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A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for a protein vaccine against SARS-CoV-2 virus

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For the Benefit-Risk Assessment of VAccines by TechnolOgy Working Group

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Abstract:

Biological E. has produced a novel protein RBD subunit vaccine for Protection Against COVID-19 Disease. The vaccine is based on the traditional protein subunit vaccine technology of a protein antigen, the SARS-CoV-2 Spike receptor-binding domain (RBD), adsorbed to the adjuvant Alhydrogel (Alum) in combination with another approved adjuvant, CpG 1018. CORBEVAX is in the final stages of completion of clinical trials in subjects aged between 5-80 years. Safety and Immunogenicity of the vaccine has been established and the vaccine has been approved by the Indian Regulatory Authority to be administered in the age group of 5-80 years.

1. Introduction

The Brighton Collaboration (www.brightoncollaboration.org) was launched in 2000 to improve the science of vaccine safety[1]. The Brighton Viral Vector Vaccine Safety Working Group (V3SWG) was formed in 2008 in recognition of the increasing importance of viral vectors for the development of new vaccines and the need to understand their associated safety issues[2]. To better meet the needs of many other platform technologies used to develop vaccines to prevent COVID-19 beyond vaccines based upon viral vectors, the V3SWG was renamed the Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group in July 2020. BRAVATO uses a standardized template to describe the key characteristics of novel vaccine vectors, compiled from the latest research, to facilitate scientific discourse among key stakeholders[2].

2. Background

In late December 2019, the Wuhan Huanan Seafood Wholesale Market in Wuhan, China, witnessed an outbreak of acute cases of respiratory tract infections with pneumonia characterized by fever, dry cough, lethargy, and occasional gastrointestinal symptoms[3]. The surge of cases in China soon spread to other nations. The new coronavirus outbreak was declared a public health emergency of international concern (PHEIC) by WHO Director-General Dr Tedros Adhanom Ghebreyesus on January 30, 2020. WHO declared COVID-19 a global pandemic on March 11, 2020[4].

The cause of the COVID-19 pandemic is a novel and highly pathogenic coronavirus, termed SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). SARS-CoV-2 is a member of the Coronaviridae family of viruses[5]. The genome of SARS-CoV-2 is similar to other coronaviruses, and is comprised of four key structural proteins: S, the spike protein, E, the envelope protein, M, the membrane protein, and N, the nucleocapsid protein[6] Coronavirus spike proteins are class I fusion proteins and harbor an ectodomain, a transmembrane domain, and an intracellular tail[6, 7]. The highly glycosylated ectodomain projects from the viral envelope surface and facilitates attachment and fusion with the host cell plasma membrane. The ectodomain can be further subdivided into host receptor-binding domain (RBD) (S1) and membrane-fusion (S2) subunits, which are produced upon proteolysis by host proteases at S1/S2 and S2' sites. S1 and S2 subunits remain associated after cleavage and assemble into crown-like homotrimers[5, 8]. In humans, both SARS-CoV (Severe Acute Respiratory Syndrome) and SARS-CoV-2 spike proteins utilize the angiotensin-converting enzyme 2 (ACE2) protein on the host cell membrane as a receptor for cellular entry[9-11]. Spike protein subunits represent a key antigenic feature of coronavirus virions, and therefore represent an important target of vaccines, novel therapeutic antibodies, and small-molecule inhibitors[12, 13].

The spike (S) protein of SARS-CoV-2 is the major inducer of neutralizing antibodies, and the receptor-binding domain (RBD) in the S1 subunit of S protein contains multiple conformational neutralizing epitopes. Recombinant proteins containing RBD and vectors or mRNA encoding the RBD sequence can be used to develop safe and effective SARS vaccines. Biological E's recombinant RBD antigen contains the major neutralizing epitopes in the S protein.

The receptor-binding domain (RBD) in the S1 subunit of the SARS-CoV-2 spike (S) protein is the most important target for developing a SARS-CoV-2 vaccine. In particular, RBD of S protein contains the critical neutralizing domain (CND), which is able to induce highly potent neutralizing antibody response and cross-protection against divergent SARS-CoV-2 strains. Furthermore, an RBD-based subunit vaccine is expected to be safer than other vaccines that may induce Th2-type immunopathology[14].

