none"> 1. BBIL team shall request to the Government Bodies/Ministry Organizations to provide for their minimal Accredited certificates to further Considerations and approval as part of qualification. 2. BBIL shall request & ensure that government bodies / Ministry Organizations has laid QTA between BBIL for continuity in business, Quality and GLP Systems for the testing of starting material, Intermediate & finished Products which shall not be carried out at site. 3. The Government Bodies/Ministry Organizations shall not be considered for execution of Paper Evaluation and On-site Lab Audit Evaluation. | | |
| TCID:31-Mar-2021 | | | | |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|--|---|---|--|--|
| 5 | As of now, firm prepared four batches of Algel 2(Adjuvant) by using aluminium hydroxide gel and TLR 7/8 agonist in PAI facility which is used for formulation of drug product. After preparation, it is kept on hold more than 48 hrs before usage for formulation of drug product. After preparation, Algel - 2 adjuvant is not tested before usage for manufacturing of drug product. Moreover, firm has not done the hold time study for the prepared algel 2. | BBIL has conducted binding studies of agonist to the Algel and results confirm that there is insignificant amount of the unbound agonist in the supernatant. The results from 1 batch i.e. 40A20006A shows insignificant unbound agonist in the supernatant. The supernatant of the Algel-2 as well as the bound Algel are enclosed to confirm the absence of the agonist in the supernatant. Analytical test reports are attached as Annexure-XIX. Study for Algel- 2 Hold time is under progress and shall be submitted by end of November 2020 | After observation raised, the manufactured Algel-2 preparation B. No. 40A20009A and 40A20010A were collected for complete analysis as per Specification no: IPS058. Description, pH and Sterility are tested In-house and rest of the test (Identification, Total Sulphate, Free Sulphate, Fe (Total), Ash residue, AL(OH)3 Al/ml EDTA Titration, Protein Adsorption capacity are outsourced for Algel-2 preparation B.No. 40A20009A and 40A20010A and reports are yet to be received. Algel-2 (B. No: 40A20008A) hold time study was executed from 15.11.2020. As per protocol 0 day, 7th day, 15th day and 30th day samples were sent to CSIR-IICT, Hyderabad for test/analysis of Algel-2 as per protocol No. SP/37/AGH/20/01 dated 15.10.2020. Report is yet to be received. | Identification, Total Sulphate, Free Sulphate, Fe (Total), Ash residue, AL(OH)3 Al/ml EDTA Titration, Protein Adsorption capacity are outsourced for Algel-2 preparation B.No. 40A20009A and 40A20010A and reports are yet to be received. Hold time study is done with only 1 batch. Algel-2 (B. No: 40A20008A) hold time study 0 day, 7 th day, 15 th day and 30 th day samples were sent to CSIR- IICT, Hyderabad for test/analysis and the reports are not received yet. |
| <p>BBIL Response : BBIL would like to confirm that manufactured Algel -2 B.No.s 40A20009A and 40A20010A are completed testing as per specification No. IPS058. Refer CoA of batches attached as Annexure-03 BBIL would like to confirm that, as per study protocol no. SP/37/AGH/21/01, Algel-2 hold time study has been executed for one batch (B. No.40A20008A) accordingly the study report no. SR/37/AGH/21/01, dated 27/02/2021 has been prepared. The same is attached as Annexure-04. Status: Closed</p> | | | | |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|---|--|---|---------------------|
| 12 | <p>Analytical method validation: The method validation of the drug substance & drug product has been carried out by using rabies vaccine. The firm has not performed method validation using Covid-19 vaccine.</p> | <p>As mentioned in the previous compliance, Method Validation by using Covid-19 Vaccine protocol is under preparation, subject to the completion of the study method validation report would be submitted.</p> | <p>Analytical method validation protocol (No: AMVP/37/04 dated 24.11.2020)for Testing of Protein Adsorption by Spectrophotometer method (Lowry's Method) in Inactivated SARSCOV-2 samples is prepared by the firm and method validation is under process. Tentative date of completion is mentioned by the firm as 15.01.2021.</p> <p>Analytical method validation protocol (No: AMVP/37/06 dated 08.12.2020)for Testing of Protein content in purified Inactivated bulk of SARCOV -2 by Lowry method is prepared by the firm and method validation is under process.</p> <p>Tentative date of completion is mentioned by the firm as 15.01.2021 Analytical method validation protocol (No: AMVP/37/05 dated 24.11.2020)for detection and identification of SARS-COV-2 virus by Elisa method is prepared by the firm and method validation is under process. Tentative date of completion is mentioned by the firm as 15.01.2021 Sterility test: Drug substance protocol number AMVP/37/02 dated 23.11.2020 and Drug product protocol number AMVP/37/03 dated 9.12.2020 prepared and analytical method validation is under execution.</p> <p>BET test: Drug substance and Drug product protocol number AMVP/37/01 dated 09.09.2020 prepared and analytical method validation is under execution.</p> | <p>Not complied</p> |

| Sl. No. | Deficiency reported by joint inspection team dated 8.7.2020 to 10.7.2020 | BBIL Compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---------|--|-----------------|---|---------|
| | <p>BBIL Compliance: As per the protocol No.: AMVP/37/04 dated 24/11/2020 the Protein Adsorption by Spectrophotometer (Lowry's Method) analytical method validation in Inactivated SARS COV-2 is carried out accordingly a summary report no AMVR/VP/37/04 dated 22/01/2021 has been prepared and is attached as Annexure-05.</p> <p>As per the protocol No.: AMVP/37/06 dated 08/12/2020 the Protein content analytical method validation is carried out for purified Inactivated bulk of SARCOV -2 accordingly a summary report no AMVR/VP/37/06 dated 22/01/2021 has been prepared and is attached as Annexure-06.</p> <p>As per the protocol No.: AMVP/37/05 dated 24/11/2020 the detection and identification of SARS-COV-2 virus by ELISA analytical method validation is carried out accordingly a summary report no AMVR/VP/37/05 dated 23/01/2021 has been prepared and is attached as Annexure-07.</p> <p>Drug substance protocol number AMVP/37/02 dated 23/11/2020 and Drug product protocol number AMVP/37/03 dated 09/12/2020 prepared and Sterility test method validation is executed accordingly the summary reports AMVR/VP/37/02 and AMVR/VP/37/03 dated 23/01/2021 and 21/01/2021 has been prepared and is attached as Annexure-08.</p> <p>Drug substance and Drug product protocol no. AMVP/37/01 dated 09/09/2020 prepared and analytical method validation for BET test is executed accordingly the summary reports no. AMVR/VP/37/01 dated 01/01/2021 has been prepared and is attached as Annexure-09.</p> <p>Status: Closed</p> | | | |

| | |
|---|---|
| Prepared By: Dy. Manager - QAS  | Approved By: AGM-QAS  |
| Sign & Date M. KISHORE | Sign & Date 02/03/2021 (MANOJ K SATU) |



| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|--------|---|---|--|--|
| 5. | <p>Firm has performed process validation for manufacturing of SARS-COV-2 Inactivated Purified whole virion viral vaccine bulk at PS2 facility” Batch Size: NLT 1.5 L. However, firm has not performed the process validation for manufacturing of SARS - COV - 2 Inactivated Purified whole virion viral vaccine bulk at proposed commercial scale batch size (output ~ 10 L & ~ 22 L).</p> <p>Firm has not performed the process validation of Whole Virion, Inactivated Corona Virus Vaccine.</p> | <p>BBIL acknowledges the observations.</p> <p>A) Drug substance: As per change control CC/PS2/20009, three Process validation batches of SARS-COV-2 Inactivated Purified whole virion viral vaccine commercial scale with the final output of NLT 10 L has been executed as per Process validation Protocol No. PVP/376/20/03 with batch no. 37620001A, 37620002A & 37620003A. The Process Validation batches are under analysis and the compiled report shall be submitted by End of December 2020.</p> <p>B) Drug product: As per change control nos. CC/PA1/20044 & CC/PA1/20045 Process validation of Whole Virion, Inactivated Corona Virus Vaccine batches have been executed with the formulation Batch size of 50 L & 250 L in different presentations [single dose & multi dose(20 dose)], sequentially under vide Protocol no. PVP/37G/20/01. PV report shall be compiled & submitted to the authority.</p> | <p>PS2 facility: At the present scenario, the manufacturing capacity is NLT 10 L. Firm manufactured 3 batches (batch nos. 37620001A, 37620002A & 37620003A, Batch size: NLT 10 L) vide Protocol No.PVP/376/20/03 dated 19.10.2020. Interim report dated 22.12.2020 submitted is verified. The tests namely Description, pH, Sterility, Total Protein content, Residual cellular DNA content, Residual BSA content, Antigenic purity by SDS - PAGE, BET, Residual BPL content and Residual Trypsin content by Elisa method is completed and the limit comply the specification limit.</p> <p>The other tests namely Identity test for Vaccine Virus, Corona Virus amplification test and Corona Virus Inactivation test is under process in-house.</p> <p>Firm manufactured Whole Virion, Inactivated Corona Virus Bulk 4 batches(37520010A, 37520011A & 37520013A & 37520014A of Batch Size : NLT 1.5 lts between June-July 2020. By using 4 stated batches, 3 formulation of Whole Virion, Inactivated Corona Virus of batch no: 37G20001A, 37G20002A & 37G20003A, Batch Size: 50 L were manufactured by the firm in the month of</p> | <p>As raised by joint inspection team dated 18.11.2020 and firm 19.11.2020, manufactured 3 batches (batch nos. 37620001A,37620002A & 37620003A, batch size:NLT 10 L) for which Identity test for Vaccine Virus, Corona Virus amplification test and Corona Virus In activity on test are under process and results yet to be received.</p> <p>3 formulation of Whole virion, Inactivated Corona Virus of batch no: 37G20001A, 37G20002A & 37G20003A, Batch Size: 50L were manufactured by the firm and</p> |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|---|--|-----------------|---|---|
| | | | <p>December 2020 vide protocol no: <i>PVP/37G/20/01</i> dated 27.11.2020. Finished product 3 batches were tested and completed the test parameters Description, pH, 2-PE content and BET test and the results comply the specification limit. The remaining test namely Protein adsorption test, Residual Bovine Serum Albumin content, Sterility, Residual cellular DNA content Identification, Aluminum content and Extractable volume are under process. Interim report no: <i>IR/PV/37G/20/01</i> dated 22.12.2020 submitted is verified.</p> <p>Protocol no: <i>PVP/37G/20/02</i> for batch size of 250 litre (multidose-20 doses) was initiated on 19.12.2020 and the formulation (3 batches) is under execution.</p> | <p>Protein adsorption test, Residual Bovine Serum Albumin content, Sterility, Residual cellular DNA content, Identification, Aluminum content and Extractable volume are under process and the results are yet to be received. Protocol no: <i>PVP/37G/20/02</i> for batch size of 250 litre (multidose-20 doses) was initiated on 19.12.2020 and the formulation (3 batches) is under execution.</p> |
| <p>BBIL Response: BBIL would like to clarify that, as per process validation protocol no. PVP/376/20/03 the process validation is executed for Whole Virion, Inactivated Corona Virus Bulk Batch nos. 37620001A, 37620002A & 37620003A batch size NLT 10L. The analysis was completed and results are meeting the acceptance criteria. Accordingly the process validation summary report no. PVR/376/21/03 was prepared and approved on dated 05/01/2021. The same is attached as Annexure- 01.</p> | | | | |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
|--------|---|---|--|---|
| | <p>BBIL would like to clarify that, as per process validation protocol no. PVP/37G/20/01 the process validation is executed for Whole Virion, Inactivated Corona Virus Vaccine Batch nos. 37G20001A, 37G20002A & 37G20003A formulation batch size size NLT 50L. The analysis was completed and results are meeting the acceptance criteria. Accordingly the process validation report no. PVR/37G/21/01 was prepared and approved on dated 07/01/2021. The same is attached as Annexure- 02</p> <p>BBIL would like to clarify that, as per process validation protocol no. PVP/37G/20/02 the process validation is executed for Whole Virion, Inactivated Corona Virus Vaccine Batch nos. 37G20004A, 37G20005A & 37G20006A formulation batch size size NLT 250L. The analysis was completed and results are meeting the acceptance criteria. Accordingly the process validation report no. PVR/37G/21/02 was prepared and approved on dated 12/01/2021. The same is attached as Annexure- 03</p> <p>Status : Closed.</p> | | | |
| 6. | <p>Firm has used PS2 facility for manufacturing of Whole virion, inactivated corona virus Drug substance and this facility comprises two separate containment facilities for manufacturing of Type-1, Type-2 and Type-3 Polio Bulks and Whole Virion, Inactivated Corona Virus Vaccine on campaign basis. Cleaning validation not performed for manufacturing of drug substance. Firm has used PA1 facility (multi product facility) for formulation and filling of Whole virion, inactivated corona virus vaccine. Firm has performed cleaning verification of small-scale batches for shared equipment (filling and sealing machine) used in the campaign changeover. Firm has not performed cleaning validation for formulation & filling of commercial scale batches.</p> | <p>BBIL acknowledges the observations.</p> <p>A) Drug substance: BBIL would like to clarify that, PS2 facility was never used for Type II Polio virus. However, for development of sIPV, BBIL used Type I and Type III viruses for product development activity till virus expansion stage only. Post the development campaign following activities in chronological sequence was performed:</p> <ol style="list-style-type: none"> i. Process containers (disposable), support containers, vessels and glassware were decontaminated. ii. Cleaning of facility and equipment with qualified disinfectants. iii. Fogging of Facility (with equipment) using hydrogen peroxide. iv. Activity (ii & iii) was repeated three consecutive times as per campaign change procedure followed by testing | <p>Whole Virion, Inactivated Corona Virus vaccine of batch nos: 37G20001A, 37G20002A & 37G20003A, Batch Size: 50 L were manufactured by the firm in the month of December 2020 and cleaning validation was carried for the stated 3 batches vide protocol no: CVP/37G/20/01 dated 27.11.2020 in PA1 facility. The product residue was estimated by rinse water samples and swab samples. For rinse water the test performed by the firm are namely pH, Conductivity, TOC, Absorbance at 280 nm, BET, Bio-burden and Detection of SARS-CoV-2 spike protein by Elisa method S1 protein of SARS-CoV-2 virus. For swab samples the test performed by the firm are namely Absorbance at 280 nm, Detection of SARS-CoV-2 spike protein by Elisa method S1 protein of SARS-CoV-2 virus and Bioburden. Results are awaited for</p> | <p>Cleaning validation protocol No: CVP/376/20/01 dated 17.12.2020 was prepared for Whole virion, Inactivated Corona Virus bulk and not executed yet Test results for Bio-burden, Detection of SARS-CoV-2 spike protein by Elisa method is yet to be received for cleaning validation carried out for Whole Virion Inactivated Corona</p> |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| | | <p>of residual virus in the facility, equipment and kill tank. The study for residual virus testing concluded satisfactory cleaning and virus was not detected.</p> <p>v. However, BBIL is also considering to perform the Cleaning validation in PS2 facility for the current product i.e. SARS-CoV-2 as per Protocol No. CVP/376/20/01.</p> <p>B) Drug Product: BBIL shall perform the Cleaning validation for the Whole Virion, Inactivated Corona Virus Vaccine for commercial Batch size of 50L as per protocol No. CVP/37G/20/01.</p> | <p>Bioburden, Detection of SARS-CoV -2 spike protein by Elisa method and rest all other test results comply the specification parameters.</p> | <p>Virus vaccine of batch nos: 37G20001A, 37G20002A & 37G20003A, Batch Size: 50 L</p> |
| <p>BBIL Response: Drug substance: As per the cleaning validation protocol no. CVP/376/20/01, the cleaning validation is executed for Whole Virion, Inactivated Corona Virus Bulk B. No.s 37620007A, 37620008A & 37621001A in PS2 facility. Accordingly the cleaning validation report no. CVR/376/21/01 dated 27/02/2021 is prepared. The same is attached as Annexure- 04 Drug product: As per the cleaning validation protocol no. CVP/37G/20/01, the cleaning validation is executed for Whole Virion, Inactivated Corona Virus Vaccine B. No.s 37G20001A, 37G20002A & 37G20003A for formulation batch size 50L is executed. Accordingly the cleaning validation report no. CVR/37G/20/01 dated 04/01/2021 is prepared. The same is attached as Annexure- 05 As per the cleaning validation protocol no. CVP/37G/20/02, the cleaning validation is executed for Whole Virion, Inactivated Corona Virus Vaccine B. No.s 37G20004A, 37G20005A & 37G20006A for formulation batch size 250L is executed. Accordingly the cleaning validation report no. CVR/37G/21/01 dated 12/01/2021 is prepared. The same is attached as Annexure- 06 Status: Closed</p> | | | | |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| 7. | <p>Firm has performed aseptic process simulation (Media fill) of Whole Virion, Inactivated viral vaccine bulk on 16.10.2020 to 17.10.2020. The testing of samples is in process. Firm has not performed aseptic process simulation (Media fill) for formulation and filling process of Whole virion, inactivated corona virus vaccine.</p> | <p>BBIL acknowledges the observations. Aseptic process simulation (Media fill) for Whole Virion, Inactivated Corona Virus Vaccine batches is under execution vide Media simulation protocol No. ASP/PAI/007/20/00 for 50 Lts and 250 Lts. Final report shall be compiled.</p> | <p>Aseptic Process Simulation Summary report (No: ASR/PS2/002/20/00) dated 07.12.2020 of SARS COV -2 Inactivated purified Whole Virion Viral Vaccine Bulk (Sterilized Media Hold time study for 250 L Bio Reactor & Inactivation Vessels (1x300 L & 2x150 L MVL) is verified. Finn has simulated each stage of the manufacturing process by using SCDM media (B. no: MS220001A) At media preparation stage water quality is tested, Sterility test is verified at Bioprocess stage, Ir_activation clarification stage and Sterile filtration. The sterility results comply for all the samples at all the stages. Records verified.</p> <p>Aseptic Process report (No:07.12.2020) of Simulation Interim Summary ASR/PAI /007/20/00 dated SARS COV -2 Inactivated purified Whole Virion Viral Vaccine was verified. Firm had performed the study by adapting bracketing approach (Minimum and Maximum container closure combination for 0.5 ml single dose and 10 ml multiple dose). Finn has simulated each stage of the manufacturing process by using SCDM media (B. no:MA120001A- 50 L Batch Size & MA120002A-250 L Batch Size). At excipient preparation stage water quality is</p> | <p>Complied.</p> <p>In-process and Finished samples for sterility test is under process and result is yet to be submitted by the firm for Aseptic Process Simulation study of SARS COV-2 Inactivated purified Whole Virion Viral Vaccine</p> |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| | <p>BBIL Response: Aseptic process simulation (Media fill) for Whole Virion, Inactivated Corona Virus Vaccine batches is executed vide Media simulation protocol No. ASP/PAI/007/20/00 for 50 Lts and 250 Lts. Final Aseptic process simulation summary report no. ASR/PAI/007/21/00 dated 16/01/2021 has been prepared. The same is attached as Annexure-07. Status : Closed.</p> | | | |
| 8. | <p>Firm has not performed analytical method validation for testing of drug substance. The firm has not done assay validation/ verification for quality control tests carried out at final bulk / lot e.g. protein adsorption test, total protein content. The firm has submitted that assay validation for these tests are done on J.E. Vaccine and are applicable to Whole Virion, Inactivated Corona virus Vaccine as well. The firm has not documented the evidence of suitability of these assays under actual conditions of use for the Whole Virion, Inactivated Corona virus Vaccine. (USP <1226>)</p> | <p>As per change control CC/QCC/20070 the method validation is in progress vide method validation protocol numbers AMVP/37/04 “Protein adsorption by Spectrophotometry method”, AMVP/37/05 “Detection and identification of SARS-COV-2 virus by ELISA method” and AMVP/37/06 for “Protein content” in drug substance.</p> | <p>tested, Sterility test is verified at Excipient solution preparation stage, Formulation stage, Filling and Sealing stage. The samples are under testing. Reports are yet to be submitted by the firm.</p> | <p>Formulation.</p> |
| | | | <p>Analytical method validation protocol (No: AMVP/37/04 dated 24.11.2020)for Testing of Protein Adsorption by spectrophotometer method (Lowry's Method) in Inactivated SARSCOV-2 samples is prepared by the firm and method validation is under process. Tentative date of completion is mentioned by the firm as 15.01.2021. Analytical method validation protocol (No: AMVP/37/06 dated 08.12.2020)for Testing of Protein content in purified Inactivated bulk of SARCOV -2 by Lowry method is prepared by the firm and method validation is under process. Tentative date of completion is mentioned by the firm as 15.01.2021 Analytical method validation protocol (No: AMVP/37/05 dated 24.11.2020)for detection and identification of SARS-COV-2 virus by Elisa method is prepared by the firm and method validation is under process.</p> | <p>Not complied</p> |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| | | | Tentative date of completion is mentioned by the firm as 15.01.2021. | |
| | <p>BBIL Response: As per the protocol No.: AMVP/37/04 dated 24/11/2020 the Protein Adsorption by spectrophotometer (Lowry's Method) analytical method validation is carried out accordingly a summary report no AMVR/VP/37/04, dated 22/01/2021 has been prepared and the same is attached as Annexure-08. As per the protocol No.: AMVP/37/06 dated 08/12/2020 the Protein content analytical method validation is carried out accordingly a summary report no AMVR/VP/37/06 dated 22/01/2021 has been prepared and the same is attached as Annexure-09. As per the protocol No.: AMVP/37/05 dated 24/11/2020 the detection and identification of SARS-COV-2 virus by ELISA analytical method validation is carried out accordingly a summary report no AMVR/VP/37/05 dated 23/01/2021 has been prepared and the same is attached as Annexure-10. Status : Closed.</p> | | | |
| 9. | <p>Firm has initiated one batch of Whole Virion, Inactivated Corona Virus Vaccine for the stability study which is manufactured under test license and also not initiated three batches of Whole Virion, Inactivated Corona Virus Vaccine for the stability study. Firm has not initiated stability study which are intended to be used for phase III clinical trial (batches).</p> | <p>BBIL acknowledges the observation, Stability studies have been initiated for batch numbers 37B20003A, 37B20004A, 37B20005A vide stability protocol number 37/B/PV/SP/20/001 for real time and accelerated stability temperatures. The data will be available for 3rd month real time and 3rd Month accelerated stability by March 1st week. The stability protocol is attached as Annexure-02.</p> | <p>Stability protocol (Doc no: 37/B/PV/SP/20/001) for Whole Virion Inactivated Corona Virus Vaccine (Human, Adsorbed) 6µg/SHD) (BBVI52B) dated 25/11/2020 is prepared by the firm to carry out stability studies for B. nos. 37B20003A, 37B20004A and 37B20005A manufactured in the month of September 2020. Stability study was initiated at 3 different conditions clinical 5±3°C for 36 months at testing frequency 0 day, 3- 6, 9, 12,24 and 36 months. Stability was initiated on 28.11.2020. The study is under process. (Real time stability) 25±2°C for 6 months at testing frequency 0day,1, 3 & 6 months. Stability was initiated on 28.11.2020. The study is under process. (Accelerated stability) 37±2°C for 14 days at testing frequency 0 day,2, 7 & 14 days. Stability was initiated on 28.11.2020. The</p> | Not Complied. |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| BBIL Response: As per stability study protocol (Doc no: 37/B/PV/SP/20/001) for Whole Virion Inactivated Corona Virus Vaccine (Human, Adsorbed) 6µg/SHD) (BBV152B) Stress stability at 37±2°C for B.Nos. 37B20003A, 37B20004A and 37B20005A have been completed on 17/12/2020. The stability study time points and results are attached as Annexure-11 . The real time stability at 5±3°C for B.Nos. 37B20003A, 37B20004A and 37B20005A the initial 0 day analysis was completed. The 3 rd month stability sample analysis scheduled on 28/02/2021. The stability study time points and scheduled dates are attached as Annexure-12 . The accelerated stability at 25±2°C for B.Nos. 37B20003A, 37B20004A and 37B20005A the initial 0 day analysis and 1 st month analysis was completed on 09/01/2021 as per stability schedule. The 3 rd and 6 th month stability sample analysis scheduled on 28/02/2021 & 28/05/2021. A copy of stability schedule & 1 st Month results were appended as Annexure- 13. (Data shall be shared upon completion of stability analysis) | | | | |
| 10. | On reviewing of specification (FPS312, Rev. No. 01 dated 28.07.2020) for Whole Virion, Inactivated Corona Virus Vaccine (Algel-2 formulation- 6µg/SHD), it is observed that specification for total protein content is kept as Not Less Than (NLT) 4.2µg/SHD of label claim. However, label claim mentioned for the applied drug product on the application of Form 27 D is NLT 6µg/SHD. | BBIL would like to clarify that, the specification is based on considering cumulative variation of analytical method and manufacturing process (considering 15% for each) for the product. Targeting 6µg/SHD as per BMR will be impacted by number of parameters including manufacturing process variability and drug product analysis variability as mentioned above. Considering these factors the limits have been set at NLT 4.2 µg/SHD. However, same shall be revisited after completion of method validation of relevant parameters and based on trends evaluation & sufficient manufactured batches. | Analytical method validation for protein content estimation is under process. Document proof and also Justification submitted by the firm is not satisfactory. | Not Complied |
| BBIL Response: As per the auditor recommendation, the specification FPS312 for Whole Virion, Inactivated Corona Virus Vaccine has been revised through change control CC/QCC/21002 and made effective on 18/02/2021. The specification for total protein content is revised as Not Less Than (NLT) 6µg/SHD to inline with the label claim. The revised Specification is attached as Annexure-14 . | | | | |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| <p>The analytical method validation for protein content estimation is completed. accordingly a summary report no. AMVR/37/06 dated 22/01/2021 has been prepared and the same is attached as Annexure-09. Status: Closed</p> | <p>11. For protein adsorption, a specification at final lot is kept as NLT 75% of the stated label claim of protein. The firm shall establish the specifications based on the adsorption percentage obtained in clinical trial batches.</p> | <p>The limits for degree of adsorption have been derived from pharmacopoeial limit as per Indian Pharmacopoeia. The monograph reference is from Japanese Encephalitis vaccine Inactivated (adsorbed, Human). However, as suggested in future, the limits shall be revised based on trends for percentage adsorption for additional batches in addition to clinical trial batches data. The reference IP document is attached as Annexure-03.</p> | <p>Firm is licensed to manufacture Japanese Encephalitis Vaccine Inactivated (Adsorbed Human). Firm state that they are using Aluminium Hydroxide gel as an Adjuvant and For Whole Virion Inactivated Corona Virus vaccine they are using Aluminium Hydroxide gel with Agonist molecule. It is stated that Adjuvant -Aluminium Hydroxide gel concentration used in both the formulation is the same and the manufacturing process is also similar for the both formulation. Hence the Degree of Adsorption limit (NLT 75%) mentioned for Japanese Encephalitis Vaccine Inactivated (Adsorbed Human) in the Indian Pharmacopoeia is adapted by the firm.</p> | <p>May be considered at this stage. However, Firm may be directed to compile the data on the adsorption Percentage obtained Clinical trial batches and revise the specification and submit the report.</p> |
| <p>BBIL Response: BBIL clarified that the specifications are as per pharmacopoeial requirement of similar kind of formulation such as Adjuvant -Aluminium Hydroxide gel concentration of Japanese Encephalitis Vaccine Inactivated (Adsorbed Human). Trend report was prepared by compiling the data available for batches manufactured at BBIL for Whole Virion Inactivated Corona Vaccine. Based on the evaluation it is decided to go ahead with the pharmacopoeial limit as mentioned in Japanese Encephalitis monograph which is been suggested by WHO to be followed in absence of TRS for SARS-CoV-2 vaccine. The protein adsorption test results Trend report is attached as Annexure-21 Status: Closed</p> | | | | |



| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| 12. | For Aluminium content, an acceptance criterion is 0.38mg/ml to 0.58mg/ml (targeted conc. 0.50mg/ml). This variation is 0.12 mg/ml in case of lower side and 0.08 mg/ml towards upper side. Firm stated that these limits are assigned based on the limits followed for J.E. Vaccine manufactured by them. The firm shall assign the specifications for proposed drug product based on the data obtained during assay validation for Aluminium content. | Maximum (almost all) vaccine formulations have the assigned limit of NMT 2.50 mg/ml as per the Pharmacopoeias which signifies that the vaccine formulations with adjuvant concentration of 2.50 mg/ml are non toxic and safe for usage. Considering the concept of quality by design these specifications are internal control limits for aluminium content to maintain the consistency of the manufactured product based on existing approved products. Hence the observation does not have any impact on the product quality. However, as suggested based on batch trend data the limits shall be revised. | Firm followed 2.3.9. Aluminium in Adsorbed Vaccines- Method A as mentioned in Indian Pharmacopoeia 2018. Firm stated that till most of the Adsorbed the limit 0.38mg/ml to 0.58mg/ml which is less Vaccines. The limit for Aluminium content is mentioned as NMT 2.50 mg/ml. Firm had fixed than the limit specified in the Indian Pharmacopoeia for Adsorbed vaccines. | Firm had followed Indian Pharmacopoeia method and the limits mentioned are justified. Hence, May be considered. However, may be directed to perform method verification for the used method of Indian Pharmacopoeia - 2.3.9. Aluminium in Adsorbed Vaccines- Method A. |
| <p>BBIL Response: As per the auditors recommendation, BBIL has prepared a analytical method verification protocol no.: AMVVP/37/13 dated 01/02/2021 for testing of Aluminium content by titration method for Inactivated SARS-CoV-2 Vaccines. The method verification shall be carried out. The analytical method verification protocol is attached as Annexure-15. TCD:31-Mar-2021</p> | | | | |
| 13. | For Antigenic purity by SDS-PAGE specifications are mentioned as “Should show only Corona Virus specific bands”. The firm shall specify that bands of which molecular weight should be present in the SDS-PAGE test. | BBIL would like to clarify that, for antigenic purity the specification as, “should show only corona virus specific bands”. The presence of spike protein band confirms the SARS-CoV-2 virus and absence of other non specific bands other than spike, nucleocapsid, membrane and envelope protein ensures the purity of the | The change control CC/QCC/20074 dated 7.12.2020 was initiated by the firm for revision of STP Doc no: <i>STP/QCC/056</i> Determination of Antigenic Purity by SDS-Page for Inactivated SARS-COV2 Bulk. Draft STP prepared by incorporating the molecular weight of protein bands of | Partly complied. |

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| | | <p>product. This information is available in various literature. Therefore the specifications are mentioned as “SDS-PAGE should show only corona virus specific bands”. However as a compliance the details for molecular weights for different protein bands shall be included in Standard testing procedure for antigenic purity of SARS-CoV-2 (STP/QCC/056). The change control CC/QCC/20074 is initiated for the same.</p> | <p>SARS- CoV2. The draft is under finalization.</p> | |
| <p>BBIL Response: BBIL would like to update that, as per the change control CC/QCC/20074, STP/QCC/056 dated has been revised to include the molecular weights of different corona virus specific bands and STP is effective from 24/02/2021. The revised STP is attached as Annexure-16. Status: Closed</p> | | | | |
| 14. | <p>Firm is used 2-Phenoxyethanol (2-PE) as preservative in the formulation of Whole Virion, Inactivated Corona Virus Vaccine and as 2-PE is light sensitive material, it needs to be dispensed & handled under Sodium lamp. However, firm has not provided Sodium lamp in dispensing area at ware house and formulation area.</p> | <p>BBIL would like to clarify that, 2 Phenoxy ethanol is received from vendor M/S Sigma Aldrich. As per MSDS from the manufacturer & Pub-chem of NCBI https://pubchem.ncbi.nlm.nih.gov/compound/2-Phenoxyethanol there are no special requirement for handling and storage of 2-Phenoxy ethanol. The MSDS is attached as Annexure-04.</p> | <p>Firm has not provided Sodium vapour lamp in the dispensing area at ware house and formulation area.</p> | <p>Not complied.</p> |
| <p>BBIL Response: BBIL would like to update that, CC/STD/21004 dated 23/02/2021 has been initiated for installation of Sodium Vapour lamp in Dispensing area. TCID:31-Mar-2021</p> | | | | |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| 15. | <p>After Algel-2 preparation, firm is testing description, pH in their QC Lab. Firm is sending sample to IICT, Hyderabad for Identification test. However, no quality agreement is available between firm (Bharat Biotech) & IICT, Hyderabad.</p> | <p>BBIL commits that, Algel 2 samples are tested by IICT, Hyderabad considering NABL accreditation and evaluated by BBIL prior to batch release. However, BBIL is in the process of making the QTA with IICT for testing of Algel 2 samples.</p> | <p>Quality Technical Agreement (Ref no. CTL/CSIR-IICTI2020) is under preparation.</p> | <p>Not complied.</p> |
| <p>BBIL Response: BBIL would like to update that, the quality technical agreement between Bharat Biotech & IICT, Hyderabad, Ref. No. CTL/CSIR-IICT/2021 is placed. A copy of QTA between BBIL & IICT is attached as Annexure-17. Status: Closed</p> | | | | |
| 16. | <p>On verification of Certificate of Analysis (CoA) of Algel-2 preparation B.No: 40A20007A, B.Size: 1500ml, it is observed that firm has not done the test for total sulphate, free sulphate, Fe(total), Ash residue, Al(OH)₃, Al/ml (EDTA Titration) and protein adsorption capacity and mentioning, reported value of Aluminium hydroxide Gel 2% on the CoA of Algel-2. Firm has not tested prepared Algel-2, as per Specification No: IPS058 dated 01.08.2020.</p> | <p>Very minimal quantities of the agonist molecule is added to the 2% aluminium hydroxide gel moiety for preparation of Algel-2. Hence there is no scientific anticipation that addition of this chemical can change the chemical properties of aluminium hydroxide gel. Therefore to prevent the repeat testing of similar kind of parameters which are not anticipated to be chemically altered same results from the source aluminium hydroxide gel are reported. However, as suggested BBIL shall test all parameters as per the specification so as to comply with the observation. CAPA/QCCC/20018 is initiated for the same.</p> | <p>After observation raised, the manufactured Algel-2 preparation B.No, 40A20009A and 40A20010A were collected for complete analysis as per Specification no: IPS058, Description, PH and Sterility are tested In -house and rest of the test (Identification Total Sulphate, free Sulphate, F e (T o t a l), Ash residue, AL(OH)₃ Adsorption capacity are yet to be received. The test reports are yet to be received.</p> | <p>Identification, Total Sulphate, Free Sulphate, Fe Total), Ash residue, AL(OH-B Al/ml EDTA Titration, Protein Adsorption capacity outsourced are outsourced Algel-2 preparation B.No. 40A20009A and 40A20010A and reports are yet to be received.</p> |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| BBIL Response: | | | | |
| BBIL would like to update that, the manufactured Algel-2 B.No, 40A20009A and 40A20010A analysis was completed as per Specification no: IPS058, Description, pH and Sterility are tested In -house and rest of the test (Identification Total Sulphate, free Sulphate, F e (Total), Ash residue, AL(OH)3 Al/ml EDTA Titration, Protein Adsorption capacity are outsourced. The batch COAs are attached as Annexure-18 . Status:Closed | | | | |
| 18. | Filter validation not performed for TLR 7/8 agonist in IPA solution, Whole Virion, Inactivated Corona Virus Vaccine drug substance & 2 PE in PBS solution. | The filter validation for Whole Virion, Inactivated corona virus vaccine drug substance and 2 PE in PBS solution used for formulated bulk shall be performed. A change control CC/SAS/20061 has been initiated for execution. | Filter validation not performed for TLR 7/8 agonist in IP A solution, Whole Virion, Inactivated Corona Virus Vaccine drug substance & 2 PE in PBS solution. | Not Complied. |
| BBIL Response: | | | | |
| BBIL would like to confirm that as per the change control CC/SAS/20061 , Bacterial retention test for Whole Virion, Inactivated corona virus vaccine drug substance and filter compatibility test for 2 PE in PBS solution is executed vide filter validation protocol no. FIV/PA1/CVV/001/20/00 & FIV/PA1/CVV/002/20/00 respectively. Accordingly the summary reports were prepared, Report numbers: FIR/PA1/CVV/001/21/00 dated 04/02/2021 & FIR/PA1/CVV/002/21/00 dated 04/02/2021. The Protocol & summary reports are attached as Annexure 19 . BBIL would like to clarify that, the vendor has been finalized for Filter leachability study which shall be carried out by external source from vendor (Sartorius). TCD: 30-Apr-2021 | | | | |
| 22. | Firm did not obtain Form CT-23 for permission to manufacture Whole Virion, Inactivated Corona Virus Vaccine for sale or for distribution | BBIL would like to clarify that, For public health interest and to meet the emergency requirement arisen due to COVID-19 pandemic, Firm has submitted an application in Form 27 D, dated, 10/11/2020 to obtain Form 28 D, in reference to Ministry of Health and Family Welfare, Notification no. S.O. 1511(E) dated 18/05/2020, to manufacture and stock the vaccine subject to the condition that BBIL shall sale and distribute the vaccine only after obtaining | Firm had not applied to obtain Permission in form CT-23 to manufacture Pharmaceutical formulation - Whole Virion, Inactivated Corona Virus Vaccine for sale or for distribution | Not complied |

| S. No. | Inspection findings/ observations 18.11.2020 and 19.11.2020 | BBIL compliance | Observations of Joint Inspection dated 22.12.2020 | Remarks |
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| | | Form CT-23 (from the central licensing authority). Refer Annexure-06 . BBIL will further apply to obtain the Form CT-23 for permission to manufacture Whole Virion, Inactivated Corona Virus Vaccine for sale or for distribution. | | |
| BBIL Response: Bharat Biotech applied for permission to manufacture for sale or for Distribution in Form CT-21 on SUGAM Application No. BIO/CT21/FF/2020/22922 dated: 07.12.2020. Hence Bharat Biotech received permission to manufacture “Whole Virion, Inactivated Corona Virus Vaccine” for sale or for distribution in Form CT-23 under Emergency Use Authorization (EUA) vide Permission No. MF/BIO/21/000002, Dated: 03.01.2021. The form CT - 23 is attached as Annexure-20 . Status:Closed | | | | |

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| Prepared By: Dy. Manager - QAS  | Approved By: AGM-QAS  |
| Sign & Date M. KISHORE | Sign & Date (NAME & V. SAHU) |



LETTER OF DECLARATION


Our Company, **BHARAT BIOTECH INTERNATIONAL LIMITED**, incorporated under Company's Act, 1956 having its registered office situated at Genome Valley, Shameerpet, Hyderabad 500078, Telangana, India, bearing CIN: U24230TG1996PLC023232 (hereinafter "**BBIL**") which included its Directors, Officers and Employees who intend to conduct business transaction with various Channel Partners and entities hereby:

PLEDGES AND UNDERTAKES THAT:

BBIL AND MADISON BIOTECH PTE LIMITED, a company incorporated as per laws of Singapore having its registered office at 31 CANTONMENT ROAD, SINGAPORE-089747, (hereinafter "**MBPL**") which included its Directors, Officers and Employees, entered into a **Supply Agreement** authorizing MBPL to supply and distribute BBIL's Manufactured Products to various channel partners and entities in different regions and territories.