CORBEVAX, the COVID-19 Vaccine from Bio E (an India based vaccine manufacturer), is based on the traditional protein subunit vaccine technology of a protein antigen, the SARS-CoV-2 Spike receptor-binding domain (RBD), adsorbed to the adjuvant Alhydrogel (Alum) in combination with another approved adjuvant, cytosine phosphoguanine (CpG) 1018. CpG motifs, which is a synthetic form of DNA that mimics bacterial and viral genetic material, inclusion in a vaccine increases the body's immune response[15]. The RBD protein is expressed in yeast *Pichia pastoris* and is similar to technology Bio E is employing for large-scale commercial production of its Hep B vaccine. Baylor College of Medicine/Texas Children's Hospital produced and licensed the recombinant *Pichia Pastoris* strain expressing RBD protein (RBD N1C1) to Biological E, based on its ease of manufacturability due to the yields of protein antigen, ease of process steps and favorable formulation. Dynavax Inc. supplied the CpG1018 adjuvant. The combination of alum with the CpG1018 antigen was chosen as it elicited a balanced, synergistic immune response in preclinical models[16]. CORBEVAX stimulates and prepares the immune system for future contacts with the coronavirus by inducing antibodies which help in prevention of severe COVID-19 disease.

3. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

4. Declaration of Competing Interest

Subhash Thuluva, Vijay Yerroju, and Vikram Paradkar are employees of Biological E Limited and they do not have any stock options or incentives. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

5. Acknowledgements

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Table 1.
Brighton Collaboration: Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Protein Vaccines

Brighton Collaboration **Standardized Template for Collection of Key Information for Risk Assessment of Protein Vaccines**		
1. Authorship	**Information**	
1.1 Author(s) and affiliation(s)	Dr. Subhash Thuluva, Dr. Vijay Yerroju, Clinical Development, Biological E. Limited. Dr. Vikram Paradkar, Research & Development, Biological E. Limited	
1.2 Date completed/updated	August 16, 2022	
2. Basic Vaccine information	**Information**	**Comments/Concerns**
2.1 Vaccine name	CORBEVAX	
2.2 Protein type (e.g., molecular clamp, virus-like particle, peptide) and any special characteristics	Receptor Binding Domain of SARS-CoV-2	Spike protein sequence published for the Wuhan strain was used to finalize the amino acid sequence of the Receptor Binding Domain (RBD). The RBD consists of Amino Acids 332-549 of the spike protein. One amino acid was changed in the sequence: C538A. This change was made for protein stability. RBD sequence consists of 9 Cys residues. The first 8 residues are paired in the form of disulphide bonds while the ninth Cys residue (#538) is unpaired and can lead to cross-linking. Hence, it was replaced with Alanine residue. The Final RBD produced in *Pichia Pastoris* expression system is a secreted protein that is then purified via standard techniques (chromatography and filtration). The purified RBD protein meets standard quality attributes of purity similar to therapeutic proteins or protein antigens (typical SDS-PAGE purity of >98%). The RBD is a

		soluble, monomeric protein. It binds to ACE-2 receptor as well as multiple monoclonal antibodies that have been developed as a therapeutic option for SARS-COV-2[17]. This indicates that recombinantly produced RBD retains all the structural attributes from the Spike protein of SARS-COV-2.
2.3 Type of heterologous expression system used for antigen production (e.g., bacteria, yeast, plants, mammalian or insect cells, chemical synthesis)	The RBD protein is expressed in yeast ***Pichia pastoris***.	The RBD protein is expressed in yeast *Pichia pastoris* and is similar to technology Bio E is employing for large-scale commercial production of its Hep B vaccine. Baylor College of Medicine/Texas Children's Hospital produced and licensed the recombinant *Pichia Pastoris* strain expressing RBD protein (RBD N1C1) to Biological E, based on its ease of manufacturability due to the yields of protein antigen, ease of process steps and favorable formulation.
2.4 Adjuvant (if applicable)	Aluminum hydroxide and CpG 1018[18]	
2.5 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g., preservatives (e.g., thimerosal, phenol, benzethonium chloride, 2-phenoxyethanol), complexing with polymers, encapsulation within microparticles, liposomes, depot formulations)		No such components in the formulation.
2.6 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)	Two doses of Vaccine as Intramuscular needle injections given at an interval of 4 weeks. CORBEVAX has also been approved as a precautionary dose (heterologous booster) in individuals who had been primed (2 doses of Covid vaccine) with Covishield or Covaxin[19]	