In, Lieu of the above declaration, all the Channel Partners and Entities are requested to accept the Invoice raised by MADISON BIOTECH PTE LTD, for every Product supplied or distributed.

For BBIL,


Mr. Venkatraman S.H.
Associate Vice President – International Business



Recibo Eletrônico de Protocolo - 1382475

Usuário Externo (signatário): Ariadne Gisele Muniz Bonvino
IP utilizado: 189.28.128.242
Data e Horário: 24/03/2021 11:48:36
Tipo de Peticionamento: Intercorrente
Número do Processo: 25351.908358/2021-66
Relacionado ao Processo Indicado: 25351.908110/2021-03

Interessados:

MINISTERIO DA SAUDE/DEPARTAMENTO DE LOGISTICA EM SAUDE-DLOG/CGLOG/DIIMP

Protocolos dos Documentos (Número SEI):

| | |
|--------------------------------------|---------|
| - Licença de Importação 21-0796694-1 | 1382470 |
| - Relatório de Conformidade Jul 2020 | 1382471 |
| - Relatório de Conformidade Nov 2020 | 1382472 |
| - Declaração Madison Biotech | 1382473 |
| - Contrato 29 - Covaxin | 1382474 |

O Usuário Externo acima identificado foi previamente avisado que o peticionamento importa na aceitação dos termos e condições que regem o processo eletrônico, além do disposto no credenciamento prévio, e na assinatura dos documentos nato-digítals e declaração de que são autênticos os digitalizados, sendo responsável civil, penal e administrativamente pelo uso indevido. Ainda, foi avisado que os níveis de acesso indicados para os documentos estariam condicionados à análise por servidor público, que poderá alterá-los a qualquer momento sem necessidade de prévio aviso, e de que são de sua exclusiva responsabilidade:

- a conformidade entre os dados informados e os documentos;
- a conservação dos originais em papel de documentos digitalizados até que decaia o direito de revisão dos atos praticados no processo, para que, caso solicitado, sejam apresentados para qualquer tipo de conferência;
- a realização por meio eletrônico de todos os atos e comunicações processuais com o próprio Usuário Externo ou, por seu intermédio, com a entidade porventura representada;
- a observância de que os atos processuais se consideram realizados no dia e hora do recebimento pelo SEI, considerando-se tempestivos os praticados até as 23h59min59s do último dia do prazo, considerado sempre o horário oficial de Brasília, independente do fuso horário em que se encontre;
- a consulta periódica ao SEI, a fim de verificar o recebimento de intimações eletrônicas.

A existência deste Recibo, do processo e dos documentos acima indicados pode ser conferida no Portal na Internet do(a) Agência Nacional de Vigilância Sanitária.

William Amorim Santana

De: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Enviado em: quarta-feira, 24 de março de 2021 00:00
Para: William Amorim Santana
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Regina Celia Silva Oliveira; Renata Marques Santana; Thiago Fernandes da Costa; DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG; Luiz Felipe Almeida Caram Guimarães; GABINETE DA SECRETARIA EXECUTIVA; Quinta Diretoria; Segunda Diretoria; Primeira Diretoria; DIRETORIA3@ANVISA.GOV.BR; DIRETORIA4@ANVISA.GOV.BR; Luis Ricardo Fernandes Miranda; Antônio Elcio Franco Filho
Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152
Anexos: Compliance Report_Jul 2020.pdf; Compliance Report_Nov 2020.pdf; BBV152-COVAXIN-EUL-12032021[1].pdf; Re: Pendência (dct incompleta) - 25351.908110/2021-03 - aquisição de Vacina COVAXIN / BBV152

Caros, boa noite.

Com o intuito de atendermos todas as demandas da ANVISA que estão em nosso alcance, e permanecermos com a atuação de forma transparente e colaborativa, informamos que com base no último *press release* emitido pela agência, temos as seguintes considerações:

<https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-recebe-pedido-de-importacao-covaxin>

1. Relatório Técnico de Avaliação emitida pela autoridade sanitária Indiana:

O CDSCO emitiu um documento (anexo BBV152 – COVAXIN – EUL – 12032021) que transmite a autorização para uso emergencial com as suas ressalvas, bem como o relatório de avaliação técnica em um único documento. Tal documento foi transmitido ao Ministério da Saúde na quinta-feira dia 18/03 com essa observação.

De maneira proativa, compartilho o CAPA Report emitido para a autoridade sanitária Indiana que apresenta os apontamentos do mesmo durante a inspeção para autorização de produção da Covaxin.

2. Certificado de liberação dos lotes:

Enviamos os Certificados de Análise dos lotes liberados* e estamos providenciando os Certificados de Origem que serão emitidos pelas autoridades indianas. De acordo com a evolução dos estudos de estabilidade, estamos atualizando os CoA's para condizerem com os resultados obtidos e novos padrões de conservação – ampliando a *shelf life* de 6 para 24 meses.

3. Licenciamento de Importação

Segundo anuência dos Fiscais do Contrato, formalizadas através de e-mail, o DIIMP tem atuado na emissão desta LI sendo o Ministério da Saúde através do seu despachante, responsável pela abertura do Licenciamento de Importação. Lembrando que, de acordo com a operacionalização do SICOMEX, iremos solicitar uma LI para cada embarque, não sendo possível solicitar para as 20 milhões de doses contratadas de uma só vez, já que os embarques – também com a anuência do fiscal do contrato – serão fracionados, e é impossível registrar mais de uma DI por LI.

Todos os passos têm sido realizados com o intuito de atender integralmente as demandas e complementar com mais informações sempre que necessário, e contamos com a solicitude que já vem sendo apresentada por todos desde o início.

Atenciosamente,

Emanuela Medrades

Diretora Executiva

Av Portugal, 1100 - Itaqui- Itapevi- SP

55 11 3080-5140 - 11 9 3257-4642

www.precisamedicamentos.com.br



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 Antes de imprimir, pense no Planeta! (Before printing, please think about our environment!)

De: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Data: terça-feira, 23 de março de 2021 22:54

Para: William Amorim Santana <william.santana@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

William,

Já havia pedido essa retificação, e me enviaram.

Segue com ajustes,

Atenciosamente,

Emanuela Medrades

Diretora Executiva

Av Portugal, 1100 - Itaqui- Itapevi- SP

55 11 3080-5140 - 11 9 3257-4642

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 Antes de imprimir, pense no Planeta! (Before printing, please think about our environment!)

De: William Amorim Santana <william.santana@saude.gov.br>

Data: terça-feira, 23 de março de 2021 22:35

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Prezada Emanuela,

Após observar a documentação, observei que está com a informação 100% advanced payment (pagamento antecipado).

Informo que o contrato 29/2021 não prevê pagamento antecipado. A modalidade é "Póstecipado".

Também foi observado que os valores de frete e seguro divergem do contrato.

Peço a gentileza que observe o valor unitário de 15.00 US\$ do produto, bem como o valor do frete e seguro. Esse valor não pode ser alterado.

Feitas as ponderações, solicito a gentileza de providenciar a correção dos apontados acima.

No aguardo.

Atenciosamente,

William Amorim Santana
DIIMP

Enviado do meu iPhone

Em 23 de mar. de 2021, à(s) 21:29, Emanuela Medrades
<emanuela.medrades@precisamedicamentos.com.br> escreveu:

William, boa noite.

Em complementação a solicitação de LI, seguem:

1. Proforma Invoice;
2. Packing List.

Atenciosamente,

<image001.jpg>

<image002.jpg>

De: William Amorim Santana <william.santana@saude.gov.br>

Data: terça-feira, 23 de março de 2021 16:57

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: RES: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Ok Manuela, ficamos no aguardo.

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br

De: Emanuela Medrades [mailto:emanuela.medrades@precisamedicamentos.com.br]

Enviada em: terça-feira, 23 de março de 2021 16:34

Para: William Amorim Santana <william.santana@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>; Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

William, boa tarde.

Enviamos a demanda ao fabricante e agente comercial. Entretanto, devido ao fuso, teremos este retorno somente amanhã.

Conto com a sua compreensão.

Atenciosamente,

<image003.jpg>
<image004.jpg>

De: William Amorim Santana <william.santana@saude.gov.br>

Data: terça-feira, 23 de março de 2021 14:03

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

*****URGENTE*****

Prezado Fornecedor, após análise de nosso despachante na INVOICE apresentada, faz-se necessário a adequação da documentação bem como prestar, na INVOIVE, os dados listados abaixo:

CONSIGNATÁRIO:

Ministério da Saúde/Departamento de Logística em Saúde - DLOG

CNPJ: 00.394.544/0008-51

Esplanada dos Ministérios, bloco "G" anexo A, 4ª andar, sala 431

Brasília- DF

CEP: 70.310-500

BRASIL

DADOS COMPLETOS DO FABRICANTE;

- Nome do Fabricante.
- Endereço.

DESCRIÇÃO COMPLETA DA MERCADORIA;

- Informar Código de Harmonização NCM (nomenclatura Comum Mercosul).
- Informar o peso líquido e o peso bruto.
- Identificar como o quantitativo vira (caixa, Frasco, etc...).
- Identificar a validade do produto (data de fabricação e vencimento).

PAÍS DE ORIGEM;

- Informar localidade.

PAÍS DE DESTINO;

- Informar o aeroporto Internacional de Guarulhos (GRU).

INCOTERMS;

- Informar CIP e acrescentar os valores de frete e seguro.

ENVIAR PAKING LIST.

Ficamos no aguardo da correção da INVOICE e envio de packing List para abertura da Licença de Importação.

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br

-----Mensagem original-----

De: Everton [<mailto:everton@wegh.com.br>]

Enviada em: terça-feira, 23 de março de 2021 13:33

Para: William Amorim Santana <william.santana@saude.gov.br>; 'Roberta' <roberta@wegh.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>

Assunto: RE: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Boa tarde Prezados

William

Por gentileza solicitar as devidas correções na Proforma Invoice:

- Nome e endereço do Ministério da Saúde está errado (Consignee - Buyer)
- Informar aeroporto de destino - GRU
- INCOTERM é CIP ? Sem sim informar o valor do frete e valor de seguro (separados)
- Qual a NCM do produto ?
- Informar o peso líquido e o peso bruto
- A quantidade está em frascos, caixas... ?
- Nome e endereço completo do Fabricante
- Informar o Lote e validade do lote
- Este produto tem registro na ANVISA ? Se sim, informar o numero
- Enviar o Packing list

No aguardo das correções para registro da LI.

ATENÇÃO PARA O NOVO ENDEREÇO DA WEGH ABAIXO NA ASSINATURA Grato

Everton F Campos

WEGH Assessoria e Logística Internacional Ltda Rua José do Patrocínio, 220 - Aclimação - São Paulo - SP - Brasil CEP 04108-000 – São Paulo-SP- Brasil Phone +55 11 5573-0877 / 5572.4330 / 5908-5050 – RAMAL: 208

E-mail: everton@wegh.com.br

www.wegh.com.br

-----Original Message-----

From: William Amorim Santana

Sent: Monday, March 22, 2021 12:19 PM

To: everton@wegh.com.br; lucas@wegh.com.br; 'Roberta Pereira' <roberta@wegh.com.br>; 'Carlos E.J. Pereira' <carlos@wegh.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>

Subject: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Prezada Equipe WEGH,

Boa tarde!

Segue documentação para análise complementar e, estando em conformidade, gentileza providenciar a abertura de Licença de Importação (LI).

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br<mailto:lilian.sa@saude.gov.br>

De: Thiago Fernandes da Costa

Enviada em: segunda-feira, 22 de março de 2021 11:54

Para: William Amorim Santana <william.santana@saude.gov.br>; Regina Celia Silva Oliveira

<Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho

<alex.marinho@saude.gov.br>; Francieli Fontana Sutile Tardetti Fantinato

<francieli.fantinato@saude.gov.br>; Lauricio Monteiro Cruz <lauricio.cruz@saude.gov.br>

Assunto: RE: SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021

VACINA COVAXIN/BBV152

Prezados, bom dia !

Informo que este Departamento formalizou o Despacho DEIDT (0019651176) no processo 25000.175250/2020-85, a fim de realizar a devida instrução quanto à importação requerida pela contratada.

Não obstante, informo também que estamos de acordo com o pleito e solicito a essa Divisão que dê andamento aos trâmites necessários para a realização da importação.

Atte.,

[cid:63368a64-85f9-4ff0-b02b-8eda019cf04c]

Thiago Fernandes da Costa

Gestão de Insumos

Departamento de Imunização e Doenças Transmissíveis - DEIDT

Secretaria de Vigilância em Saúde - SVS

* (61) 3315-3646

De: William Amorim Santana
<william.santana@saude.gov.br<mailto:william.santana@saude.gov.br>>
Enviado: segunda-feira, 22 de março de 2021 10:27
Para: Regina Celia Silva Oliveira
<Regina.Oliveira@saude.gov.br<mailto:Regina.Oliveira@saude.gov.br>>; Renata Marques Santana
<renatam.santana@saude.gov.br<mailto:renatam.santana@saude.gov.br>>; Thiago Fernandes da
Costa <thiago.fernandes@saude.gov.br<mailto:thiago.fernandes@saude.gov.br>>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO
<lista.divisaoimportacao@saude.gov.br<mailto:lista.divisaoimportacao@saude.gov.br>>; Alex Lial
Marinho <alex.marinho@saude.gov.br<mailto:alex.marinho@saude.gov.br>>
Assunto: SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA
COVAXIN/BBV152

Prezado Fiscal Contrato 29/2021

Bom dia!

Chegou a esta Divisão de Importação (DIIMP), na data de 18/03/2021, documentação proveniente da empresa PRECISA MEDICAMENTOS referente a solicitação de autorização de embarque para 1ª parcela Contrato 29/2021 VACINA COVAXIN/BBV152.

Considerando o cronograma de entrega das parcelas, devidamente exposto abaixo, o qual demonstra que a entrega da 1ª parcela encontra-se com atraso se 05 (cinco) dias até a presente data:

CRONOGRAMA DE ENTREGA CONTRATUAL

PARCELA

COMPRIMIDOS

ENTREGA

RECEBIMENTO

1ª

4.000.000

17/03/2021

EM TRAMITE

2ª

4.000.000

27/03/2021

3ª

4.000.000

11/04/2021

4ª

4.000.000

26/04/2021

5ª

4.000.000

06/05/2021

TOTAL

20.000.000

Considerando tratar-se de vacina que não possui registro sanitário, junto a Agencia Nacional de Vigilância Sanitária (ANVISA), cabendo a necessidade de solicitação de concessão de excepcionalidade para essa importação;

Considerando os demais parâmetros devidamente expostos no Termo de Referência (TR) do Contrato 29/2021 para esta aquisição a fim de atender o Departamento de Imunização e Doenças Transmissíveis (DEIDT/SVS); e

Considerando que o objeto do contrato em questão é um insumo essencial para o enfrentamento da Pandemia de SARS-COV-2.

Esta Divisão de Importação (DIIMP), pelo presente exposto, solicita autorização do fiscal do contrato ou seu respectivo substituto eventual para prosseguir com o processo de autorização de embarque desta parcela.

Aguardo resposta.

OBS: Documento disposta no link: <https://www.dropbox.com/t/HFj13mkBO2irwJ7C>

Atenciosamente,

William Amorim Santana

Ministério da Saúde

DIIMP/CGLOG/DLOG-SE

Ed. Anexo, 4º andar, Sala 431-A

55-61-3315-3760

william.santana@saude.gov.br<mailto:lilian.sa@saude.gov.br>

De: Cassiana Perinazzo da Veiga Schio Em nome de DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG Enviada em: quinta-feira, 18 de março de 2021 14:39
Para: LISTA - DIVISÃO DE IMPORTAÇÃO
<lista.divisaoimportacao@saude.gov.br<mailto:lista.divisaoimportacao@saude.gov.br>>; William Amorim Santana <william.santana@saude.gov.br<mailto:william.santana@saude.gov.br>>; Luis Ricardo Fernandes Miranda <luisf.miranda@saude.gov.br<mailto:luisf.miranda@saude.gov.br>>
Cc: 'emanuela.medrades@precisamedicamentos.com.br'
<emanuela.medrades@precisamedicamentos.com.br<mailto:emanuela.medrades@precisamedicamentos.com.br>>; DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG
<dlog@saude.gov.br<mailto:dlog@saude.gov.br>>
Assunto: ENC: AUTORIZAÇÃO EXCEPCIONAL DE IMPORTAÇÃO - VACINA COVID

Prezados, boa tarde!

Encaminho para conhecimento e providências no que couber documentos encaminhados pela Precisa Medicamentos, referente autorização excepcional de importação para vacina Covid-19.

Atenciosamente,

Equipe DLOG/SE/MS

De: Emanuela Medrades
<emanuela.medrades@precisamedicamentos.com.br<mailto:emanuela.medrades@precisamedicamentos.com.br>>
Enviada em: quinta-feira, 18 de março de 2021 09:20
Para: DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG
<dlog@saude.gov.br<mailto:dlog@saude.gov.br>>
Cc: Lenice Guimaraes Araujo <lenice.araujo@saude.gov.br<mailto:lenice.araujo@saude.gov.br>>
Assunto: AUTORIZAÇÃO EXCEPCIONAL DE IMPORTAÇÃO - VACINA COVID

Senhores, bom dia.

Solicitamos em concordância com a RDC 476/2.021 a autorização excepcional de importação de vacina para Covid19.

Enviamos os documentos através do link a seguir: <https://www.dropbox.com/t/HFj13mkBO2irwJ7C>

Permanecemos a disposição,

Atenciosamente,

[Uma imagem contendo guarda-chuva Descrição gerada automaticamente]

[signature_631106945]

IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.
EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.
EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET

<PACKING LIST-2.pdf>
<PI ON LETTER HEAD-2.pdf>

Esta mensagem pode conter informação confidencial e/ou privilegiada. Se você não for o destinatário ou a pessoa autorizada a receber esta mensagem, não pode usar, copiar ou divulgar as informações nela contidas ou tomar qualquer ação baseada nessas informações. Se você recebeu esta mensagem por engano, por favor avise imediatamente o remetente, respondendo o e-mail e em seguida apague-o.

IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET

Recibo Eletrônico de Protocolo - 1382496

Usuário Externo (signatário): Ariadne Gisele Muniz Bonvino
IP utilizado: 189.28.128.242
Data e Horário: 24/03/2021 11:52:09
Tipo de Peticionamento: Intercorrente
Número do Processo: 25351.908361/2021-80
Relacionado ao Processo Indicado: 25351.908110/2021-03
Interessados:
MINISTERIO DA SAUDE/DEPARTAMENTO DE LOGISTICA EM SAUDE-DLOG/CGLOG/DIIMP
Protocolos dos Documentos (Número SEI):
- E-mail Explicativo do Fornecedor 1382495

O Usuário Externo acima identificado foi previamente avisado que o peticionamento importa na aceitação dos termos e condições que regem o processo eletrônico, além do disposto no credenciamento prévio, e na assinatura dos documentos nato-digitais e declaração de que são autênticos os digitalizados, sendo responsável civil, penal e administrativamente pelo uso indevido. Ainda, foi avisado que os níveis de acesso indicados para os documentos estariam condicionados à análise por servidor público, que poderá alterá-los a qualquer momento sem necessidade de prévio aviso, e de que são de sua exclusiva responsabilidade:

- a conformidade entre os dados informados e os documentos;
- a conservação dos originais em papel de documentos digitalizados até que decaia o direito de revisão dos atos praticados no processo, para que, caso solicitado, sejam apresentados para qualquer tipo de conferência;
- a realização por meio eletrônico de todos os atos e comunicações processuais com o próprio Usuário Externo ou, por seu intermédio, com a entidade porventura representada;
- a observância de que os atos processuais se consideram realizados no dia e hora do recebimento pelo SEI, considerando-se tempestivos os praticados até as 23h59min59s do último dia do prazo, considerado sempre o horário oficial de Brasília, independente do fuso horário em que se encontre;
- a consulta periódica ao SEI, a fim de verificar o recebimento de intimações eletrônicas.

A existência deste Recibo, do processo e dos documentos acima indicados pode ser conferida no Portal na Internet do(a) Agência Nacional de Vigilância Sanitária.

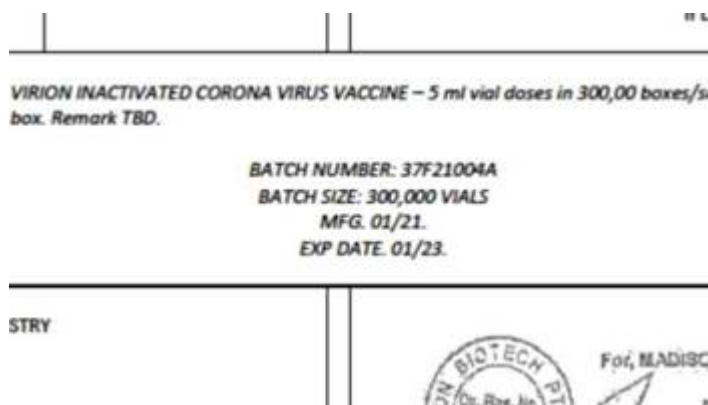
Ariadne Gisele Muniz Bonvino

De: William Amorim Santana
Enviado em: quarta-feira, 24 de março de 2021 13:58
Para: Emanuela Medrades
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Ariadne Gisele Muniz Bonvino; Alex Lial Marinho
Assunto: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152
Anexos: PACKING LIST-2.pdf; PI ON LETTER HEAD-2.pdf

Prezada Emanuela,

Boa tarde!

Ao observar a Commercial Invoice, bem como o Paking Llst, ambos citam o lote nº 37F11004A com data de fabricação 01/2021 e vencimento 01/2023.



No entanto, os documento técnicos recebidos até a presente data não contemplam este lote. Elenco abaixo os referidos:

- 37620001A;
- 37620002A;
- 37620003A

Considerando que este processo encontra-se em análise junta a Agencia Nacional de Vigilância Sanitária (ANVISA), solicito a gentileza verificar quais os lotes seriam efetivamente enviados para este Ministério da Saúde (MS), estando este na Invoice, gentileza proceder com o devido envio da documentação técnica referente ao lote citado, caso contrário, providência a correção na INVOICE.

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br

De: Emanuela Medrades [mailto:emanuela.medrades@precisamedicamentos.com.br]

Enviada em: terça-feira, 23 de março de 2021 21:30

Para: William Amorim Santana <william.santana@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>; Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

William, boa noite.

Em complementação a solicitação de LI, seguem:

1. Proforma Invoice;
2. Packing List.

Atenciosamente,



Esta mensagem pode conter material confidencial, privilegiado e para uso exclusivo do destinatário. A autorização expressa, é estritamente proibido. Se você não for o destinatário desta mensagem, por

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 Antes de imprimir, pense no Planeta! (Before printing, please think about our environment!)

De: William Amorim Santana <william.santana@saude.gov.br>

Data: terça-feira, 23 de março de 2021 16:57

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: RES: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Ok Manuela, ficamos no aguardo.

Atenciosamente,

William Amorim Santana

Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br

De: Emanuela Medrades [<mailto:emanuela.medrades@precisamedicamentos.com.br>]
Enviada em: terça-feira, 23 de março de 2021 16:34
Para: William Amorim Santana <william.santana@saude.gov.br>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>; Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>
Assunto: Re: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

William, boa tarde.

Enviamos a demanda ao fabricante e agente comercial. Entretanto, devido ao fuso, teremos este retorno somente amanhã.

Conto com a sua compreensão.

Atenciosamente,



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 Antes de imprimir, pense no Planeta! (Before printing, please think about our environment!)

De: William Amorim Santana <william.santana@saude.gov.br>
Data: terça-feira, 23 de março de 2021 14:03
Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Regina Celia Silva Oliveira

<Regina.Oliveira@saude.gov.br>, Renata Marques Santana <renatam.santana@saude.gov.br>, Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>

Assunto: * URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152**

*****URGENTE*****

Prezado Fornecedor, após análise de nosso despachante na INVOICE apresentada, faz-se necessário a adequação da documentação bem como prestar, na INVOICE, os dados listados abaixo:

CONSIGNATÁRIO:

Ministério da Saúde/Departamento de Logística em Saúde - DLOG

CNPJ: 00.394.544/0008-51

Esplanada dos Ministérios, bloco "G" anexo A, 4ª andar, sala 431

Brasília- DF

CEP: 70.310-500

BRASIL

DADOS COMPLETOS DO FABRICANTE;

- Nome do Fabricante.
- Endereço.

DESCRIÇÃO COMPLETA DA MERCADORIA;

- Informar Código de Harmonização NCM (nomenclatura Comum Mercosul).
- Informar o peso líquido e o peso bruto.
- Identificar como o quantitativo vira (caixa, Frasco, etc...).
- Identificar a validade do produto (data de fabricação e vencimento).

PAÍS DE ORIGEM;

- Informar localidade.

PAÍS DE DESTINO;

- Informar o aeroporto Internacional de Guarulhos (GRU).

INCOTERMS;

- Informar CIP e acrescentar os valores de frete e seguro.

ENVIAR PAKING LIST.

Ficamos no aguardo da correção da INVOICE e envio de packing List para abertura da Licença de Importação.

Atenciosamente,

William Amorim Santana

Ministério da Saúde

DIIMP/CGLOG/DLOG-SE

Ed. Anexo, 4º andar, Sala 431-A

55-61-3315-3760

william.santana@saude.gov.br

-----Mensagem original-----

De: Everton [mailto:everton@wegh.com.br]

Enviada em: terça-feira, 23 de março de 2021 13:33

Para: William Amorim Santana <william.santana@saude.gov.br>; 'Roberta' <roberta@wegh.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>

Assunto: RE: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Boa tarde Prezados

William

Por gentileza solicitar as devidas correções na Proforma Invoice:

- Nome e endereço do Ministério da Saúde está errado (Consignee - Buyer)
- Informar aeroporto de destino - GRU
- INCOTERM é CIP ? Sem sim informar o valor do frete e valor de seguro (separados)
- Qual a NCM do produto ?
- Informar o peso líquido e o peso bruto
- A quantidade está em frascos, caixas... ?
- Nome e endereço completo do Fabricante
- Informar o Lote e validade do lote
- Este produto tem registro na ANVISA ? Se sim, informar o numero
- Enviar o Packing list

No aguardo das correções para registro da LI.

ATENÇÃO PARA O NOVO ENDEREÇO DA WEGH ABAIXO NA ASSINATURA Grato

Everton F Campos

WEGH Assessoria e Logística Internacional Ltda Rua José do Patrocínio, 220 - Aclimação - São Paulo - SP - Brasil CEP 04108-000 – São Paulo-SP- Brasil Phone +55 11 5573-0877 / 5572.4330 / 5908-5050 – RAMAL: 208

E-mail: everton@wegh.com.br

www.wegh.com.br

-----Original Message-----

From: William Amorim Santana

Sent: Monday, March 22, 2021 12:19 PM

To: everton@wegh.com.br; lucas@wegh.com.br; 'Roberta Pereira' <roberta@wegh.com.br>; 'Carlos E.J. Pereira' <carlos@wegh.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>

Subject: *** URGENTE *** SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Prezada Equipe WEGH,

Boa tarde!

Segue documentação para análise complementar e, estando em conformidade, gentileza providenciar a abertura de Licença de Importação (LI).

Atenciosamente,

William Amorim Santana

Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br<mailto:lilian.sa@saude.gov.br>

De: Thiago Fernandes da Costa
Enviada em: segunda-feira, 22 de março de 2021 11:54
Para: William Amorim Santana <william.santana@saude.gov.br>; Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>; Francieli Fontana Sutile Tardetti Fantinato <francieli.fantinato@saude.gov.br>; Lauricio Monteiro Cruz <lauricio.cruz@saude.gov.br>
Assunto: RE: SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Prezados, bom dia !

Informo que este Departamento formalizou o Despacho DEIDT (0019651176) no processo 25000.175250/2020-85, a fim de realizar a devida instrução quanto à importação requerida pela contratada. Não obstante, informo também que estamos de acordo com o pleito e solicito a essa Divisão que dê andamento aos trâmites necessários para a realização da importação.

Atte.,

[cid:63368a64-85f9-4ff0-b02b-8eda019cf04c]

Thiago Fernandes da Costa

Gestão de Insumos

Departamento de Imunização e Doenças Transmissíveis - DEIDT

Secretaria de Vigilância em Saúde - SVS

* (61) 3315-3646

De: William Amorim Santana <william.santana@saude.gov.br<mailto:william.santana@saude.gov.br>>
Enviado: segunda-feira, 22 de março de 2021 10:27
Para: Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br<mailto:Regina.Oliveira@saude.gov.br>>; Renata Marques Santana <renatam.santana@saude.gov.br<mailto:renatam.santana@saude.gov.br>>; Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br<mailto:thiago.fernandes@saude.gov.br>>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br<mailto:lista.divisaoimportacao@saude.gov.br>>; Alex Lial Marinho <alex.marinho@saude.gov.br<mailto:alex.marinho@saude.gov.br>>
Assunto: SOLICITAÇÃO DE AUTORIZAÇÃO DE EMBARQUE 1ª PARCELA CONTRATO 29/2021 VACINA COVAXIN/BBV152

Prezado Fiscal Contrato 29/2021

Bom dia!

Chegou a esta Divisão de Importação (DIIMP), na data de 18/03/2021, documentação proveniente da empresa PRECISA MEDICAMENTOS referente a solicitação de autorização de embarque para 1ª parcela Contrato 29/2021 VACINA COVAXIN/BBV152.

Considerando o cronograma de entrega das parcelas, devidamente exposto abaixo, o qual demonstra que a entrega da 1ª parcela encontra-se com atraso de 05 (cinco) dias até a presente data:

CRONOGRAMA DE ENTREGA CONTRATUAL

PARCELA

COMPRIMIDOS

ENTREGA

RECEBIMENTO

1ª

4.000.000

17/03/2021

EM TRAMITE

2ª

4.000.000

27/03/2021

3ª

4.000.000

11/04/2021

4ª

4.000.000

26/04/2021

5ª

4.000.000

06/05/2021

TOTAL

20.000.000

Considerando tratar-se de vacina que não possui registro sanitário, junto a Agência Nacional de Vigilância Sanitária (ANVISA), cabendo a necessidade de solicitação de concessão de excepcionalidade para essa importação;

Considerando os demais parâmetros devidamente expostos no Termo de Referência (TR) do Contrato 29/2021 para esta aquisição a fim de atender o Departamento de Imunização e Doenças Transmissíveis (DEIDT/SVS); e

Considerando que o objeto do contrato em questão é um insumo essencial para o enfrentamento da Pandemia de SARS-COV-2.

Esta Divisão de Importação (DIIMP), pelo presente exposto, solicita autorização do fiscal do contrato ou seu respectivo substituto eventual para prosseguir com o processo de autorização de embarque desta parcela.

Aguardo resposta.

OBS: Documento disposta no link: <https://www.dropbox.com/t/HFj13mkBO2irwJ7C>

Atenciosamente,

William Amorim Santana

Ministério da Saúde

DIIMP/CGLOG/DLOG-SE

Ed. Anexo, 4º andar, Sala 431-A

55-61-3315-3760

william.santana@saude.gov.br<<mailto:lilian.sa@saude.gov.br>>

De: Cassiana Perinazzo da Veiga Schio Em nome de DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG Enviada em: quinta-feira, 18 de março de 2021 14:39

Para: LISTA - DIVISÃO DE IMPORTAÇÃO

<lista.divisaoimportacao@saude.gov.br<<mailto:lista.divisaoimportacao@saude.gov.br>>>; William Amorim Santana <william.santana@saude.gov.br<<mailto:william.santana@saude.gov.br>>>; Luis Ricardo Fernandes Miranda <luisf.miranda@saude.gov.br<<mailto:luisf.miranda@saude.gov.br>>>

Cc: 'emanuela.medrades@precisamedicamentos.com.br'

<emanuela.medrades@precisamedicamentos.com.br<<mailto:emanuela.medrades@precisamedicamentos.com.br>>>; DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG <dlog@saude.gov.br<<mailto:dlog@saude.gov.br>>>

Assunto: ENC: AUTORIZAÇÃO EXCEPCIONAL DE IMPORTAÇÃO - VACINA COVID

Prezados, boa tarde!

Encaminhado para conhecimento e providências no que couber documentos encaminhados pela Precisa Medicamentos, referente autorização excepcional de importação para vacina Covid-19.

Atenciosamente,

Equipe DLOG/SE/MS

De: Emanuela Medrades

<emanuela.medrades@precisamedicamentos.com.br<mailto:emanuela.medrades@precisamedicamentos.com.br>>

>

Enviada em: quinta-feira, 18 de março de 2021 09:20

Para: DEPARTAMENTO DE LOGÍSTICA EM SAÚDE - DLOG <dlog@saude.gov.br<mailto:dlog@saude.gov.br>>

Cc: Lenice Guimaraes Araujo <lenice.araujo@saude.gov.br<mailto:lenice.araujo@saude.gov.br>>

Assunto: AUTORIZAÇÃO EXCEPCIONAL DE IMPORTAÇÃO - VACINA COVID

Senhores, bom dia.

Solicitamos em concordância com a RDC 476/2.021 a autorização excepcional de importação de vacina para Covid19.

Enviamos os documentos através do link a seguir: <https://www.dropbox.com/t/HFj13mkBO2irwJ7C>

Permanecemos a disposição,

Atenciosamente,

[Uma imagem contendo guarda-chuva Descrição gerada automaticamente]

[signature_631106945]

IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.

EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA.

É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.

EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.

EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET

Ariadne Gisele Muniz Bonvino

De: William Amorim Santana
Enviado em: quarta-feira, 24 de março de 2021 17:15
Para: Emanuela Medrades
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Ariadne Gisele Muniz Bonvino; Alex Lial Marinho
Assunto: Solicitação de documentação complementar para envio a ANVISA

Prezada Emanuela,

Boa tarde!

Recebemos comunicado da ANVISA, no qual esta solicita complementação de documentos para continuidade do processo:

Faço uma observação quanto aos itens abaixo, com destaque para os em negrito:

Após verificação da instrução processual, permanecem pendentes os seguintes documentos: Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa – Comercialização de Medicamentos Ltda;

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

O prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. De acordo com as datas de fabricação dos lotes a serem importados, observa-se que o prazo de validade irá expirar nos meses de abril e maio/2021. Solicita-se esclarecer se é possível a utilização de todo o quantitativo previamente à data de expiração dos lotes.

Ficamos no aguardo do envio deste, com devida urgência que o caso requer, para encaminha-los a ANVISA.

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br

Ofício Precisa Contrato_29/2021 nº 002/2021

Brasília/DF, 25 de março de 2021.

A Sua Senhoria
Karin Schuck Hemesath Mendes
Chefe de Gabinete
Presidência
Agência Nacional de Vigilância Sanitária
SAI Trecho 05, Área Especial 57
71205-005 Brasília/DF

Com cópia
A Sua Senhoria
Roberto Ferreira Dias
Departamento de Logística em Saúde
Secretaria Executiva
Ministério da Saúde
Esplanada dos Ministérios Bloco G
Anexo A - 4º Andar sala 464
70058-900 Brasília/DF

Ref. Processo 25351.908110/2021-03

Senhora Chefe de Gabinete,

1. Em atenção ao Ofício nº 643/2021/SEI/GADIP-CG/ANVISA, de 23/03/2021, relativo às pendências apontadas por vossa senhoria, vimos por meio deste esclarecer os seguintes pontos:
2. Em relação ao parágrafo 2, item I, certificados de liberação dos lotes a serem importados (inciso IV do art. 16 da RDC 476/2021), restando pendente os certificados de liberação dos respectivos lotes emitidos pelo fabricante, informamos que todos os lotes se encontram no CDL – *Central Drugs Laboratory* responsável pela emissão dos Certificados de Origem bem como indicação de qual lote será destinado as exportações. Os certificados já foram requisitados e estamos aguardando sua disponibilização em breve.

3. Sobre o parágrafo 2, item II, relativo ao relatório técnico de avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial, apresentamos o relatório como forma de comprovação que o produto atende aos padrões de qualidade, eficácia e segurança emitido pelo CDSCO – *Central Drugs Standard Control Organization (Biological Division)*, sendo este documento a liberação para uso emergencial e ao mesmo tempo o relatório técnico de avaliação contendo todas as ressalvas. Em complementação, fornecemos também o GMP – *Good Manufacturing Practice* emitido pela mesma autoridade para a produção da Covaxin e o GMP - *Good Manufacturing Practice* emitido pela OMS – Organização Mundial de Saúde para todas as linhas de produção.
4. Referente ao parágrafo 2, item III, relativo ao licenciamento de importação (LI) registrado no SICOMEX entendemos que tal item já fora atendido, sendo referido no Licenciamento de número 21/0796694-1 com situação atual para análise.
5. Já em referência ao parágrafo 3, sobre a necessidade de prestarmos os esclarecimentos devidos, assim os esclarecemos.
6. Sobre o parágrafo 3, item I, esclarecemos que o importador será o Ministério da Saúde, inclusive já sendo apresentado através do SISCOMEX com anuência do fiscal do contrato.
7. Relativo ao parágrafo 3, item II, esclarecemos que a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância estão observando as regras definidas na RDC n° 406/2020 e também na IN n° 63/2020, além dos demais protocolos de vigilância epidemiológica e sanitária de eventos adversos pós vacinação. Toda estrutura de monitoramento, inclusive fluxos e plataformas de notificação, foi planejada e estarão ativas antes do primeiro embarque. E também já fora enviada a declaração de adoção e cumprimento de todas as diretrizes de Farmacovigilância.
8. No parágrafo 3, item III, a *in voice* apresentada, corresponde às entregas parceladas relativas ao cronograma do contrato 29/2021, conforme solicitado pelo Ministério da Saúde. Considerando que os embarques serão fracionados, e a impossibilidade de registrar mais de uma DI – Declaração de Importação através de somente um Licenciamento de Importação, informamos que iremos solicitar de forma contínua com anuência do Ministério da Saúde cada uma das Licenças de Importação até concluir o quantitativo contratado de 20.000.000 (vinte milhões) de doses.
9. Sobre o parágrafo 3, item IV, o prazo de validade aprovado pela autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8°, porém, os estudos de estabilidade acelerada já avançaram tal período. Dessa forma, a Precisa Medicamentos, apresenta a possibilidade de assinatura de um termo de compromisso assegurando que nenhum produto importado, terá percorrido mais que 30% de sua validade.