3. Target Pathogen and Population	Information	Comments/Concerns
3.1 What is the target pathogen?	SARS-CoV-2	
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people	Fever, cough, dyspnea, malaise, fatigue and sputum/secretion[20]	
• In immunocompromised people	Fever, dry cough, dyspnea, and diarrhea, increased rate of hospitalization due to acute respiratory distress syndrome and other complications[21]	
• In neonates, infants, children	Fever, cough, nasal symptoms, diarrhea, and nausea/vomiting[22]	
• During pregnancy and in the fetus	Cough, fever, and breathlessness[23]. Increased chances of spontaneous miscarriage, fetal growth restriction, preterm delivery, and maternal mortality rate of as high as 25% compared to 10% in normal population[24]	
• In elderly	Fever, cough, dyspnea, fatigue, and myalgia, severe pneumonia and they may present with acute respiratory distress syndrome[25]	
• In any other special populations	NA	
3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g., incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio *(R_0),* and spontaneous mutation)?	Incubation period ranges from 4.2 to 12.1 days[26]. The exact duration of infectivity of COVID-19 patients is not yet known with certainty. In studies of non-severe cases, the virus was successfully isolated for 10 days from the onset of symptoms. SARS-CoV-2 is commonly spread via respiratory droplets formed while talking, coughing, and sneezing of an infected patient[27]. To date, the WHO estimates that the R0, or basic reproduction number, the virus is somewhere between 1.4 and 2.5, although other estimates give a range between 2 and 3. As of date, several major lineages (A, B, B.1, B.1.1, B.1.177, B.1.1.7	SARS-CoV is classified to β coronaviruses. The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. After binding to host receptors, the virus enters host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Then, new viral particles are released. Coronaviruses consist of four structural proteins; Spike (S), membrane (M), envelop (E) and nucleocapsid (N).

	(Alpha), B.1.351 (Beta), B.1.617.2 (Delta), B.1.1.529, **BA.4/5** (Omicron) had been identified[28].	Spike protein is composed of a transmembrane trimetric glycoprotein on the viral surface, which determines the diversity of coronaviruses and host tropism. Spike protein comprises two functional subunits; S1 subunit, which is responsible for binding to the host cell receptor and S2 subunit, which is for the fusion of the viral and cellular membranes. Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV. ACE2 is highly expressed on the apical side of lung epithelial cells in the alveolar space. The symptom of patients infected with SARS-CoV-2 ranges from minimal symptoms to severe respiratory failure with multiple organ failure. Covid-19 infection can spread through both direct means (droplet and human-to-human transmission) and by indirect contact (contaminated objects and airborne contagion). Person-to-person spread of SARS-CoV-2 is supposed to occur mainly via respiratory droplets, when a patient coughs, sneezes, or even talks. Average duration of shredding of virus can range from 8-12 days from the onset of symptoms.
3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast feeding), adult, elderly)	Data indicating that infants, older adults, pregnant women, and persons with certain medical conditions or with multi-morbidities are at increased risk for severe illness from COVID-19. Men with COVID-19 have higher risk of all-cause death, severe infection, or ICU	