10. Certos de que as informações apresentadas e os esclarecimentos prestados, além de reapresentar todos os documentos aqui citados, sejam suficientemente capazes de ilidir as dúvidas suscitadas, solicitamos a continuidade na análise do Ofício nº 62/2021/DLOG/SE/MS para autorização da importação da vacina Covaxin.

Atenciosamente.

EMANUELA BATISTA DE SOUZA MEDRADES
Diretora Técnica



Ministério da Saúde
Secretaria Executiva
Departamento de Logística em Saúde

DESPACHO

DLOG/SE/MS

Brasília, 26 de março de 2021.

À CGLOG,

Assunto: **Solicita autorização para importação, em caráter excepcional, de 20.000.000 (vinte milhões) de doses da vacina COVAXIN.**

1. Em atenção ao Despacho SE/GAB/SE/MS(0019715459) que trata do Ofício nº 643/2021/SEI/GADIP-CG/ANVISA (0019715346), de 23/03/2021, oriundo da Agência Nacional de Vigilância Sanitária - Anvisa, que, em atenção ao Ofício nº 62/2021/DLOG/SE/MS (0019668812), informa que, após verificação, permanecem pendentes os seguintes documentos, para avaliação da autorização de importação da vacina COVAXIN:

I - Certificados de liberação dos lotes a serem importados (inciso IV do art. 16 da RDC 476/2021). Foram enviados apenas os laudos analíticos dos lotes 37620001A, 37620002A e 37620003A, restando pendente os certificados de liberação dos respectivos lotes emitidos pelo fabricante;

II - Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

III - Licenciamento de importação (LI) registrado no SISCOMEX (inciso VI do art. 17 da RDC 476/2021).

2. Ressalta-se que, quanto aos documentos apresentados, fazem-se necessários os seguintes esclarecimentos:

I - Declaração da Precisa - Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa - Comercialização de Medicamentos Ltda;

II - Declaração da Precisa - Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

III - No *Invoice* apresentado, o quantitativo de doses (3 milhões) não corresponde ao requisitado no Ofício nº 62/2021/DLOG/SE/MS (20 milhões);

IV - O prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. De acordo com as datas de fabricação dos lotes a serem importados, observa-se que o prazo de validade irá expirar nos meses de abril e maio/2021. Solicita-se esclarecer se é possível a utilização de todo o quantitativo previamente à data de expiração dos lotes.

2. Desta forma, encaminha-se os autos à essa Coordenação Geral para ciência e providências necessárias, tendo em vista o § 3º do art. 17 da RDC 476/2021, o qual estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo, até que sejam atendidas.



Documento assinado eletronicamente por **Roberto Ferreira Dias, Diretor(a) do Departamento de Logística**, em 30/03/2021, às 08:23, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



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Referência: Processo nº 25000.043170/2021-42

SEI nº 0019766131



Gabinete do Diretor-Presidente - Chefe de Gabinete
SIA Trecho 05, Área Especial 57, Brasília/DF, CEP 71.205.05
Telefone: 0800 642 9782 - www.anvisa.gov.br

Ofício nº 663/2021/SEI/GADIP-CG/ANVISA

Ao Senhor
Antônio Elcio Franco Filho
Secretário-Executivo
Secretaria-Executiva do Ministério da Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Com cópia
Ao Senhor
Roberto Ferreira Dias
Diretor do Departamento de Logística em Saúde
Departamento de Logística em Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Assunto: Solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN

Referência: Caso responda este Ofício, indicar expressamente o Processo nº 25351.908110/2021-03.

Senhor Secretário-Executivo,

1. Cumprimentando-o, nos dirigimos a Vossa Senhoria para consignar que o pedido de importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152, processo SEI nº 25351.908110/2021-03, constitui processo administrativo formal, de caráter sigiloso.
2. O peticionamento em tal processo deve ser formulado pelo importador legitimado, no caso, o Ministério da Saúde.
3. Dessa forma, encarecemos que as manifestações no âmbito desse processo sejam centralizadas por esse Ministério. O motivo de tal solicitação se deve ao fato de que a interveniente, Precisa Medicamentos, tem, por intermédio de mensagens eletrônicas (e-mail), copiado setores e diretorias da Anvisa com informações alusivas ao processo, o que pode causar tumulto à instrução processual.
4. Em atenção à documentação complementar encaminhada pelo Ministério da Saúde pelos processos 25351.908361/2021-80 e 25351.908358/2021-66, informo que:

I - De acordo com a Precisa Medicamentos, o CDSCO emitiu um documento (anexo BBV152 – COVAXIN – EUL – 12032021) que transmite a autorização para uso emergencial

com as suas ressalvas, bem como o relatório de avaliação técnica em um único documento. No entanto, a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152-COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade;

II - Foi apresentado o Licenciamento de Importação (LI), no qual consta o lote nº 37F21004A . Tal lote é diferente daqueles para os quais foram apresentados os certificados de análise (lotes 37620001A, 37620002A e 37620003A) no pleito inicial. Ademais, no LI consta a data de validade do lote 37F21004A como sendo 01/2023. No entanto, o prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. Portanto, a data de validade do referido lote não corresponde ao prazo de validade aprovado pela autoridade da Índia. Para o lote nº 37F21004A, não foi apresentado o Certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade, emitido pelo fabricante;

III - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo.

5. Esclarecemos que, conforme Lei nº 14.124, de 10 de março de 2021, os prazos para decisão da Anvisa estão vinculados com o conteúdo das informações apresentadas. Ademais, o § 3º do art. 17 da RDC 476/2021 estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo até que sejam atendidas.

6. Solicitamos ainda, ao Ministério da Saúde, que os próximos documentos sejam enviados como peticionamento intercorrente ao processo SEI nº 25351.908110/2021-03.

7. Agradecemos antecipadamente pela compreensão.

Atenciosamente,



Documento assinado eletronicamente por **Karin Schuck Hemesath Mendes, Chefe de Gabinete**, em 24/03/2021, às 20:32, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015 http://www.planalto.gov.br/ccivil_03/_Ato2015-2018/2015/Decreto/D8539.htm.



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RES: Ofício nº 663/2021/SEI/GADIP-CG/ANVISA

Zania Maria dos Santos Pires

Para: APOIO DA SECRETARIA-EXECUTIVA; Lisiane Martins Collares; Thairo Gomes Zampierri Costa

Cc: administrativo.gadip@anvisa.gov.br

Categorias: finalizado

segunda-feira, 29 de março de 2021 3:04

Boa tarde,

Prezado (as),

Referente: Ofício nº 663/2021/SEI/GADIP-CG/ANVISA - 24.03.2021.

Assunto: Solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN

Referência: Processo nº 25351.908110/2021-03.

Informamos que o documento foi registrado no Sistema Eletrônico de Informação - SEI/MS sob o número 25000.043170/2021-42, e encaminhado à área competente, sendo, portanto, dispensado o envio do documento físico.

Caso seja necessária a complementação de informações, favor indicar o número do processo e encaminhar ao e-mail apoio.se@saude.gov.br.

Para informações quanto aos trâmites e encaminhamentos segue o link para pesquisa: <https://sei.saude.gov.br/pesquisa/>

atenciosamente,

Zania Pires - Apoio/SE/MS.
3315-2370.

De: Lisiane Martins Collares em nome de APOIO DA SECRETARIA-EXECUTIVA

Enviado: segunda-feira, 29 de março de 2021 0:47

Para: Zania Maria dos Santos Pires

Cc: APOIO DA SECRETARIA-EXECUTIVA

Assunto: ENC: Ofício nº 663/2021/SEI/GADIP-CG/ANVISA

-----Mensagem original-----

De: ANVISA/Coordenação de Apoio Administrativo

<administrativo.gadip@anvisa.gov.br>

Enviada em: quarta-feira, 24 de março de 2021 20:37

Para: APOIO DA SECRETARIA-EXECUTIVA <apoio.se@saude.gov.br>

Assunto: Ofício nº 663/2021/SEI/GADIP-CG/ANVISA

Prezados,

Encaminha-se o Ofício nº 663/2021/SEI/GADIP-CG/ANVISA com nova manifestação da



Ministério da Saúde
Secretaria Executiva
Gabinete da Secretaria Executiva

DESPACHO

SE/GAB/SE/MS

Brasília, 29 de março de 2021.

Assunto: Solicita autorização para importação, em caráter excepcional, de 20.000.000 (vinte milhões) de doses da vacina COVAXIN.

1. Trata-se do Ofício nº 663/2021/SEI/GADIP-CG/ANVISA (0019786170), de 24/3/2021, da Agência Nacional de Vigilância Sanitária - Anvisa, o qual informa que o pedido de importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin/BBV152, processo SEI nº 25351.908110/2021-03, constitui processo administrativo formal, de caráter sigiloso. Ainda, em atenção à documentação complementar encaminhada por este Ministério da Saúde pelos processos 25351.908361/2021-80 e 25351.908358/2021-66, informa que:

I - De acordo com a Precisa Medicamentos, o CDSCO emitiu um documento (anexo BBV152 - COVAXIN - EUL - 12032021) que transmite a autorização para uso emergencial com as suas ressalvas, bem como o relatório de avaliação técnica em um único documento. No entanto, a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152- COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade;

II - Foi apresentado o Licenciamento de Importação (LI), no qual consta o lote nº 37F21004A . Tal lote é diferente daqueles para os quais foram apresentados os certificados de análise (lotes 37620001A, 37620002A e 37620003A) no pleito inicial. Ademais, no LI consta a data de validade do lote 37F21004A como sendo 01/2023. No entanto, o prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. Portanto, a data de validade do referido lote não corresponde ao prazo de validade aprovado pela autoridade da Índia. Para o lote nº 37F21004A, não foi apresentado o Certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade, emitido pelo fabricante;

III - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo.

2. O referido documento solicita que os próximos documentos sejam enviados como peticionamento intercorrente ao processo SEI nº 25351.908110/2021-03.

3. Ao Departamento de Logística em Saúde - **DLOG/SE/MS**, para conhecimento e demais providências, tendo em vista o § 3º do art. 17 da RDC 476/2021, o qual estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo, até que sejam atendidas.

PAULO MARCOS C. R. DE OLIVEIRA
Chefe de Gabinete



Documento assinado eletronicamente por **Paulo Marcos Castro Rodopiano de Oliveira, Chefe de Gabinete da Secretaria Executiva**, em 29/03/2021, às 17:32, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



A autenticidade deste documento pode ser conferida no site http://sei.saude.gov.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0019789165** e o código CRC **9748302B**.

Referência: Processo nº 25000.043170/2021-42

SEI nº 0019789165

Data de Envio:

29/03/2021 15:10:15

De:

MS/DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>

Para:

Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>
'LISTA - DIVISÃO DE IMPORTAÇÃO' <lista.divisaoimportacao@saude.gov.br>
renatam.melo@saude.gov.br
Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>
Marcelo Calado <marcelo.calado@saude.gov.br>
Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>
katiane.torres@saude.gov.br
alex.marinho@saude.gov.br
Genivano Pinto de Araújo <genivano.araujo@saude.gov.br>

Assunto:

Pendência Anvisa quanto a autorização da Covaxin CT 29/2021 (25000.043170/2021-42)

Mensagem:

Prezados fiscais e colegas do DEIDT,

De acordo com o Ofício 663/2021 da Anvisa, a agência relata que sendo o Ministério da Saúde o importador, somos nós que devemos apresentar a declaração que ateste adoção de estratégias de monitoramento, conforme disposto abaixo:

...

III - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo.

Diante da exigência exarada pela Anvisa, solicitamos providenciar junto ao PNI tal declaração, uma vez que é a área responsável por executar tais ações

Desde já agradecemos.

Att.

Ariadne Bonvino
DIIMP/CGLOG/DLOG/SE

Anexos:

Oficio_0019786170_RES__VACINACAO__RPP_5002083_77.2021.4.03.6100__PJe_1__Grau_.pdf

Ariadne Gisele Muniz Bonvino

De: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Enviado em: segunda-feira, 29 de março de 2021 12:03
Para: Ariadne Gisele Muniz Bonvino; William Amorim Santana; Marcelo Calado
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Alex Lial Marinho
Assunto: Re: Solicitação de documentação complementar para envio a ANVISA

Ariadne, bom dia.

Iremos enviar nas próximas horas os estudos de estabilidade. E de antemão informamos que as vacinas serão transportadas em envirotainers.

@William Amorim Santana, pode por gentileza me reiterar quais são os documentos faltantes da LI ?

Atenciosamente,

Emanuela Medrades
Diretora Executiva

Av Portugal, 1100 - Itaqui- Itapevi- SP
55 11 3080-5140 - 11 9 3257-4642
www.precisamedicamentos.com.br



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De: Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>
Data: sexta-feira, 26 de março de 2021 11:18
Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>, William Amorim Santana <william.santana@saude.gov.br>, Marcelo Calado <IMCEAEX-
_O=SAUDE_OU=EXCHANGE+20ADMINISTRATIVE+20GROUP+20+28FYDIBOHF23SPDLT+29_CN=RECIPIENTS
_CN=Marcelo+20Caladoae8@saude.gov.br>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Alex Lial Marinho <alex.marinho@saude.gov.br>
Assunto: RES: Solicitação de documentação complementar para envio a ANVISA

Emanuela, bom dia!

Reitero a solicitação do William quanto ao envio do estudo de estress/estabilidade. Esse documento é importante para análise da Anvisa e do INCQS, além disso, também para caso haja excursões de temperatura durante a importação e a nível local (tem acontecido muito).

A fim de evitar excursões durante a importação, recomendamos fortemente que as vacinas sejam acondicionadas e enviadas em envirotainers.

Abraços,

Ariadne Bonvino
farmacêutica
DIIMP/CGLOG/DLOG/SE

De: Emanuela Medrades [emanuela.medrades@precisamedicamentos.com.br]

Enviado: sexta-feira, 26 de março de 2021 10:12

Para: William Amorim Santana

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Ariadne Gisele Muniz Bonvino; Alex Lial Marinho

Assunto: Re: Solicitação de documentação complementar para envio a ANVISA

William, bom dia.

Recebemos este ofício da SE com questionamentos semelhantes e que devem ser respondidos pelo MS.

Compartilho nosso ofício com as respostas enumeradas para que possam atuar por ai.

Atenciosamente,

Emanuela Medrades
Diretora Executiva

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De: William Amorim Santana <william.santana@saude.gov.br>

Data: quarta-feira, 24 de março de 2021 17:15

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>, Alex Lial Marinho <alex.marinho@saude.gov.br>

Assunto: Solicitação de documentação complementar para envio a ANVISA

Prezada Emanuela,

Boa tarde!

Recebemos comunicado da ANVISA, no qual esta solicita complementação de documentos para continuidade do processo:

Faço uma observação quanto aos itens abaixo, com destaque para os em negrito:

Após verificação da instrução processual, permanecem pendentes os seguintes documentos: Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa – Comercialização de Medicamentos Ltda;

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

O prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. De acordo com as datas de fabricação dos lotes a serem importados, observa-se que o prazo de validade irá expirar nos meses de abril e maio/2021. Solicita-se esclarecer se é possível a utilização de todo o quantitativo previamente à data de expiração dos lotes.

Ficamos no aguardo do envio deste, com devida urgência que o caso requer, para encaminha-los a ANVISA.

Atenciosamente,

William Amorim Santana

Ministério da Saúde

DIIMP/CGLOG/DLOG-SE

Ed. Anexo, 4º andar, Sala 431-A

55-61-3315-3760

william.santana@saude.gov.br

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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Ariadne Gisele Muniz Bonvino

De: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Enviado em: segunda-feira, 29 de março de 2021 13:21
Para: Ariadne Gisele Muniz Bonvino; William Amorim Santana; Marcelo Calado
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Alex Lial Marinho
Assunto: Re: Solicitação de documentação complementar para envio a ANVISA
Anexos: CoA BR Full_batches CDL.pdf; DECLARACAO_ART_12_III_Ateste de adoção das estratégias de monitoramento e cumprimento das diretrizes de Farmacovigilância.pdf; Índia EUL 12032021.pdf

William,

Em tempo, segue certificado de análise para todos os batches que estão no CDL e serão destinados ao Brasil.

Reitero também:

1. Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). **Anexo Índia EUL.**
2. Declaração da Precisa – Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de Farmacovigilância. **Anexo Declaração conforme artigo.**

Atenciosamente,

Emanuela Medrades
Diretora Executiva

Av Portugal, 1100 - Itaqui- Itapevi- SP
55 11 3080-5140 - 11 9 3257-4642
www.precisamedicamentos.com.br



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De: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Data: segunda-feira, 29 de março de 2021 12:03
Para: Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>, William Amorim Santana

<william.santana@saude.gov.br>, Marcelo Calado <IMCEAEX-
_O=SAUDE_OU=EXCHANGE+20ADMINISTRATIVE+20GROUP+20+28FYDIBOHF23SPDLT+29_CN=RECIPIENTS
_CN=Marcelo+20Caladoae8@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Alex Lial Marinho
<alex.marinho@saude.gov.br>

Assunto: Re: Solicitação de documentação complementar para envio a ANVISA

Ariadne, bom dia.

Iremos enviar nas próximas horas os estudos de estabilidade. E de antemão informamos que as vacinas serão transportadas em envirotainers.

@William Amorim Santana, pode por gentileza me reiterar quais são os documentos faltantes da LI ?

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Emanuela Medrades

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De: Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>

Data: sexta-feira, 26 de março de 2021 11:18

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>, William Amorim Santana <william.santana@saude.gov.br>, Marcelo Calado <IMCEAEX-
_O=SAUDE_OU=EXCHANGE+20ADMINISTRATIVE+20GROUP+20+28FYDIBOHF23SPDLT+29_CN=RECIPIENTS
_CN=Marcelo+20Caladoae8@saude.gov.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Alex Lial Marinho <alex.marinho@saude.gov.br>

Assunto: RES: Solicitação de documentação complementar para envio a ANVISA

Emanuela, bom dia!

Reitero a solicitação do William quanto ao envio do estudo de estress/estabilidade. Esse documento é importante para análise da Anvisa e do INCQS, além disso, também para caso haja excursões de temperatura durante a importação e a nível local (tem acontecido muito).

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Abraços,

Ariadne Bonvino
farmacêutica
DIIMP/CGLOG/DLOG/SE

De: Emanuela Medrades [emanuela.medrades@precisamedicamentos.com.br]
Enviado: sexta-feira, 26 de março de 2021 10:12
Para: William Amorim Santana
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Ariadne Gisele Muniz Bonvino; Alex Lial Marinho
Assunto: Re: Solicitação de documentação complementar para envio a ANVISA

William, bom dia.

Recebemos este ofício da SE com questionamentos semelhantes e que devem ser respondidos pelo MS.

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Atenciosamente,

Emanuela Medrades
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De: William Amorim Santana <william.santana@saude.gov.br>
Data: quarta-feira, 24 de março de 2021 17:15

Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>

Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>, Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>, Alex Lial Marinho <alex.marinho@saude.gov.br>

Assunto: Solicitação de documentação complementar para envio a ANVISA

Prezada Emanuela,

Boa tarde!