	admission than women; the excess risk is not explained by age and comorbidities. Race and ethnicity are also risk factors for severe illness. American Indian, Alaska Natives, Asian, Black or African American, and Hispanic or Latino are at higher risk for illness, hospitalization, and death compared with White, Non-Hispanic Persons[29, 30].	
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?	Challenge studies with other human coronavirus indicate multiple immune responses (serum IgG, IgA, neutralizing titer, and mucosal IgA) that may serve as potential correlates of protection. In animal models, elicitation of high titers of neutralizing antibodies targeting the receptor binding domain (RBD) of the spike (S) protein are protective against re-challenge with SARS-CoV-2. Correlates of protection and their durability, however, have not been established in humans[31, 32].	In an outbreak of SARS-CoV-2 on a fishing vessel with high (>85%) attach rate, neutralizing antibodies correlate with protection from SARS-CoV-2. The SARS-CoV-2 virus infects through the naso-oral route, followed by infection in cells expressing ACE2 receptor in the lung, such as type 2 alveolar cells. The viruses dampen anti-viral IFNγ responses by evading the innate immune cells as a consequence of unrestrained virus replication. The infiltration of monocytes/macrophages, neutrophils, and several other adaptive immune cells leads to increased pro-inflammatory cytokines. Stimulation of Th1/Th17 cells with viral epitopes may lead to aggravated inflammatory responses which results in “cytokine storms” that lead to immunopathologies like pulmonary edema and pneumonia.
3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk	NA	
4. Characteristics of Antigen	**Information**	**Comments/ Concerns**

4.1 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence?	It has been reported that the vast majority of neutralizing antibodies against SARS-CoV-2 target the RBD[33]. Tai W. et al. had shown that the lipid nanoparticle-encapsulated (LNP) RBD-based mRNA COVID-19 vaccine elicited in mice highly potent neutralizing antibodies (NT50: ~10,000) against SARS-CoV-2 PsV infection[25]. These antibodies could also cross-neutralize infection of pseudotyped SARS-CoV strains Tor2 and GD03 from humans, and SZ3 from palm civets, indicating that this RBD-based mRNA vaccine is able to induce neutralizing antibodies against both SARS-CoV-2 and SARS-CoV infection[34].	Sera from CORBEVAX clinical trial subjects were tested to determine neutralization titers against SARS-COV-2 strains: Wuhan, Beta and Delta. Consistent nAb titers were observed against all three strains with minimal decrease against the Delta strain (approximately 50% reduction) and approximately 2-4-fold decrease was observed against the Beta strain. This consistent cross-neutralization elicited by CORBEVAX may be significantly superior to the majority of other vaccines that have shown significant drop in nAb titers against Beta and Delta strains (ref). Similar data was also obtained from the sera collected from Non-Human Primates in the challenge study. Neutralizing antibodies against Omicron: Neutralizing Antibody (nAb) titers against Omicron variant with CORBEVAX™ is among the highest observed when compared with published data for other marketed COVID19 vaccines developed based on mRNA, adenovector and inactivated platforms post two dose regimens. The Geometric mean titres against Omicron is indicative of high vaccine effectiveness against symptomatic infection based on the Phase III efficacy study analysis of marketed vaccines.
4.2 What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	Immunization of mice with a candidate subunit vaccine consisting of SARS-CoV-2 RBD and Fc fragment of human IgG, as an immunopotentiator, elicited high titer of RBD-specific antibodies with robust neutralizing activity against both pseudotyped and live SARS-CoV-2	Cellular immune response generated by Corbevax vaccination has been assessed by two methods:

	infections. The mouse antisera could also effectively neutralize infection by pseudotyped SARS-CoV-2 with several natural mutations in RBD and the IgG extracted from the mouse antisera could also show neutralization against pseudotyped SARS-CoV and SARS-related coronavirus (SARSr-CoV). Vaccination of human ACE2 transgenic mice with RBD-Fc could effectively protect mice from the SARS-CoV-2 challenge. These results suggest that SARS-CoV-2 RBD-Fc has good potential to be further developed as an effective and broad-spectrum vaccine to prevent infection of the current SARS-CoV-2 and its mutants, as well as future emerging SARSr-CoVs and re-emerging SARS-CoV[35].	a) ELISPOT: PBMC's from the whole blood sample were isolated and then stimulated with peptides from Spike-protein. The IFN-gamma secreting PBMC's were identified & enumerated to report Spot Forming Units/million PBMC's. This testing was done for blood samples from clinical trials as well as in Non-Human Primates during challenge studies. Overall IFN-g SFU's were on par with vaccines that demonstrate very high immune response[36]. b) TrueCulture: Whole blood samples from clinical trials were incubated in tubes coated with SARS-CoV-2 peptides. The cytokines secreted by the PBMC's present in the whole blood samples were then measured by standard ELISA kits. Both IFN-gamma and IL-4 cytokines were measured to assess the Th1 vs Th2 skew. Significant IFN-gamma expression was observed and very low IL-4 expression was observed indicating Th1 skew in cellular response[36].
4.3 Is there homology in the sequence of the vaccine antigen and human proteins?	NA	
5. Adjuvant (if applicable)	**Information**	**Comments/ Concerns**
5.1 Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant	**CpG 1018** is a Toll-like receptor 9 (TLR-9) antagonist adjuvant composed of a short (22-mer) oligonucleotide sequence containing CpG motifs**. CpG 1018** has been studied clinically and developed as a vaccine adjuvant for Dynavax's hepatitis B vaccine, HEPLISAV-B®[15] The pre-clinical and clinical studies demonstrate that the	

	addition of CpG 1018 increases antibody concentrations, stimulates CD4+ T helper and CD8+ cytotoxic T-cell populations and generates robust T- and B-cell memory responses. Additionally, CpG 1018 strongly favors development of the Th1 subset of helper T cells, the type of helper T cell that is essential for protection from infections with viruses and intracellular bacteria. **Aluminum hydroxide**: Aluminum-containing adjuvants are vaccine ingredients that have been used in vaccines since the 1930s. Small amounts of aluminum are added to help the body build stronger immunity against the antigen in the vaccine	
5.2 What is the evidence that an adjuvant improves/boosts/enhances the immune response?	An important benefit of CpG oligodeoxynucleotides (ODNs) is their ability to boost immunity in groups with reduced immune function, such as the elderly, newborns and the immunosuppressed. Difficulty inducing strong pathogen-specific responses in those populations represents a stumbling block in efforts to achieve 'herd immunity'. Preclinical and clinical studies demonstrate that CpG ODNs can boost immunity in subjects with weak adaptive immune systems[37]. Animals immunized intravaginally with a herpes simplex virus (HSV)-2 vaccine combined with CpG ODN rapidly developed strong mucosal and systemic Th1 immune responses that protected against lethal HSV-2 infection[38].	
5.3 What is the mechanism of action of the adjuvant (if known)?	CpG 1018 adjuvant: • Stimulates TLR-9 in plasmacytoid dendritic cells (PDC). • Converts PDCs into activated dendritic cells (DCs) that present antigen epitopes to the immune system (CD4+ cells)	

	• Promotes differentiation of CD4+ cells that leads to antibody secretion by antigen-specific B cells	
5.4 How is the adjuvant formulated with the antigen?	Formulated in tris-saline buffer.	
5.5 How might the adjuvant impact the safety profile of the vaccine?	CpG 1018 is a recently developed adjuvant used in HEPISLAV-B® vaccine. In pre-licensure clinical trials, adverse events after HEPISLAV-B® were comparable to those observed after another U.S.-licensed, non-adjuvanted hepatitis B vaccine.	
5.6 Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen	The most common side effects with HEPISLAV-B® (which may affect more than 1 in 10 people) are pain at the injection site, headache, feeling generally unwell, tiredness, muscle pain and fever.	
6. Delivery and Administration	**Information**	**Comments/ Concerns**
6.1 How might the vaccine formulation (antigen and adjuvant already formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?	CORBEVAX is a subunit vaccine with Alum and CPG1018 as adjuvant. There is no risk of disease transmission because the vaccination does not contain "live" pathogen components, and it is safer and more stable than vaccines that contain complete pathogens. In pre-licensure toxicological and clinical trials, safety of CORBEVAX vaccine containing RBD of SARS-CoV-2 was comparable to another licensed, adjuvanted and non-adjuvanted vaccines.	
6.2 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety	NA	
6.3 Describe how components of the vaccine formulation that facilitate stability and delivery into cells	NA	