Recebemos comunicado da ANVISA, no qual esta solicita complementação de documentos para continuidade do processo:

Faço uma observação quanto aos itens abaixo, com destaque para os em negrito:

Após verificação da instrução processual, permanecem pendentes os seguintes documentos: Relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária da Índia, responsável pela concessão da autorização para uso emergencial (inciso II do art. 17 da RDC 476/2021). De acordo com a RDC, o relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s; e

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto ao enquadramento na RDC 476/2021. Solicita-se esclarecer quem será o importador, se o Ministério da Saúde ou a Precisa – Comercialização de Medicamentos Ltda;

Declaração da Precisa – Comercialização de Medicamentos Ltda quanto à adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância;

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Ficamos no aguardo do envio deste, com devida urgência que o caso requer, para encaminha-los a ANVISA.

Atenciosamente,

William Amorim Santana

Ministério da Saúde

DIIMP/CGLOG/DLOG-SE

Ed. Anexo, 4º andar, Sala 431-A

55-61-3315-3760

william.santana@saude.gov.br

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.
EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

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IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA. É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS.
EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET

BHARAT

B I O T E C H

Genome Valley, Turkapally- Shameerpct

Hyderabad- 500078, INDIA

Department: Quality Control

CERTIFICATE OF ANALYSIS

Product : WHOLE VIRION, INACTIVATED CORONA VIRUS BULK

Batch Number : 37F21004A

A.R. Number : IP-37-21-415

Batch size : NLT 250 L x 60

Date of Receipt : 19/03/2021

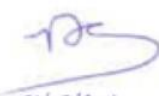
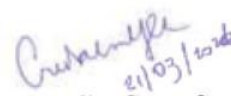
Mfg. Date : 02/21

Qty. Sampled : 102 mL

Exp. Date : To be established

Batch Release Date : 21/03/2021

Specification No. :37F21004A on CDL for Brazilian MoH. (3,000,000).

| TESTS | SPECIFICATIONS | RESULTS ~ |
|--|---|--|
| Identity test for vaccine virus (In-vitro) | ELISA test and SDS PAGE serve as an identity test | Complies |
| Description | Clear colourless, translucent liquid, free from particulate matter | Clear colourless, translucent liquid, free from particulate matter |
| pH | 7.00 - 8.00 | 7.41 |
| Sterility | No growth should be observed (Sterile) | No growth observed |
| Total Protein content (Lowry et al) | NLT 15.00 kg/mL | 112.05 kg/mL |
| Corona virus amplification test | No residual live virus should be observed in Corona virus Amplification test | No residual live virus observed |
| qCorona virus inactivation test | No CPE should be observed | No CPE observed |
| Residual cellular DNA Content | NMT 10.00 ng/SHD | 0.42 ng/SHD |
| Residual Bovine serum Albumin content | NMT 50.00 ng/SHD | 12.36 ng/SHD |
| Antigenic purity by SDS-PAGE | Should show only Corona virus specific bands | Complies |
| Bacterial Endotoxin | Less than 25 international Units (IU) per mL | <12.5 IU per mL |
| Residual BPL Content | No Residual BPL Content should be present | No Residual BPL Content present |
| Residual trypsin content by ELISA method | For information only | 0 ng/mL |
| OPINION: Sample DOES NOT COMPLY COMPLIES as per specification No.: 37F21004A | | |
| Prepared By: I.C. Saug 21/03/2021 | Checked By:  21/03/2021 | Approved By:  (Head — Quality Control) 21/03/2021 |

Form No.: FMQCG/024/001.00

Page No.: 01 of 01

FOR RESTRICTED CIRCULATION

UNCONTROLLED COPY

DECLARAÇÃO

Ateste de adoção das estratégias de monitoramento e cumprimento das diretrizes de Farmacovigilância nos termos da RDC/ANVISA 476, de 10 de março de 2021 artigo 12 inciso III e Anexo

A **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA.**, pessoa jurídica de direito privado, com endereço na Avenida Portugal, n.º 1100, Rua 5, parte A-14, Bairro Itaquí, Cidade de Itapevi, Estado de São Paulo, CEP 06696-060, CNPJ 03.394.819/0005-00, neste ato representada por **Emanuela Batista de Souza Medrades**, brasileira, farmacêutica, portador do RG 35.435.759-1- SSP-SP e CPF 330.976.208-42, considerando o disposto na Resolução de Diretoria Colegiada - RDC nº 476, de 10 de março de 2021, considerando o disposto na Resolução de Diretoria Colegiada - RDC nº 476, de 10 de março de 2021, o importador, na pessoa de **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA**, CPF/CNPJ 03.392.918/0005-00, **DECLARA** cumprir o disposto nas normas sanitárias vigentes para a importação e distribuição de medicamentos e vacinas para Covid-19. O importador declara que realiza todos os procedimentos necessários e possui capacidade técnica e administrativa para garantir a qualidade, segurança e eficácia do medicamento ou vacina para Covid-19 objeto da importação, bem como adotará as estratégias de monitoramento e cumprirá as diretrizes de farmacovigilância estabelecidas pela Anvisa. O importador, na pessoa de **PRECISA - COMERCIALIZACAO DE MEDICAMENTOS LTDA**, se responsabiliza pela veracidade e fidedignidade das informações aqui prestadas e declara que está ciente de que é responsável pela qualidade, segurança e eficácia do medicamento ou vacina para Covid-19, bem como assegura que este está adequado aos fins a que se destina e cumpre os requisitos legais e sanitários. Declaro estar ciente que o descumprimento das disposições contidas nesta Resolução e nas demais vinculadas constitui infração sanitária, nos termos da Lei nº 6437, de 20 de agosto de 1977, sem prejuízo das responsabilidades civil, administrativa e penal cabíveis.

Por ser expressão da verdade, firmamos a presente para que surta os seus efeitos legais.

Brasília/DF, 17 de março de 2021.

EMANUELA BATISTA DE SOUZA MEDRADES

CPF 330.976.208-42

Representante Legal/Técnica

F. No. BIO/MA/20/000103
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FDA Bhawan, Kotla Road,
New Delhi- 110002

Dated: 11/3/2021

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500078.

Subject- Permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in Form CT-23 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940 - regarding.

Reference:

1. Permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021.
2. Your letter nos. BBIL/RA/21/173, 177, 187 dated 06.03.2021, 08.03.2021 & 10.03.2021 submitted to this office vide email dated 06.03.2021, 08.03.2021 & 10.03.2021.


Sir,

This is with reference to the permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021 to manufacture Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in public interest use in as an abundant precaution, in clinical trial mode with various conditions.

In this regard, the interim safety and efficacy data of phase III clinical trial of Whole Virion, Inactivated Corona Virus Vaccine (BBV152) in the country submitted to this office was reviewed in consultation with SEC (COVID-19) committee on 08.03.2021 & 10.03.2021 respectively, wherein after detailed deliberation the committee recommended for omission of the condition of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation condition. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The firm should update the prescribing information and factsheet accordingly (under restricted use in emergency situation condition). All other conditions of the marketing authorisation shall continue to remain the same.

Accordingly, based on the recommendations of SEC, the condition "*This permission is for restricted use in emergency situation in public interest use in as an abundant precaution, in clinical trial mode*" as mentioned in the said permission is amended to read as "*This permission is for restricted use in emergency situation in public interest*". However, you are required to continue ongoing Phase III clinical trial as per approved clinical trial protocol & submit revised summary of product characteristics (SmPC), Prescribing Information (PI) and Factsheet.

Yours faithfully,


(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Drugs Controller Telangana, Directorate of Drug Control Administration, Drug Control Bhavan, Vengal Rao Nagar, Hyderabad-500 038, India.

New Delhi-110002
Date: 17/3/2021

Ms. Bharat Biotech International Ltd.,
Genome Valley, Shamshabad,
Hyderabad, India - 500078.

Subject: Permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in Form CT-33 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940 - regarding.

1. Permission granted by the Directorate in Form CT-33 vide no. MF/BIC/100003 dated 03.01.2021.
2. Your letter no. BIL/BIA/21/177, dt. 08.03.2021, 08.03.2021 & 10.03.2021 submitted to this office vide email dated 08.03.2021, 08.03.2021 & 10.03.2021.

This is with reference to the permission granted by the Directorate in Form CT-33 vide no. MF/BIC/100003 dated 03.01.2021 to manufacture Whole-virion inactivated SARS-CoV-2 Vaccine (BBV152) for restricted use in emergency situation in public interest use as an adjunct product, in clinical trial mode with various conditions.

In this regard, the interim safety and efficacy data of phase III clinical trial of Whole Virion, Inactivated Coronavirus Vaccine (BBV152) in the country submitted to this office was reviewed in consultation with SEC (BIVD-18) committee on 08.03.2021 & 10.03.2021 respectively, wherein after detailed deliberation the committee recommended for omission of the restriction of the use of the vaccine in clinical trial mode. However, the vaccine should be continued to be used under restricted use in emergency situation. Further, the ongoing phase III clinical trial should be continued as per the approved protocol. The trial should update the presiding information and label as per the restricted use in emergency situation condition. All other conditions of the marketing authorization shall continue to remain the same.

Accordingly, based on the recommendations of SEC, the condition "This permission is for restricted use in emergency situation in public interest use as an adjunct product, in clinical trial mode" as mentioned in the said permission is amended to read as "This permission is for restricted use in emergency situation in public interest. However, you are required to continue ongoing Phase III clinical trial as per approved clinical trial protocol & submit revised summary of product characteristics (SPC), Prescribing Information (PI) and Package Insert.

Yours faithfully,
/s/

(Dr. V. G. Srinivas)
Drugs Controller General (India)
Central Licensing Authority

File No: BIO/MA/20/000103
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Biological Division)

FDA Bhawan, Kotla Road,
New Delhi- 110002.
Dated: 8/11/2021

To,

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500 078.

Subject: Request for amend the Form CT-23 for permission to manufacture Whole Virion, Inactivated Corona Virus Vaccine (BBV152) for sale and distribution – regarding.

References:

1. Your letter vide no. BBIL/RA/20/006 dated 05.01.2021 submitted to this office vide diary no. 120 dated 06.01.2021.
2. Permission granted by this Directorate in Form CT-23 vide no. MF/BIO/21/000002 dated 03.01.2021.

Sir/Madam,

With reference to the subject cited above and based on the submission of information/documents to this office, the name of product code of Whole Virion, Inactivated Corona Virus Vaccine mentioned in the cover letter and permission is hereby amended to read as "BBV152" instead of BBV152C or BBV152B respectively.

Further, as per the license issued in Form 28D, 2.5ml, 5ml & 10 ml vial presentations, are also permitted subject to condition mentioned in permission, license & communication in this regard including the provisions of New Drugs and & Clinical trials Rules, 2019 under Drugs and Cosmetics Act, 1940.

Yours faithfully,

V.G.S

(Dr. V. G. Somani)
Drugs Controller General (India)

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Director, CDL, Kasauli, HP



सत्यमेव जयते

File No. BIO/MA/20/000103

From:

**The Drugs Controller General, India
Directorate General of Health Services**

FDA Bhawan, Kotla Road,
New Delhi- 110002, India.
Dated: 03-JAN-2021

To

M/s Bharat Biotech International Ltd.,
Genome Valley, Shameerpet,
Hyderabad, India -500 078.

Subject: Application for permission to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152C) for restricted use in emergency situation in Form CT-23 as per the provisions of New Drugs and Clinical Trials Rules, 2019 under Drugs & Cosmetics Act, 1940- regarding.

Reference: SUGAM application no. BIO/CT21/FF/2020/22922 dated 07-Dec-2020.

Sir,

Please find enclosed herewith permission no. MF/BIO/21/000002 dated 03-Jan-2021 in Form CT-23 to manufacture of Whole-virion Inactivated SARS-CoV-2 Vaccine (BBV152C) for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode as per the provisions of New Drugs and Clinical Trial Rules, 2019 under Drugs & Cosmetics Act, 1940.

Yours faithfully,

VENUGOPAL
GIRDHARILAL
SOMANI

Digitally signed by VENUGOPAL
GIRDHARILAL SOMANI
DN: c=IN, o=MINISTRY OF HOME AFFAIRS,
ou=CDSCO DGHS, postalCode=431401,
serialNumber=25420=173403345df62d489632379a147
1b1d6e90b2b6a56c83f0be2154e39b1af
7, cn=VENUGOPAL GIRDHARILAL SOMANI
Date: 2021.01.03 17:43:16 +05'30'

(Dr. V. G. Somani)

**Drugs Controller General (India)
Central Licensing Authority**

Copy to:

1. The Deputy Drugs Controller (India), CDSCO Zonal office, CDSCO Bhavan, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad - 500038, India.
2. The Drugs Controller Telangana, Directorate of Drug Control Administration, Drug Control Bhavan, Vengal Rao Nagar, Hyderabad-500 038, India.

FORM CT-23

(See rules 81, 82, 83 and 84)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licensing Authority hereby grant permission to M/s Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com, Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com to manufacture for sale of pharmaceutical formulation manufactured by a manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this license:

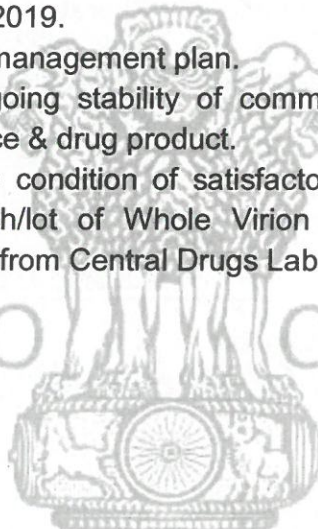
| S. No | Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer). | Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site). | | | | | | |
|----------------|--|---|-----------|------------------------|----------------|----------------------------|--------------|----------------------------|
| 1. | Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com | Bharat Biotech International Limited, Sy. No. 230, 231 & 235, Genome Valley, Shameerpet Mandal, Medchal-Malkajgiri District, Telangana State- 500078. Telephone No.: nil, Fax: nil, E-Mail:dra@bharatbiotech.com | | | | | | |
| | | <table border="1"> <thead> <tr> <th>Component</th> <th>Manufacturing facility</th> </tr> </thead> <tbody> <tr> <td>Drug substance</td> <td>• Facility PS2, Building S</td> </tr> <tr> <td>Drug Product</td> <td>• Building A, Facility PA1</td> </tr> </tbody> </table> | Component | Manufacturing facility | Drug substance | • Facility PS2, Building S | Drug Product | • Building A, Facility PA1 |
| Component | Manufacturing facility | | | | | | | |
| Drug substance | • Facility PS2, Building S | | | | | | | |
| Drug Product | • Building A, Facility PA1 | | | | | | | |

3. Details of pharmaceutical formulation:

| Name of the New drug to be manufactured: | Whole Virion Inactivated Corona Virus Vaccine, [BBV152B] | | | | | | | | | | | | | | |
|---|--|--------------------|----------|---|-------|----------------------|----------|---|---------|-----------------|--------|-----------------------------|--------|---------------------------|----------------|
| Dosage form: | Suspension for injection Presentation: single dose glass vial (0.5ml) Route of Administration: Intramuscular | | | | | | | | | | | | | | |
| Composition: | Each dose of 0.5ml contains: <table border="1"> <thead> <tr> <th>Active Ingredients</th> <th>Quantity</th> </tr> </thead> <tbody> <tr> <td>Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770)</td> <td>6 mcg</td> </tr> <tr> <th>Inactive Ingredients</th> <th>Quantity</th> </tr> <tr> <td>Aluminium Hydroxide gel equivalent to Al+++</td> <td>250 mcg</td> </tr> <tr> <td>TLR 7/8 Agonist</td> <td>15 mcg</td> </tr> <tr> <td>2-Phenoxyethanol (2PE) I.P.</td> <td>2.5 mg</td> </tr> <tr> <td>Phosphate Buffered Saline</td> <td>q.s. to 0.5 mL</td> </tr> </tbody> </table> * Produced in Vero cells. | Active Ingredients | Quantity | Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770) | 6 mcg | Inactive Ingredients | Quantity | Aluminium Hydroxide gel equivalent to Al+++ | 250 mcg | TLR 7/8 Agonist | 15 mcg | 2-Phenoxyethanol (2PE) I.P. | 2.5 mg | Phosphate Buffered Saline | q.s. to 0.5 mL |
| Active Ingredients | Quantity | | | | | | | | | | | | | | |
| Whole Virion, Inactivated Corona Virus antigen (Strain: NIV-2020-770) | 6 mcg | | | | | | | | | | | | | | |
| Inactive Ingredients | Quantity | | | | | | | | | | | | | | |
| Aluminium Hydroxide gel equivalent to Al+++ | 250 mcg | | | | | | | | | | | | | | |
| TLR 7/8 Agonist | 15 mcg | | | | | | | | | | | | | | |
| 2-Phenoxyethanol (2PE) I.P. | 2.5 mg | | | | | | | | | | | | | | |
| Phosphate Buffered Saline | q.s. to 0.5 mL | | | | | | | | | | | | | | |
| Indication: | For active immunization against Corona Virus Disease (COVID-19) for age ≥18 years when administered in two doses interval of day 0 & day 28. | | | | | | | | | | | | | | |
| Shelf life with storage condition: | 6 months when stored at 2 to 8 °C. | | | | | | | | | | | | | | |

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.
5. This permission is for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode.
6. The firm should provide the protocol for rolling out for the restricted use of the vaccine in emergency situation.
7. The firm should provide the updated prescribing information/ Package Insert and Summary of Product Characteristics (SmPC) for Whole Virion Inactivated Corona Virus Vaccine (BBV152B) and also disseminate the necessary information, instructions and educational materials through their website.
8. The firm should submit updated safety, efficacy & immunogenicity data from the ongoing Phase I, II & III clinical trials till the completion of trials as per requirement of New Drugs & Clinical Trials, 2019.
9. The firm should submit safety data including the data on AEFI and AESI, with due analysis, every 15 days for the first two months & monthly thereafter and also as per requirement of New Drugs & Clinical Trials, 2019.
10. The firm should submit Risk management plan.
11. The firm should submit ongoing stability of commercial scale batches (real time and accelerated) of drug substance & drug product.
12. The permission is subject to condition of satisfactory evaluation & lot release by CDL, Kasauli. Further, each batch/lot of Whole Virion Inactivated Corona Virus Vaccine, (BBV152B) shall be released from Central Drugs Laboratory, Kasauli.

CDSCO CDSCO



सत्यमेव जयते

Place: New Delhi
Date: 03-Jan-2021

VENUGOPAL
GIRDHARILA
L SOMANI

Digitally signed by VENUGOPAL GIRDHARILA SOMANI
DN: cn=B, o=MINISTRY OF HOME AFFAIRS,
ou=CDSCO DGHE, postalCode=110011,
serialNumber=254, c=IN
254, o=117693315882588912379141184
serialNumber=215467981247,
ou=VENUGOPAL GIRDHARILA SOMANI
Date: 2021.01.03 17:42:43 +05'30'

(Dr. V. G. Somani)
Drugs Controller General (India)
Central Licensing Authority

Dr. V. G. SOMANI
Drugs Controller General (India)
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O.
New Delhi-110002

Ariadne Gisele Muniz Bonvino

De: Ariadne Gisele Muniz Bonvino
Enviado em: segunda-feira, 29 de março de 2021 16:32
Para: William Amorim Santana; Emanuela Medrades
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO; Regina Celia Silva Oliveira; Renata Marques Santana; Thiago Fernandes da Costa; Alex Lial Marinho; Marcelo Calado
Assunto: RES: Novas recomendações da ANVISA para esse processo de importação - Vacina COVAXIN

Emanuela, boa tarde!

Em aditamento ao e-mail do William, a Agência solicitou esclarecer sobre a data de validade da vacina:

“Na LI consta a data de validade do lote 37F21004A como sendo 01/2023. No entanto, o prazo de validade aprovado pela Autoridade Indiana para a vacina Covaxin é de 6 meses, se conservada de 2-8 °C. Portanto, a data de validade do referido lote não corresponde ao prazo de validade aprovado pela autoridade da Índia. Para o lote nº 37F21004A, não foi apresentado o Certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade, emitido pelo fabricante; “

Abraços e ficamos no aguardo.

Atenciosamente,

Ariadne Bonvino
Farmacêutica
DIIMP/CGLOG/DLOG/SE

De: William Amorim Santana
Enviada em: segunda-feira, 29 de março de 2021 16:05
Para: Emanuela Medrades <emanuela.medrades@precisamedicamentos.com.br>
Cc: LISTA - DIVISÃO DE IMPORTAÇÃO <lista.divisaoimportacao@saude.gov.br>; Regina Celia Silva Oliveira <Regina.Oliveira@saude.gov.br>; Renata Marques Santana <renatam.santana@saude.gov.br>; Thiago Fernandes da Costa <thiago.fernandes@saude.gov.br>; Alex Lial Marinho <alex.marinho@saude.gov.br>; Ariadne Gisele Muniz Bonvino <ariadne.bonvino@saude.gov.br>; Marcelo Calado <marcelo.calado@saude.gov.br>
Assunto: Novas recomendações da ANVISA para esse processo de importação - Vacina COVAXIN

Prezada Emanuela,

Boa tarde!

Recebemos novo comunicado da Agencia Nacional de Vigilância Sanitária (ANVISA) no qual transcrevo a seguinte exigência/orientações:

De acordo com a Precisa Medicamentos, o CDSCO emite um documento (anexo BBV152 – COVAXIN – EUL – 12032021) que transmite a autorização para uso emergencial 29/03/2021 SEI/ANVISA - 1383578 com as suas ressalvas, bem como o relatório de avaliação técnica em um único documento. No entanto, a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152- COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade;

Com relação a solicitação anterior, ficamos no aguardo do envio dos certificados litados abaixo:

I - Certificados de liberação dos lotes a serem importados (inciso IV do art. 16 da RDC 476/2021). Foram enviados apenas os laudos análogos dos lotes 37F21004A, restando pendente os certificados de liberação dos respectivos lotes emitidos pelo fabricante;

Atenciosamente,

William Amorim Santana
Ministério da Saúde
DIIMP/CGLOG/DLOG-SE
Ed. Anexo, 4º andar, Sala 431-A
55-61-3315-3760
william.santana@saude.gov.br



Gabinete do Diretor-Presidente - Chefe de Gabinete
SIA Trecho 05, Área Especial 57, Brasília/DF, CEP 71.205.05
Telefone: 0800 642 9782 - www.anvisa.gov.br

Ofício nº 693/2021/SEI/GADIP-CG/ANVISA

Ao Senhor
Secretário-Executivo
Secretaria-Executiva do Ministério da Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Com cópia
Ao Senhor
Roberto Ferreira Dias
Diretor do Departamento de Logística em Saúde
Departamento de Logística em Saúde
Esplanada dos Ministérios, Bloco G - Bairro Zona Cívico-Administrativa
CEP: 70058-900 - Brasília/DF
E-mail: apoio.se@saude.gov.br

Assunto: Solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN

Referência: Caso responda este Ofício, indicar expressamente o Processo nº 25351.908110/2021-03.

Senhor Secretário-Executivo,

1. Cumprimentando-o, nos dirigimos a Vossa Senhoria para continuidade das tratativas referentes ao pedido de importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152, processo SEI nº 25351.908110/2021-03.
2. Em que pese a suspensão do prazo para análise pela Anvisa por força do § 3º do art. 17 da RDC 476/2021, que estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo até que sejam atendidas, informa a Quinta Diretoria (DIRE5), responsável pela análise do tema, que todos os documentos entregues até o momento seguem em análise.
3. Seguem as considerações após verificação do último protocolo efetuado no âmbito do referido processo, Ofício Precisa Contrato_29/2021 nº 002/2021:
 - I - Foi informado que todos os lotes se encontram no CDL – *Central Drugs Laboratory* responsável pela emissão dos Certificados de Origem bem como indicação de qual lote será destinado às exportações. De acordo com a empresa Precisa Medicamentos, os certificados já foram requisitados e a empresa aguarda sua disponibilização em breve. Portanto, resta pendente a apresentação do Certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade do produto acabado, emitido pelo fabricante;

II - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo;

III - De acordo com o importador, em relação à necessidade do relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária internacional responsável pela concessão da autorização para uso emergencial, foi apresentado o relatório emitido pelo CDSCO – Central Drugs Standard Control Organization (Biological Division) como forma de comprovação que o produto atende aos padrões de qualidade, eficácia e segurança, sendo este documento a liberação para uso emergencial e, ao mesmo tempo, o relatório técnico de avaliação contendo todas as ressalvas. No entanto, reafirmamos que a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152-COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade.

4. No que se refere ao item III, esta Agência está envidando todos os esforços necessários, por meio da Assessoria de Assuntos Internacionais, inclusive com a interveniência do Ministério das Relações Exteriores (MRE), a fim de agendar reunião com a CDSCO e de prospectar informações que possam se consubstanciar no requerido pela Lei nº 14.124/2021, para subsidiar a Anvisa na avaliação do pleito. Nesse sentido, requer-se, também, o apoio por parte do Ministério da Saúde junto ao MRE, para que a referida reunião possa ser agendada com a brevidade que o caso requer. Assim que houver o agendamento da mesma, esta Agência irá requisitar a participação de representante do Ministério da Saúde.

5. Por oportuno, a Anvisa solicita reunião de trabalho urgente junto ao Ministério da Saúde, com o objetivo de sanar as pendências remanescentes para completude da documentação necessária à instrução e avaliação do pedido de importação.

6. Agradecemos antecipadamente pela compreensão.

Atenciosamente,



Documento assinado eletronicamente por **Karin Schuck Hemesath Mendes, Chefe de Gabinete**, em 26/03/2021, às 19:20, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015 http://www.planalto.gov.br/ccivil_03/_Ato2015-2018/2015/Decreto/D8539.htm.



A autenticidade deste documento pode ser conferida no site <https://sei.anvisa.gov.br/autenticidade>, informando o código verificador **1386917** e o código CRC **8BDA0100**.

Guilherme Augusto Silva Ribeiro

De: Guilherme Augusto Silva Ribeiro
Enviado em: segunda-feira, 29 de março de 2021 17:14
Para: 'administrativo.gadip@anvisa.gov.br'
Cc: APOIO DA SECRETARIA-EXECUTIVA
Assunto: RES: Ofício nº 693/2021/SEI/GADIP-CG/ANVISA

Prezados Senhores,
Bom dia.

Confirmamos o recebimento do ofício nº693/2021/SEI/GADIP-CG/ANVISA.

Informamos que o documento foi inserido dentro do SEI/MS, sob o nº 25000.043170/2021-42, e foi encaminhado as áreas competentes para que as providências pertinentes sejam adotadas, sendo dispensado o envio do documento físico.

Atenciosamente,

Guilherme Augusto Ribeiro
SEATA/GAB/SE/MS
Gabinete da Secretaria Executiva
guilherme.augusto@saude.gov.br
Ministério da Saúde
Esplanada dos Ministérios, Bloco G, Ed. Sede, 3º Andar Brasília - DF

-----Mensagem original-----

De: ANVISA/Coordenação de Apoio Administrativo <administrativo.gadip@anvisa.gov.br>
Enviada em: sexta-feira, 26 de março de 2021 19:28
Para: APOIO DA SECRETARIA-EXECUTIVA <apoio.se@saude.gov.br>
Assunto: Ofício nº 693/2021/SEI/GADIP-CG/ANVISA

Prezados,

Encaminha-se o Ofício nº 693/2021/SEI/GADIP-CG/ANVISA, com manifestações datadas de 26/03/2021, da Agência Nacional de Vigilância Sanitária, quanto à solicitação de autorização para importação em caráter Excepcional de 20.000.000 (vinte milhões) de doses da Vacina COVAXIN.

Por gentileza, solicita-se confirmação de recebimento da presente mensagem e seus anexos.

Atenciosamente,

Coordenação de Apoio Administrativo - Coadi Gabinete do Diretor-Presidente - Gadip Agência Nacional de Vigilância Sanitária - Anvisa
(pco)

IMPORTANTE: FORAM IDENTIFICADOS LINKS NESTA MENSAGEM PARA ACESSO A SITES EXTERNOS, CUJA SEGURANÇA NÃO PÔDE SER VERIFICADA.

É DE FUNDAMENTAL IMPORTÂNCIA COMPORTAR-SE DE MANEIRA SEGURA EM NOSSA REDE, NÃO ABRINDO ANEXOS E LINKS DESCONHECIDOS, AINDA QUE SUPOSTAMENTE ENVIADOS POR PESSOAS CONHECIDAS. LEMBRANDO QUE INSTITUIÇÕES FINANCEIRAS, DO PODER JUDICIÁRIO, SERVIÇO DE PROTEÇÃO AO CRÉDITO, NÃO ENVIAM E-MAILS COM AVISOS DE DÉBITOS, PROCESSOS E RECADASTRAMENTOS. EM CASO DE DÚVIDA, CONTATE A CENTRAL DE ATENDIMENTO AO USUÁRIO.

ADMINISTRAÇÃO DA REDE MSNET



Ministério da Saúde
Secretaria Executiva
Gabinete da Secretaria Executiva

DESPACHO

SE/GAB/SE/MS

Brasília, 29 de março de 2021.

Assunto: Solicita autorização para importação, em caráter excepcional, de 20.000.000 (vinte milhões) de doses da vacina COVAXIN.

1. Trata-se do Ofício nº 693/2021/SEI/GADIP-CG/ANVISA (0019797040), de 29/03/2021, oriundo da Agência Nacional de Vigilância Sanitária - Anvisa, que, para continuidade das tratativas referentes ao pedido de importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152, quanto as atualizações a Agência informa:

I - Foi informado que todos os lotes se encontram no CDL – Central Drugs Laboratory responsável pela emissão dos Certificados de Origem bem como indicação de qual lote será destinado às exportações. De acordo com a empresa Precisa Medicamentos, os certificados já foram requisitados e a empresa aguarda sua disponibilização em breve. Portanto, resta pendente a apresentação do certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade do produto acabado, emitido pelo fabricante; 29/03/2021 SEI/ANVISA - 1386917 - Ofício

II - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo;

III - De acordo com o importador, em relação à necessidade do relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária internacional responsável pela concessão da autorização para uso emergencial, foi apresentado o relatório emitido pelo CDSCO – Central Drugs Standard Control Organizaon (Biological Division) como forma de comprovação que o produto atende aos padrões de qualidade, eficácia e segurança, sendo este documento a liberação para uso emergencial e, ao mesmo tempo, o relatório técnico de avaliação contendo todas as ressalvas. No entanto, reafirmamos que a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152-COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade.

2. Ao Departamento de Logística em Saúde - **DLOG/SE/MS**, para conhecimento e demais providências, tendo em vista o § 3º do art. 17 da RDC

476/2021, o qual estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo, até que sejam atendidas.

PAULO MARCOS C. R. DE OLIVEIRA
Chefe de Gabinete



Documento assinado eletronicamente por **Paulo Marcos Castro Rodopiano de Oliveira, Chefe de Gabinete da Secretaria Executiva**, em 30/03/2021, às 14:30, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



A autenticidade deste documento pode ser conferida no site http://sei.saude.gov.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0019797139** e o código CRC **4C84E9AD**.

Referência: Processo nº 25000.043170/2021-42

SEI nº 0019797139



Ministério da Saúde
Secretaria Executiva
Departamento de Logística em Saúde

DESPACHO

DLOG/SE/MS

Brasília, 31 de março de 2021.

À CGLOG,

Assunto: **Solicita autorização para importação, em caráter excepcional, de 20.000.000 (vinte milhões) de doses da vacina COVAXIN.**

1. Trata-se do DESPACHO SE/GAB/SE/MS (0019797139) que trata do Ofício nº 693/2021/SEI/GADIP-CG/ANVISA (0019797040), de 29/03/2021, oriundo da Agência Nacional de Vigilância Sanitária - Anvisa, que, para continuidade das tratativas referentes ao pedido de importação em caráter excepcional de 20.000.000 (vinte milhões) de doses da vacina Covaxin / BBV152, quanto as atualizações a Agência informa:

I - Foi informado que todos os lotes se encontram no CDL – Central Drugs Laboratory responsável pela emissão dos Certificados de Origem bem como indicação de qual lote será destinado às exportações. De acordo com a empresa Precisa Medicamentos, os certificados já foram requisitados e a empresa aguarda sua disponibilização em breve. Portanto, resta pendente a apresentação do certificado de liberação do lote, incluindo o laudo analítico de controle de qualidade do produto acabado, emitido pelo fabricante; 29/03/2021 SEI/ANVISA - 1386917 - Ofício

II - Na LI (1382702), o Ministério da Saúde configura como importador. Dessa forma, deve ser apresentada a declaração que ateste a adoção das estratégias de monitoramento e cumprimento das diretrizes de farmacovigilância, conforme modelo Anexo à RDC 476/2021, assinada pelo Chefe do Poder Executivo;

III - De acordo com o importador, em relação à necessidade do relatório técnico da avaliação da vacina emitido ou publicado pela autoridade sanitária internacional responsável pela concessão da autorização para uso emergencial, foi apresentado o relatório emitido pelo CDSCO – Central Drugs Standard Control Organizaon (Biological Division) como forma de comprovação que o produto atende aos padrões de qualidade, eficácia e segurança, sendo este documento a liberação para uso emergencial e, ao mesmo tempo, o relatório técnico de avaliação contendo todas as ressalvas. No entanto, reafirmamos que a Lei 14.124/2021 e a RDC 476/2021 determinam que o referido relatório deve ser capaz de comprovar que o produto atende aos padrões de qualidade, de eficácia e de segurança estabelecidos pela OMS ou pelo ICH e pelo PIC/s. O documento BBV152-COVAXIN-EUL refere-se ao comprovante de autorização de uso emergencial pela autoridade indiana, mas não contempla aspectos técnicos de qualidade, segurança e eficácia referentes à avaliação da vacina por esta autoridade.

2. Considerando que o referido Despacho encaminha para conhecimento

e demais providências, tendo em vista o § 3º do art. 17 da RDC 476/2021, o qual estabelece que as solicitações de esclarecimentos feitas pela Anvisa suspendem a contagem do prazo, até que sejam atendidas.

3. Desta forma, encaminha-se os autos a essa Coordenação Geral para as providências necessárias.



Documento assinado eletronicamente por **Roberto Ferreira Dias**, **Diretor(a) do Departamento de Logística**, em 31/03/2021, às 12:06, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#); e art. 8º, da [Portaria nº 900 de 31 de Março de 2017](#).



A autenticidade deste documento pode ser conferida no site http://sei.saude.gov.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0019824577** e o código CRC **630E8600**.



AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

Quinta Diretoria – DIRE5

Setor de Indústria e Abastecimento - SIA
Trecho 5 – Quadra Especial 57 – Lote 200
Bloco D – 3º andar - Brasília – DF – 71205-050

ATA DE REUNIÃO 2021

Reunião: Ministério da Saúde e Precisa

Pauta: Vacina Covaxin

Local: DIRE5

Data: 09/04/2021

Horário: 17h

Participantes: Lista de assinatura em anexo

Assuntos Tratados:

O Ministério da Saúde solicitou a reunião para tratar da importação da vacina Covaxin.

O Diretor Alex Campos abriu a reunião destacando a importância dos pedidos de importação pelo Ministério da Saúde. Informou que as questões referentes às Boas Práticas de Fabricação devem ser tratadas com a GGFIS/DIRE4 e que a DIRE5 atua no tema importação.

A empresa esclareceu que será iniciado novo processo de importação, a partir do Voto deliberado em DICOL. Foi relatado que representantes da empresa irão à Índia para obter as informações necessárias ao novo pedido de importação em caráter excepcional.

O Diretor Alex Campos esclareceu que o relatório de avaliação da Autoridade deve ser capaz de demonstrar a análise dos aspectos de qualidade, segurança e eficácia pela Agência indiana. Importante haver robustez das informações a serem enviadas à Anvisa. Na ausência do relatório, devem ser fornecidas informações que supram os aspectos de qualidade, segurança e eficácia requeridos pela Lei 14.124/2021. Sobre a certificação de Boas Práticas de Fabricação (BPF), o Diretor destacou que a empresa deve fornecer expediente específico tratando dos apontamentos feitos durante a inspeção.

O representante do Ministério da Saúde destacou que o referido processo de importação é um processo novo e que o novo pedido será instruído pelo Ministério. Ressaltou que a empresa deve prover todas as informações técnicas relevantes e disponíveis para embasar novo pedido de importação.

A empresa irá à Índia para tratativas com a Bharat e a CDSCO. Informou que diversas não conformidades apontadas durante a inspeção já foram atendidas pela fabricante e que todas as pendências serão resolvidas até o final de maio/2021.

O Diretor Alex Campos ressaltou que a instrução processual deve ser realizada pelo Ministério da Saúde.

Após obtenção dos novos dados, poderá ser realizada reunião de trabalho com a empresa e o Ministério, à semelhança de reunião de pré-submissão.

A empresa solicitou que tal reunião seja realizada no início da próxima semana.

Foi realizada apresentação pela empresa, listando os documentos a serem apresentados em nova submissão. No que se refere à apresentação dos certificados de liberação dos lotes a serem importados, a Anvisa destacou que trata-se de documento necessário à instrução do processo de importação e que será verificado pela PAF e INCQS. No entanto, no dossiê de autorização de importação, a empresa poderá encaminhar certificados de liberação de lotes anteriores aos que serão importados, a fim de exemplificar sua adequabilidade às especificações de qualidade.

A Anvisa sugeriu que a empresa faça contato com o INCQS a fim de antecipar as tratativas referentes à liberação dos lotes da vacina em caso de aprovação da importação.

A empresa informou que é possível disponibilizar ao Brasil apenas lotes fabricados após a adequação dos aspectos de BPF. Também informou que possui relatório de avaliação emitido pela Cofepris e que o mesmo será enviado à Anvisa.

ENCAMINHAMENTOS:

OBSERVAÇÕES:



AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

Quinta Diretoria – DIRE5

Setor de Indústria e Abastecimento - SIA
Trecho 5 – Quadra Especial 57 – Lote 200
Bloco D – 3º andar - Brasília – DF – 71205-050

ATA DE REUNIÃO 2021

Reunião: Ministério da Saúde e Precisa

Pauta: Vacina Covaxin

Local: DIRE5

Data: 15/04/2021

Horário: 18h

Participantes: Lista de assinatura em anexo

Assuntos Tratados:

O Ministério da Saúde solicitou a reunião para tratar da importação da vacina Covaxin.

O Diretor Alex Campos abriu a reunião destacando que as reuniões de pré-submissão se constituem em momento importante para orientação pela Agência quanto à instrução processual. Costumam ser momentos de discussão técnica, que objetivam a submissão de dossiês adequados, superando lacunas de informação e dando maior celeridade à análise pela Anvisa ao reduzir a necessidade de emissão de diligências. No entanto, o mérito dos documentos é analisado apenas após a submissão formal do protocolo, momento em que podem surgir novos questionamentos pelas áreas técnicas. Ressaltou que poderão ser realizadas quantas reuniões de pré-submissão forem necessárias.