(Section 2.5) may impact the safety profile of the vaccine		
6.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)	NA	
* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purpose.		
7. Toxicology and Nonclinical	**Information**	**Comments/ Concerns**
7.1 What is known about biodistribution of the antigen in its final formulation and mode of administration in animal models?	No information is available	Biodistribution studies have not been done. CORBEVAX is a classical adjuvanted protein sub-unit vaccine. In non-clinical toxicology studies, minimal reactogenicity and toxicity was observed due to lack of inherent toxicity or biological activity of the antigen. Three dose (full human dose, 14 days apart) studies were conducted in Rats and Rabbits. Development and Reproductive Toxicity study was conducted in rats. Both the studies showed excellent immune response and minimal reactogenicity or toxicity. Significant transmission of anti-RBD IgG and nAbs was observed from mother to fetus & pups.
7.2 How long does the vaccine antigen persist in vivo (may specify in tissue/serum; proximal/distal to site of administration)?	No information is available	
7.3 What is the possible risk of autoimmunity or a harmful immune response?	No information is available	
7.4 Summarize the preclinical safety data that support the use of this product in humans including any	The pre-clinical toxicological studies in Rats, Rabbits indicated that the formulation containing the highest concentration of antigen and adjuvant revealed that the	

related information from similar products	vaccine formulation is safe. The immunogenicity studies in rats and mice also indicated that the vaccine formulation is immunogenic. These studies instilled confidence and encouraged for proceeding to Human clinical trials.	
7.5 Summarize the preclinical immunogenicity and efficacy data that support the use of this product in humans including any related information from similar products	The pre-clinical immunogenicity studies mice and Sprague Dawley rats indicated that the vaccine formulation containing the vaccine antigen, aluminum hydroxide and CpG 1018 is found to be immunogenic.	
7.6 What is the evidence of disease enhancement or absence thereof *in vitro* or in animal models?[8]	The animal challenge studies in Non-Human Primate models revealed that the vaccination regimens prevented infection in the animals.	The challenge studies conducted in Non-Human Primate model at UKHSA included a two and three dose vaccination regimen of CORBEVAX via intramuscular route into NHP's which were then challenged with the SARS-COV-2 virus. The study also included a placebo control. This study showed both vaccination regimens prevented infection in the animals as indicated by either absence or significant reduction in Total Viral RNA and Total sub-genomic Viral RNA in nasal and throat swabs, Bronchoalveolar Lavage and Lung tissues in comparison with the animals that did not receive any vaccine. Lung histopathology conducted post euthanasia showed absence of infiltration in lung tissue that are hallmarks of ADE. The vaccine contains Alum and CpG1018 as adjuvants and the immunogenicity data from the clinical trials has demonstrated Th1 skew in both humoral and cellular immune responses. No instances of ADE have been reported during long-term monitoring post vaccination in Phase II/III clinical trials (total surveillance duration of

		approximately 1200 person years) (ref). Thus, the nature of immune response coupled with data from NHP challenge studies conclusively shows absence of ADE due to CORBEVAX vaccination.
7.7 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?	No specific observations were noticed that impacts the innate immunity as part of the studies conducted till date.	
8. Human Efficacy and Other Important Information	**Information**	**Comments/ Concerns**
8.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	Clinical trials conducted in children, adolescents and adults showed that the vaccine is found to be immunogenic after administration of 2 doses of BE's CORBEVAX Vaccine containing Receptor Binding Domain of SARS-CoV-2.	
8.2 Describe other key information that may impact benefit-risk	No adverse effect that would affect the benefit-risk occurred during the trial conducted so far.	
9. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	**Information**	**Comments/ Concerns**
9.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately. _____	360 subjects received the Biological E's Covid 19 vaccination in Phases I & II study where, 4 different formulations were tested as part of selection of optimum formulation of RBD-based protein sub-unit COVID-19 vaccine (CORBEVAX) 4032 subjects received CORBEVAX vaccine in Phase II & III clinical trials.	4 different formulations were tested in the Phase I & II study. 4 different formulations differing in the RBD antigen, Aluminum Hydroxide and CPG 1018 content were tested in the Phase I & II clinical trial.

	As on 10 May 2022, more than 40 million children between 12-15 years of age have received CORBEVAX post Emergency Use Listing (EUL).	To enhance immunogenicity, CpG 1018 content of the formulation was increased from 500 to 750 mcg per dose in final formulation which was used in the Phase II & III clinical trials.
9.2 Method(s) used for safety monitoring:		
● Spontaneous reports/passive surveillance	Yes	If yes, describe method: ___ Submission of Individual Case Safety Reports (ICSR) to the regulatory and National Pharmacovigilance center.
● Diary	Yes	If yes, number of days: 7__days_____
● Other active surveillance	Yes	If yes, describe method (e.g., LTFU) and list the AEs solicited: Fever, Headache Chills, Myalgia, Arthralgia, (Generalized joint pain) Fatigue, (feeling tired) or malaise, Nausea, Urticaria.
9.3 What criteria were used for grading the AEs?		Graded as per CTCAE and DAIDS scale.
● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	No	
● If no criteria were used for grading, or if other metrics were employed, please describe:	Graded as per Common Terminology Criteria for Adverse Events (CTCAE) and Division of AIDS (DAIDS) scale.	
9.4 List and provide frequency of any or possibly related serious* AEs and well as any severe expected or	Nil No serious unwanted adverse event related to vaccine has been encountered so far during the ongoing clinical trial.	

unexpected AEs observed: (*see Instructions):		
9.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:	Nil	
• Describe the control group: .	Phase III clinical trial involved a comparator which was an approved vaccine under EUL.	
9.6. List and provide frequency of Adverse Events of Special Interest	No Adverse Events of Special Interest related to vaccine have been reported so far during the ongoing clinical trials. As on 16.08.22, a total of 69 million doses of CORBEVAX™ have been administered as part of Vaccination campaign by the Government of India. No cases of Adverse Events of Special Interest have been reported till date.	
9.7 What is the evidence of disease enhancement (if any) in humans?	Nil	
9.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes	Yes
• Did it identify any safety issue of concern?	No	No
• If so describe:		
10. Overall Risk Assessment	**Information**	**Comments/ Concerns**
10.1 Please summarize key safety issues of concern identified to date, if any:	Nil	Majority of adverse events were mild and there were no serious adverse events related to Study vaccine reported in all the trials. None of the adverse reactions led to the withdrawal of study participants. No adverse event of special interest

		or serious concern have been encountered in Clinical trials and post EUL.
● how should they be addressed going forward	Nil	
10.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as:** **none, minimal, low, moderate, high, or unknown**
● healthy humans?	No serious unwanted adverse events related to vaccine have been encountered in the ongoing clinical trials.	none
● immunocompromised humans?	Not Studied	unknown
● human neonates, infants, children?	Majority of adverse events were mild and there were no serious adverse events reported in the clinical trial in children and adolescents aged 5-18 years. None of the adverse reactions led to the withdrawal of study participants.	the vaccine was well tolerated in children and adolescents aged 5-18 years.
● pregnancy and in the fetus in humans?	Not Studied	▪ Pre-, Peri-, and Post-natal Reproductive / Developmental Toxicity Study was conducted with CORBEVAX in Sprague Dawley (SD) Rats by Intramuscular Route. ▪ The objective was to detect potential toxic/adverse effects of intramuscular administration of the SARS-CoV-2 (Covid-19) Vaccine on mating performance, fertility, gestation, parturition, lactation and maternal behavior (from implantation through lactation and weaning) and on the development of the offspring (embryo-fetal development, pre- and post-natal development) in female Sprague Dawley rats.

		▪ The immunogenicity was also evaluated in female rats and fetus/pups. ▪ Based on the study results, it was found that two doses of CORBEVAX given at two-week intervals prior to mating, on Gestation Days 6 and 18 and on Lactation Day 7 to Sprague Dawley female rats did not have any adverse effects on fertility and reproductive performance, pre-natal and post-natal maternal reproductive toxicity or survival and development of the offspring. ▪ Significant immune response was observed in female rats specific to RBD antigen present in SARS-CoV-2 Vaccine. Also, significant and consistent transmission of maternal antibodies to fetus/pups was observed in SD rats confirming the immunogenicity of the vaccine formulation.
● elderly?	No serious unwanted adverse event related to the vaccine has been encountered so far during the ongoing clinical trials in elderly individuals. The vaccine was well tolerated in the elderly individuals.	none
● in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	Not Studied	unknown

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