Os representantes do Ministério da Saúde e da empresa informaram estar cientes quanto aos objetivos da reunião de pré-submissão.

A empresa informou já ter elaborado nova proposta de dossiê para solicitação de autorização para importação excepcional da vacina Covaxin, o qual foi compartilhado com o Ministério da Saúde. Relatou que o relatório técnico de análise da Cofepris foi incorporado ao dossiê.

A empresa realizou apresentação sobre os documentos submetidos em março para autorização de importação e sobre a lista dos documentos a serem submetidos no novo pedido. Informou que será submetido o dossiê em formato CTD completo, incluindo dados de eficácia, avaliação de potência, dados atualizados de estabilidade, protocolo de inativação viral, dentre outros. Sobre o CBPF, a empresa irá submeter a evolução das ações após inspeção da Anvisa e relatório do CAPA.

Os representantes da Anvisa questionaram sobre os relatórios de estudos clínicos a serem submetidos, se serão completos. Também informaram sobre a importância de submissão do relatório de inativação viral e não apenas do protocolo, aspecto esse também importante para o CBPF. Quanto aos aspectos de CBPF, as tratativas devem ser realizadas junto à GGFIS/DIRE4. A empresa informou que o relatório de inativação viral está em fase final de elaboração e poderá ser submetido. Confirmou que submeterá os relatórios completos dos estudos clínicos e que os dados serão submetidos no formato CTD.

O Diretor Alex questionou se trata-se da submissão de um novo processo de autorização de importação, ao passo que os representantes do Ministério e da Precisa confirmaram. Reforçou que o dossiê deve ser instruído de acordo com a RDC 476/2021, de forma organizada e na ordem constante na norma. No caso da ausência do relatório técnico de análise da autoridade internacional, os dados de qualidade, segurança e eficácia que possam atestar o requerimento legal (§ 3º do art. 16 da Lei 14.124/2021) devem ser apresentados como atendimento ao inciso II do art. 17 da RDC 476/2021.

No que se refere à submissão, devem ser seguidas as orientações abaixo:

- Estados, municípios e União podem ter acesso aos sistemas de peticionamento da Anvisa por meio do Cadastro de Instituições. Para tanto, é necessário o cadastro no endereço: <https://www1.anvisa.gov.br/cadastramento/>, a fim de obter o usuário e senha para acesso ao sistema de Peticionamento Eletrônico ou Solicita, conforme orientações: <https://www.gov.br/anvisa/pt-br/sistemas/cadastros/cadastro-de-instituicoes>.

Código de assunto a ser submetido: **90278 - MEDICAMENTOS - Solicitação de autorização excepcional e temporária para importação de medicamentos e vacinas para Covid-19 (RDC 476/2021)**, o qual se encontra disponível no Sistema de Peticionamento.

Foi marcada nova reunião para apresentação técnica dos documentos propostos para o novo pedido de importação.

ENCAMINHAMENTOS:

OBSERVAÇÕES:



AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

Quinta Diretoria – DIRE5

Setor de Indústria e Abastecimento - SIA
Trecho 5 – Quadra Especial 57 – Lote 200
Bloco D – 3º andar - Brasília – DF – 71205-050

ATA DE REUNIÃO 2021

Reunião: Ministério da Saúde e Precisa

Pauta: Vacina Covaxin

Local: DIRE5

Data: 16/04/2021

Horário: 15:30

Participantes: Daniela Cerqueira e Daniel Cruz (DIRE5)
Precisa Medicamentos: Elaine Giglioli, Túlio Silveira e Emanuela Medrades
Ministério da Saúde: Ariadne Bonvino.

Assuntos Tratados:

O Ministério da Saúde solicitou a reunião para tratar da importação da vacina Covaxin.

Os representantes da DIRE5 ressaltaram o objetivo da reunião de pré-submissão, que é orientar o solicitante quanto à instrução processual, a fim de que o processo possa ser analisado com maior celeridade. O mérito dos documentos é analisado somente após a submissão formal dos documentos, podendo gerar diligências. De acordo com a RDC 476/2021, as áreas técnicas emitem parecer sobre os documentos apresentados no pedido de importação excepcional. Portanto, todos os documentos serão analisados pelas áreas de registro, inspeção e farmacovigilância.

No que se refere ao quantitativo a ser importado, foi informado ao Ministério e à Precisa que, a depender da avaliação dos documentos, poderá ser emitida autorização de importação para todo o quantitativo programado ou para cada embarque específico a ser realizado. Ressaltou-se que, normalmente, os pedidos de importação são analisados para cada LI específica.

Sobre as declarações previstas na RDC 476/2021, a DIRE5 esclareceu que todas devem ser assinadas pelo importador, no caso, o Ministério da Saúde. A RDC ainda prevê a assinatura pelo chefe do Poder Executivo. A declaração referente ao descumprimento do Plano de Operacionalização da Vacinação contra a Covid-19 não precisa ser apresentada nesse caso. A representante do Ministério informou que estão providenciando a assinatura pelo secretário da SVS e pelo secretário executivo do Ministério da Saúde.

A empresa Precisa esclareceu que a vacina Covaxin foi co-desenvolvida pelo Governo da Índia. Dessa forma, não foi emitido nenhum relatório de avaliação além do comprovante de autorização de uso emergencial

apresentado no pedido de importação anterior. Sobre esse aspecto, a DIRE5 esclareceu que o referido comprovante não corresponde ao relatório técnico de avaliação da autoridade sanitária internacional nos moldes estabelecidos pela Lei nº 14.124/2021. Portanto, tal documento deve ser apresentado como comprovante de autorização do uso emergencial, mas não como o relatório técnico requerido pela Lei. Na ausência do relatório, o importador deve apresentar os aspectos de qualidade, segurança e eficácia que cumpram o ditame legal. A empresa concordou e informou que submeterá o relatório técnico de avaliação da Cofepris, além dos documentos de qualidade, segurança e eficácia da vacina.

Por ser importação pelo Ministério da Saúde, a AFE não se aplica.

Sobre a liberação de lotes pelo INCQS, a empresa informou que já realizou reuniões com o Instituto para alinhamento das ações necessárias.

No que se refere aos aspectos de BPF, a empresa informou ter realizado reunião com a GGFIS no dia 12/04 para apresentação da proposta de CAPA. As ações para adequação das não conformidades identificadas durante a inspeção serão finalizadas até o final de maio. A empresa informou que a planta da Bharat possui 3 linhas produtivas pré-qualificadas pela OMS. Também relatou que a Malásia, Turquia e Ucrânia já inspecionaram a Bharat. O site possui 10 prédios, sendo 4 específicos para a Covaxin. Considerando a importância de que a empresa solicite nova certificação de BPF previamente ao novo pedido de importação, dada a motivação do indeferimento do pedido anterior, a empresa irá solicitar reunião com a DIRE4 e GGFIS para verificar a possibilidade de submissão do pedido de certificação de BPF mediante a apresentação de termo de compromisso para os documentos que estiverem faltantes.

A empresa apresentou o PGR (plano de gerenciamento de risco) e informou que o mesmo está de acordo com o Guia nº 42 e com as normas de farmacovigilância. Os representantes da DIRE5 ressaltaram que o PGR deverá contemplar as responsabilidades do importador (Ministério da Saúde) definidas pela RDC 476/2021. A DIRE5 também ressaltou que dados de monitoramento do uso da vacina em outros países são importantes para subsidiar o novo pedido de importação. Sobre esse aspecto, a empresa informou que o fabricante poderá disponibilizar esses dados.

Sobre o estudo clínico a ser conduzido no Brasil, a empresa informou que as alterações solicitadas pela Conep já foram realizadas e que as exigências emitidas pela Anvisa para o DDCM serão cumpridas até o dia 19/4. Os representantes da DIRE5 informaram que a anuência do estudo clínico pode ser aspecto relevante para o novo pedido de importação.

O estudo clínico da Índia terá 12 meses de prazo de acompanhamento e o do Brasil terá 18 meses. Até o momento, já estão disponíveis os dados de análise interina de eficácia após a ocorrência de 43 casos de Covid-19. Nos próximos dias, deverão estar disponíveis os dados de eficácia após 130 casos de Covid-19, com nova análise interina e com dados por faixa etária. A empresa informou ser possível incluir essa nova análise interina no novo pedido de importação. A DIRE5 ressaltou a importância de que esses novos dados sejam disponibilizados à Anvisa.

Os artigos científicos já publicados sobre a vacina também serão incluídos no pedido de importação.

Sobre o transporte da vacina, a empresa informou que, inicialmente, a vacina será enviada via Turquia em Envirotainer com data logger para monitoramento da temperatura. A documentação de qualificação do transporte será apresentada no novo pedido de importação.

Após a apresentação, os representantes da DIRE5 questionaram sobre a submissão do CTD, conforme informado na reunião do dia 15/4, visto que os dados de qualidade estavam ausentes na lista de documentos apresentada. A empresa esclareceu que seu acordo com a Bharat determina que o CTD só pode ser disponibilizado às autoridades sanitárias e, portanto, não poderia ser submetido pelo Ministério da Saúde. A DIRE5 esclareceu que a empresa pode utilizar o código de assunto para submissão de pleitos pela RDC 476/2021 para submissão do CTD diretamente à Anvisa, devendo, nesse caso, informar que a submissão está vinculada ao pedido de importação do Ministério.

ENCAMINHAMENTOS:

OBSERVAÇÕES:



AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

Quinta Diretoria – DIRE5

Setor de Indústria e Abastecimento - SIA
Trecho 5 – Quadra Especial 57 – Lote 200
Bloco D – 3º andar - Brasília – DF – 71205-050

ATA DE REUNIÃO 2021

Reunião: Ministério da Saúde e Precisa

Pauta: Vacina Covaxin

Local: DIRE5

Data: 30/04/2021

Horário: 09:30

Participantes: Daniela Cerqueira e Daniel Cruz (DIRE5); Gustavo Mendes, Maria Fernanda Thees, Brenda Valente, Claudiovam Martins, Francis Reisdorfer (GGMED), Helaine Capucho e Pauliana Almeida (GFARM).
Precisa Medicamentos: Elaine Giglioli, Túlio Silveira e Emanuela Medrades
Ministério da Saúde: Ariadne Bonvino.

Assuntos Tratados:

O Ministério da Saúde solicitou a reunião para tratar da importação da vacina Covaxin.

Os representantes da DIRE5 ressaltaram o objetivo da reunião de pré-submissão, que é orientar o solicitante quanto à instrução processual, a fim de que o processo possa ser analisado com maior celeridade. O mérito dos documentos é analisado somente após a submissão formal dos documentos, podendo gerar diligências.

- **Fundamentação legal:** o pedido de importação será baseado na Lei 14.124/2021 e RDC 476/2021. Ademais, a empresa utilizará a RDC 475/2021 e o guia 42/2020 quanto à documentação técnica de qualidade, segurança e eficácia a ser apresentada. A Anvisa confirmou que, de acordo com a Lei nº 14.124/2021, o prazo para análise é de até 30 dias na ausência do relatório técnico de avaliação da vacina pela autoridade internacional. A empresa destacou que o relatório da Cofepri não é tão detalhado e não está fundamentado em OMS, ICH e PIC/S, não correspondendo, portanto, ao relatório técnico requerido pela Lei. Na submissão, será informado o status mundial de autorização da vacina. Sobre esse aspecto, a DIRE5 pediu que sejam informados os países que estão efetivamente utilizando a vacina, quais os quantitativos já utilizados e dados de monitoramento disponíveis.

- **CBPF:** a empresa informou que mais de 70% das adequações já foram concluídas. As validações faltantes devem estar finalizadas até o dia 15/5. A partir do dia 15/4, todos os lotes já estão sendo fabricados com as adequações realizadas na planta fabril. A previsão é que o novo pedido de BPF seja solicitado no dia 15/5. A empresa informou já estar alinhada com a GGFIS a possibilidade de emissão de exigência após a submissão do novo pedido de CBPF, mas a Bharat está resistente em submeter o protocolo sem possuir todas as

adequações necessárias. A DIRE5 ressaltou a importância da submissão do novo pedido de BPF e da anuência do DDCM de forma simultânea ou prévia ao novo pedido de importação, a fim de trazer maior robustez técnica ao pleito. A Precisa informou já possuir informação suficiente para nova submissão de BPF, mas não pode submeter sem a concordância da Bharat. A GPBIO questionou sobre validação dos testes de potência, adsorção de antígeno, inativação viral e outros importantes para a qualidade da vacina. A empresa informou que já possui implantação de todos os testes e que a validação será concluída até o dia 15/5. A área técnica precisa entender que testes estão sendo realizados e se os mesmos estão validados. A GPBIO informou que a empresa pode submeter de forma informal a documentação para uma análise prévia antes da submissão. Nesse caso, a submissão do pedido de importação não ficará vinculada ao retorno da GPBIO, cabendo ao importador avaliar o momento adequado para submissão do pedido de importação.

- A GFARM solicitou o envio de dados de pós-comercialização, pois existem poucos dados disponíveis nas bases globais de farmacovigilância. Ressaltou que o perfil das notificações é bem diferente daquele das demais vacinas em avaliação pela Anvisa. A empresa informou que enviará todos os dados de farmacovigilância disponíveis até o momento.

- A GPBIO informou ser importante a empresa encaminhar dados sobre a avaliação de eventos adversos de interesse especial nos estudos clínicos. A vacina utiliza adjuvante novo, o que traz preocupações sobre a segurança. Os eventos graves e óbitos devem ser descritos de forma detalhada e com a investigação de relação causal. A empresa informou já possuir o material e que os dados estarão prontos para ser apresentados à Precisa e ao Einstein no dia 4/5. O material será tratado para apresentação à Anvisa. A GPBIO destacou que a Anvisa não teve acesso ao protocolo do estudo de fase 3 na Índia e nem aos relatórios de estudos de fase 2. Os artigos científicos são avaliados como suporte, mas a empresa deve apresentar os protocolos e relatórios completos dos estudos clínicos, conforme guias do ICH. A documentação deve ser apresentada de forma organizada, a fim de facilitar a avaliação da Anvisa.

- Sobre o teste de RT-PCR, a empresa informou que se trata de teste comercial e que foi validado pela Bharat. Os testes in house para avaliação de anticorpos foram validados pela Bharat e serão revisados pela Precisa. A GPBIO destacou que os relatórios de validação dos ensaios devem ser submetidos de forma organizada, seguindo os guias do ICH.

- É importante que a empresa apresente dados de imunogenicidade após a 2ª dose da vacina.

- A empresa informou que não realiza teste de fotoestabilidade, mas está implementando. A GPBIO informou não ser essencial para a importação excepcional. Pode ser apresentado como compromisso.

- Não foi feita análise do efeito da vacina em indivíduos soropositivos. A GPBIO informou ser importante que tais dados sejam avaliados para submissão. A empresa ressaltou que tal avaliação foi incluída no protocolo do estudo clínico a ser realizado no Brasil.

- A GFARM informou que os eventos de especial interesse devem constar do Relatório de Monitoramento.

- A empresa vai submeter a documentação prevista no guia 42 de maneira prévia à GPBIO por e-mail e os dados de monitoramento à Gfarm. Dessa forma, as áreas iniciarão a análise dos documentos previamente à submissão do pedido de importação.

- A DIRE5 esclareceu que a submissão do pedido de importação pelo Ministério da Saúde deve ocorrer pela RDC 476/21 e no item referente ao relatório técnico devem ser apresentados os dados técnicos de qualidade, segurança e eficácia que cumpram o requisito da Lei 14.124/21.
- A interlocução com o INCQS deve ser realizada o quanto antes e o MS pode solicitar reunião com a Gelas da Anvisa para essas tratativas.
- O MS informou que as declarações previstas pela RDC 476/21 já foram assinadas pelo secretário executivo do Ministério.
- O solicitante da importação deve ser o MS. O pleito pode ser submetido por e-mail ao gabinete do diretor presidente. No caso da documentação técnica a ser submetida pela Precisa, a empresa deve usar o código de assunto 90278 - MEDICAMENTOS - Solicitação de autorização excepcional e temporária para importação de medicamentos e vacinas para Covid-19 (RDC 476/2021), o qual se encontra disponível no Sistema de Peticionamento. A empresa deve informar claramente que esta submissão está vinculada ao pedido de importação efetuado pelo MS.
- A GAfrm ressaltou que o importador (MS) é o responsável pelas atividades de farmacovigilância. Nesse sentido, a empresa informou que irá apresentar à SVS o material de monitoramento já elaborado pela Precisa para os alinhamentos necessários. Após esse alinhamento com a SVS, o MS irá solicitar reunião específica com a DIRE5 e GGMON para tratar do plano de gerenciamento de riscos.
- A empresa deve destacar na submissão quais são os documentos novos ainda não avaliados pela Anvisa, a fim de facilitar e agilizar a análise da Agência. Deve ser submetido o CTD completo, sinalizando quais itens foram atualizados e com índice organizado.
- A empresa deve ser apresentar a comparabilidade entre os processos produtivos.
- A empresa informou que os lotes do estudo clínico no Brasil serão do PQ3. Dessa forma, a empresa precisa fazer o estudo de comparabilidade.
- Estabilidade: a empresa deve enviar resultados atualizados dos estudos. A empresa informou que o estudo em uso não está adaptado às condições apresentadas, mas será refeito pela empresa.
- A vacina será enviada ao Brasil com VVM e em Envirotainer, com rota de transporte pela Turquia. Serão enviadas as documentações da qualificação de transporte.
- Para as doses do estudo clínico, a COPEC esclareceu que não há exigência sobre validação do transporte. A empresa destacou que as doses serão trazidas com data logger para monitoramento da temperatura.
- A validação do transporte pode ser realizada com lotes clínicos, desde que seguindo o protocolo estabelecido.
- A Gpbio esclareceu que não há obrigação de adjuvante no placebo.
- Os dados sobre o adjuvante serão enviados na documentação. Trata-se de adjuvante americano, que possui ensaios europeus e americanos. Existe apenas um produto tóxico aprovado com esse adjuvante.

- Os dados brutos do estudo de fase 3 são importantes para avaliação da Anvisa. A Anvisa esclareceu que todos os dados são tratados pela Agência como confidenciais e que a empresa pode incluir *disclaimer* relacionado a esse aspecto. Pode ser fornecido o link para acesso aos dados, dado o volume dos mesmos.
- Todos os dados do estudo de fase 3 atualizados que já estiverem disponíveis devem ser enviados à Anvisa. A empresa informou que o relatório interino com 127 casos só estará disponível em meados de junho.
- A GPBIO esclareceu que a função do VVM é dar suporte durante o transporte, mas não durante o uso da vacina.
- A empresa informou que pretende submeter os documentos técnico à GPBIO até 4ª feira (5/5).
- A COPEC esclareceu que a via para importação ocorre por meio do CE, após anuência do estudo clínico. Pode ser emitido documento para importação por conta e risco da empresa para viabilizar a importação apenas para o lote do estudo clínico. A empresa está trabalhando em gerenciamento de risco referente ao lote disponível para estudo clínico e gostaria de já possuir o lote no Brasil no momento da anuência do estudo. A COPEC esclareceu que os casos excepcionais são levados à deliberação do Comitê Covid-19 e que tentará viabilizar a discussão o mais rápido possível. A empresa vai formalizar o pleito como aditamento ao DDCM e comunicar a COPEC por e-mail.
- A DIRE5 se colocou à disposição para novas reuniões que se façam necessárias.

ENCAMINHAMENTOS:

OBSERVAÇÕES: