AGREED PEDIATRIC STUDY PLAN (PSP)

Product: COVID-19 Vaccine (BNT162, PF-07302048)

Dosage Form: Liquid formulation for intramuscular injection

IND #: 019736

Drug Class: Vaccine

Approved Indication: Not applicable

Proposed Initial Indication: Active immunization against COVID-19 in individuals ≥16 years of age

Proposed Supplemental Indications: Active immunization against COVID-19 in children and adolescents 12 through 15 years of age; Active immunization against COVID-19 in children and infants <12 years of age

Proposed General Plan:

- Deferral of assessment in adolescents, children, and infants 15 years of age and younger

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin-converting enzyme 2
A:G	Albumin: Globulin ratio
CAS	Chemical Abstracts Service
CBER	Center for Biologics Evaluation and Research
COVID-19	coronavirus disease 2019
DART	developmental and reproductive toxicity
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
GLP	Good Laboratory Practice
HCoV-229E	human coronavirus 229E
HCoV-NL63	human coronavirus NL63
ICU	intensive care unit
IFNγ	interferon-gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IND	investigational new drug
PSP	pediatric study plan
LNP	lipid nanoparticles
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified RNA
NAAT	nucleic acid amplification test
NaCl	sodium chloride
P2 S	prefusion spike glycoprotein
PCR	polymerase chain reaction
PLT	platelet
RBC	red blood cell
RDW	red cell distribution width
RETIC	reticulocyte
RNA	ribonucleic acid
S	spike protein
S1	spike protein S1 subunit
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Th1	Type 1 T helper cells
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization

1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION

1.1. Pathophysiology of the Disease

SARS-CoV-2 is the causative agent of COVID-19. There are several other coronaviruses already circulating in humans, such as HCoV-229E or HCoV-NL63, very often as asymptomatic infections or infections causing mild respiratory symptoms.[1]

SARS-CoV-2 uses a densely glycosylated S to bind to the angiotensin-converting enzyme 2 (ACE2) receptor of the human host cell, as found previously in SARS-CoV, to fuse the viral and host cell membranes.[2] The distribution of the ACE2 receptor in pulmonary tissues underlies the predominantly respiratory nature of COVID-19.[3]

1.2. Clinical Presentation of SARS-CoV-2–Associated Disease in Adults and in the Pediatric Population

COVID-19 is generally milder in children than adults, possibly because common risk factors for severe COVID-19 in adults are generally less prevalent in pediatric age groups. Like adults, over half of children present with fever and dry cough.[4] Gastrointestinal symptoms, including diarrhea and vomiting, which occur rarely in adults, occur more commonly in children and may, in some cases, be the only presenting features.[5] Rhinorrhea and sore throat may also be more prominent in children with SARS-CoV-2 infection, although this picture is likely confounded by coinfection with other respiratory pathogens common in children.[5,6] Pulmonary involvement in symptomatic children is generally mild.[7] In a systematic review of the clinical characteristics and outcomes of SARS-CoV-2 infections in 7480 children from around the world, mild (42.5%; 608/1432) or moderate (39.6%; 567/1432) signs of infection were reported, and approximately 2% were admitted to pediatric intensive care.[8]

Nevertheless, severe cases, including those requiring intensive care support, have been reported.[9] In a nationwide case series of 2135 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention,[10] severe/critical disease defined by a combination of clinical, radiographic, and laboratory criteria was identified in 10.6%, 7.3%, and 3.9% of patients within the <1, 1 to 5, and 6 to 18 years of age groups, respectively, compared with 18.5% in adults.[11,12] In a retrospective review of 341 pediatric patients with a definite diagnosis of COVID-19 reported to health authorities in China, severe or critical disease was reported in 0.6% and 0.3%, respectively.[13] In an analysis of pediatric COVID-19 hospitalization data from 14 states in the US, although the cumulative rate of COVID-19-associated hospitalization was lower among children (8.0 per 100,000 population) compared with that in adults (164.5), 33.2% were admitted to an intensive care unit.[14] Common radiographic findings in severe disease are similar to those in adults and include the presence of ground-glass opacities and segmental consolidation in bilateral lung fields,[7,15] especially in the peripheral zones.[15]

In addition to the above, children may acquire multisystem inflammatory syndrome in children (MIS-C), an emerging condition that appears to be temporally related to recent exposure to SARS-CoV-2, frequently requires intensive care admission, and may have a fatal outcome.[16,17] MIS-C is a febrile hyperinflammatory condition with frequent evidence of cardiac damage and dermatological, mucocutaneous, and gastrointestinal features.[17] MIS-C

can lead to shock and multiple organ failure requiring admission to an intensive care unit (ICU).[18] The syndrome appears to have some overlap with Kawasaki disease shock syndrome.[19,20] Compared with Kawasaki disease, patients with MIS-C are older, have more cardiac injury, and are more likely to be black, Hispanic, or of South Asian descent.[21] As of 30 June 2020, over 1000 cases have been reported.[21] As of 29 July 2020, a total of 570 cases were reported in the US to the CDC. Of these, 86.0% involved four or more organ systems, 63.9% of patients required ICU admission, and severe complications included cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilation or aneurysm (18.6%), and acute kidney injury (18.4%).[22] Death rates of 2% to 4% have been reported.[21] MIS-C has been reported in many countries throughout North America, Europe, Asia, and Latin America,[18] including the US,[16,17] Italy,[23] and France.[24]

COVID-19 has been reported in neonates born to infected mothers.[25,26] There is limited evidence that neonates acquire infection through intrauterine vertical transmission; thus, neonatal infection likely mostly occurs from postnatal contact.[26] Outcomes were generally good in neonates, though assessment may be complex in neonates where other conditions may be relevant.[25,26]

1.3. Incidence and Prevalence Overall and in the Pediatric Population

In general, COVID-19 affects pediatric populations less frequently as compared with other age groups.[11,27,28] In the US, individuals <17 years of age represent 10.9% of reported cases with 1.9% of cases reported in children 0-4 years of age, and 9.0% reported in children and adolescents 5-17 years of age.[29] The hospitalization rate as of 16 January 2021 in the US was 36.9/100,000 in children 0 to 4 years of age and 22/100,000 in children and adolescents 5 to 17 years of age, compared with 380.3/100,000 of the overall population.[30]

Between March 1–December 12, 2020, a total of 2,871,828 laboratory-confirmed cases of COVID-19 were reported in children, adolescents, and young adults aged 0–24 years in the United States. Among these cases, 16.3% were reported in children and adolescents aged 14–17 years old, 7.9% were reported in children 11–13 years old, 10.9% were reported in children 5–10 years old, and 7.4% were reported in those 0–4 years old. Hospitalizations, ICU admission, and death were available for 41.9%, 8.9%, and 49.1% of the cases (respectively) and among children, adolescents, and young adults, 30,229 (2.5%) were hospitalized, 1,973 (0.8%) required ICU admission, and 654 (<0.1%) died. Children 0-4 years of age accounted for the largest percentage of hospitalizations (4.6%), and ICU admissions (1.8%).[31]

In China, out of a series of 72,314 cases, children 0 to 9 years of age represented only 0.9% of COVID-19 cases, while children and adolescents 10 to 19 years of age represented 1.2% of cases.[32] In the United Kingdom (UK), children and adolescents accounted for 9,944 out of a total of 257,029 confirmed COVID-19 cases (3.87%) (0.62% [0-4 years of age], 0.70% [5-9 years of age], 0.81% [10-14 years of age], to a maximum of 1.74% [15-19 years of age]) as of 30 July 2020.[33] However, these figures may be related to pediatric and adolescent SARS-CoV-2 infections generally being asymptomatic or mild, limiting presentation to hospital or other medical care, as well as reduced diagnostic testing.[1,9,10,34,35]

An analysis conducted in the province of Shenzhen, China, examined household contacts of infected cases as well as primary subjects presenting with symptoms.[36] Children 0 to 9 years of age represented 14.9% of cases identified as household contacts but only 2.1% of those presenting with symptoms.[36] Children were as likely to be infected through household exposure as any other age group.[36]

1.4. Methods of Diagnosis

As in adults, the primary diagnostic method for children presenting with symptoms suggestive of COVID-19 is by polymerase chain reaction (PCR), also termed nucleic acid amplification test (NAAT), on respiratory tract secretions, typically nasopharyngeal or midturbinate nasal swabs, although the virus can be detected in other samples.[1,34,35,37] Serological methods rely on the development of immunoglobulin G (IgG) and/or immunoglobulin M (IgM) to SARS-CoV-2 antigens following infection. Serological methods are not useful diagnostics in acute disease but are useful for diagnosing prior infection.[38]

1.5. Currently Available Treatments and/or Prevention Strategies in the Pediatric Population, Including Neonates

Currently, there are no FDA-approved vaccines for prevention of COVID-19 in pediatric populations. BNT162b2 has Emergency Use Authorization (EUA) in the United States for individuals 16 years of age and older. The Moderna COVID-19 vaccine has an EUA in the United States for individuals 18 years of age and older.

For pediatric subjects with COVID-19, the standard of care is generally supportive therapy, as indicated for children infected with other known respiratory viruses.[1]

Remdesivir is approved for the treatment of children ≥12 years of age and ≥40 kg (as well as adults) requiring hospitalization for COVID-19, and can be used under FDA EUA for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.[39]

A combination of two monoclonal antibodies, casirivimab and imdevimab administered together, are authorized for emergency use for the treatment of mild to moderate COVID-19 in adults, as well as in pediatric patients at least 12 years of age and weighing at least 40 kg, who have received positive results of direct SARS-CoV-2 viral testing and are at high risk for progressing to severe COVID-19 and/or hospitalization.[40]

Baricitinib in combination with remdesivir is authorized for emergency use for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[40]

Bamlanivimab is authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients with positive results of direct SARS-CoV-2 viral

testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.[40]

1.6. Summary

SARS-CoV-2 infection may be common in children and adolescents, but compared to adults, severe disease and hospitalizations are rare. Nevertheless, severe disease may occur at any age, and there is a unique severe pediatric manifestation of SARS-CoV-2 infection termed MIS-C. These data indicate a need for a pediatric immunization strategy.

2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including COVID-19. BNT162b2 is based on a platform of nucleoside--modified messenger RNA (modRNA) that expresses the SARS–CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9). The RNA is encapsulated in lipid nanoparticles, which enable entry of the RNA into host cells. The stabilized S antigen is expressed from the RNA in the host cells and elicits virus neutralizing antibody and cell mediated immune responses.

BNT162b2 is currently authorized for Emergency Use.

Emergency Use Authorized Indication: Active immunization against COVID-19 in individuals ≥16 years of age.

Proposed Initial Indication: Active immunization against COVID-19 in individuals ≥16 years of age.

Proposed Supplemental Indications: Active immunization against COVID-19 in children and adolescents 12 through 15 years of age; Active immunization against COVID-19 in children and infants <12 years of age.

Planned Pediatric Clinical Studies are discussed in Table 1.

3. OVERVIEW OF PLANNED EXTRAPOLATION OF EFFECTIVENESS TO SPECIFIC PEDIATRIC POPULATIONS

No extrapolation is planned.

4. PLAN TO REQUEST DRUG-SPECIFIC WAIVER(S)

Not applicable.

5. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES

Pfizer and BioNTech propose to request a deferral of the evaluation of the COVID-19 vaccine in individuals ≤15 years of age (Attachment A) based on the following Criteria for Deferral (Section 505B(a)(4)(A)(i)(I) of the Act): "*Pediatric studies should be delayed until additional safety or effectiveness data have been collected" and "The drug or biological product will be ready for approval for use in adults before pediatric studies are complete*."

Adequate evidence of safety and efficacy has been established in the pivotal study C4591001 in individuals ≥16 years of age to allow Emergency Use Authorization in that age group. Study C4591001 includes subjects 12 through 17 years of age. It was appropriate to defer studies in children 6 months to <12 years of age until adequate safety and immunogenicity information was available in 12- through 15-year-old children and adolescents. It would then be appropriate to defer further age-de-escalation to <6 months until adequate safety data is available in 6 month through 11-year-old children.

6. TABULAR SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES

6.1. Planned Nonclinical Studies

No juvenile toxicity studies are planned because the current nonclinical and clinical data are sufficient to support pediatric clinical studies in children.

6.2. Planned Clinical Studies

Pfizer and BioNTech request a deferral for a planned pediatric evaluation of the COVID-19 vaccine in adolescents, children, and infants ≤15 years of age (Table 1). Details for this planned pediatric study can be found in Section 10.

Table 1. Table of Clinical Studies for COVID-19 Vaccine

PLANNED PEDIATRIC CLINICAL STUDIES			
Pediatric Pharmacokinetic Studies			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
Not applicable			
Clinical Studies Including Safety, and Effectiveness			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
16 through 17 years	Safety and effectiveness	Study C4591001	N
12 through 15 years	Safety and effectiveness	Study C4591001	Y
5 through 11 years	Dose finding followed by safety and effectiveness	Study C4591007	Y
6 months to <5 years	Age de-escalating dose finding followed by safety and effectiveness	Study C4591007	Y
< 6 months	Dose finding followed by safety and effectiveness	Study C4591023	Y

7. AGE-APPROPRIATE FORMULATION DEVELOPMENT

No formulation changes are planned for the pediatric development.

7.1. Description of the drug product

The drug product is a preservative-free, sterile dispersion of RNA formulated in LNP in aqueous cryoprotectant buffer for intramuscular (IM) administration. The RNA drug substance is the only active ingredient in the drug product. The product is a concentrate for solution at 0.5 mg/mL drug product.

The composition of RNA drug products for use in the planned clinical trials and the function of the respective components are given in Table 2.

Table 2. Composition of Drug Products

Component	Quality Standard	Function
Drug substance	In-house	Active
ALC-0315[a]	In-house	Functional lipid
ALC-0159[b]	In-house	Functional lipid
DSPC[c]	In-house	Structural lipid
Cholesterol	Ph. Eur.	Structural lipid
Sucrose	NF/Ph. Eur.	Cryoprotectant
NaCl	USP/Ph. Eur.	Buffer
KCl	USP/Ph. Eur.	Buffer
Na2HPO4	USP/Ph. Eur.	Buffer
KH2PO4	NF/Ph. Eur.	Buffer
Water for injection	Ph. Eur.	Solvent/Vehicle

[a] ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate).
[b] ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.
[c] DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine.

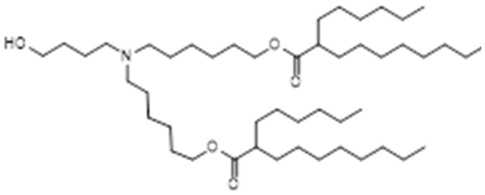
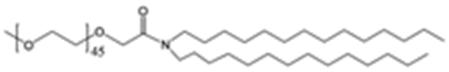
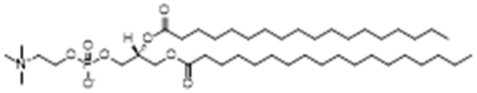
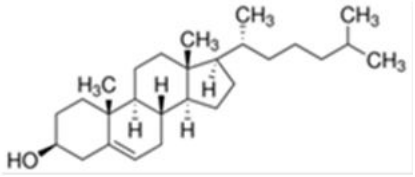
7.2. Description of the excipients

All excipients used in the formulation of the drug product are listed in Table 3.

The drug product contains the 2 functional lipids ALC-0315 and ALC-0159 and the 2 structural lipids DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and cholesterol.

Physicochemical properties and the structures of the 4 lipids are shown in Table 3.

Table 3. Lipid Excipients in the Drug Product

Lipid (CAS Number)	Molecular Weight [Da]	Molecular Formula	Physical State and Storage Condition	Chemical Name (Synonyms) and Structure
ALC-0315 (not applicable)	766	$C_{48}H_{95}NO_5$	Liquid (oil) -20ºC	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159 (1849616-42-7)	~2400-2600	$C_{30}H_{60}NO(C_2H_4O)_nOCH_3$ n=45-50	Solid -20ºC	2-[(polyethylene glycol)-2000]-N,N-ditetradecyclacetamide 
DSPC (816-94-4)	790	$C_{44}H_{88}NO_8P$	Solid -20ºC	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol (57-88-5)	387	$C_{27}H_{46}O$	Solid -20ºC	

7.3. Description of the diluent

For the dilution of drug products for IM injection, isotonic NaCl solution (0.9%) is sourced as an approved medicinal product. The composition is according to the supplier's specifications.

8. NONCLINICAL STUDIES

8.1. Nonclinical Pharmacology

Nonclinical studies in mice and nonhuman primates for BNT162b2 (V9), a nucleoside-modified mRNA (modRNA) vaccine that encodes the SARS-CoV-2 full-length spike glycoprotein (S), demonstrated a strong neutralizing antibody response, Th1-type $CD4^+$ T-cell response, and a $CD8^+$ IFNγ response. Antigen-binding IgG and neutralizing antibody responses were detectable as early as 14 d post-immunization, with substantial increases observed in nonhuman primates after the second dose. BNT162b2 (V9) provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease

enhancement. A strong humoral response was also observed in an accessory study to the GLP-compliant repeat-dose toxicology study with BNT162b2 (V8) in rats (Study 38166). Nonclinical development is further described in Module 2.4 of BB-IND 019736 (Nonclinical Overview).

For nonclinical mouse immunogenicity studies, a pseudotype neutralization assay has been used as a surrogate of virus neutralization. For nonhuman primate nonclinical studies and for clinical testing was performed using, qualified SARS-CoV-2 neutralization and SARS-CoV-2 S1-binding IgG Luminex assays (VR-MQR-10214 and VR-MQR-10211).

8.2. Nonclinical Safety Data

The nonclinical toxicity assessment of BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048) includes 2 GLP-compliant repeat-dose toxicity studies and a developmental and reproductive toxicity (DART) study in Wistar Han rats outlined below in Table 4. The nonclinical safety evaluation included 2 variants of BNT162b2: V8 and V9. BNT162b2 (V9), the candidate granted EUA approval, differs from BNT162b2 (V8) only in the presence of optimized codons to improve antigen expression, but the amino acid sequences of the encoded antigens are identical. Two GLP repeat-dose toxicity studies for BNT162b2 (V8) and BNT162b2 (V9), one study for each variant, have been completed. In both studies, the nonclinical toxicology findings were similar between BNT162b2 (V9) and BNT162b2 (V8). BNT162b2 (V9) was assessed for development and reproductive toxicity in rats.

The IM route of exposure was selected as it is the intended route of clinical administration. The selection of rats as the toxicology test species is consistent with the WHO guidance documents on nonclinical evaluation of vaccines,[44] which recommend that vaccine toxicity studies be conducted in a species in which an immune response is induced by the vaccine. Generation of an immune response to BNT162b2 has been confirmed in rats in both repeat-dose toxicity and DART studies. The Wistar Han rat is used routinely for regulatory toxicity studies, and there is an extensive historical safety database on this strain of rat.

Table 4. Overview of Toxicity Testing Program

Study[a]	Study (Sponsor) No.	Group/ Dose, µg RNA	Total Volume (µL)[b]	No. of Animals/ Group	Study Status
Repeat-Dose Toxicity					
17-Day, 2 or 3 Dose (1 Dose/Week) IM Toxicity With a 3 Week Recovery Phase in Rats[c,d]	38166	Control[e], 0	200[f]	15/sex	Completed
		BNT162b2 (V8)[i], 100	200[f]	15/sex	
17-Day, 3 Dose (1 Dose/Week) IM Toxicity With a 3 Week Recovery Phase in Rats[g]	20GR142	Saline[h], 0	60	15/sex	Completed
		BNT162b2 (V9)[i], 30	60	15/sex	
Developmental and Reproductive Toxicity					
Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by the IM route in Rats	20256434 (RN9391 R58)	Saline[h], 0	60	44 F	Completed
		BNT162b2 (V9)[i], 30	60	44 F	

a. All studies are GLP-compliant and were conducted in an OECD mutual acceptance of data-compliant member state.
b. Doses were administered as 1 application at 1 site unless otherwise indicated.
c. Study also evaluated the BNT162a1, BNT162b1 and BNT162c1 vaccine candidates.
d. QW x 3 (Days 1, 8, 15) for BNT162a1, BNT162b1, and BNT162b2 (V8); QW x 2 (Days 1, 8) for BNT162c1.
e. Phosphate buffered saline, 300 mM sucrose.
f. One application (100 µL) at 2 sites for a total dose volume of 200 µL.
g. Study also evaluated BNT162b3.
h. Sterile saline (0.9% NaCl).
i. BNT162b2 (V8) and BNT162b2 (V9) both encode the same amino acid sequence of the spike protein antigen with two prefusion conformation-stabilizing amino acids in the stalk.

In both repeat dose toxicity studies, administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Expected immune responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants, and decreased A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reductions in body weights and transient reductions in RETIC, PLT, and RBC mass parameters.[41,42,43] All changes in hematology parameters and acute phase proteins were similar to control at the end of the

recovery phase for BNT162b2 with the exception of higher RDW and lower A:G ratios in animals administered BNT162b2 (V9). Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and weight of spleen. Vaccine-related microscopic findings at the end of dosing for BNT162b2 were evident in injection sites and surrounding tissues, in the draining iliac lymph nodes, bone marrow, spleen, and liver. Microscopic findings at the end of the dosing phase were partially (recovery in progress) or completely recovered in all animals at the end of the recovery phase for BNT162b2. A robust immune response was elicited to the BNT162b2 vaccine antigen.

In the DART study, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day) was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring through the end of lactation. An immune response to the vaccine was confirmed in F0 female rats prior to mating, at the end of gestation and at the end of lactation and these responses were also detectable in the F1 offspring (fetuses and pups).

Stand-alone safety pharmacology, genotoxicity, and carcinogenicity studies have not been performed with the COVID-19 vaccine. This is consistent with the World Health Organization guidance on the nonclinical safety assessment of vaccines.[44]

No nonclinical studies have been conducted in juvenile animals.

9. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS

BNT162b2 has been studied in three clinical trials in adults. These are BNT162-01, a phase 1/2 study in Germany, C4591001 (BNT162-02), and C4591005 (BNT162-05), a phase 1/2 safety and immunogenicity study in Japan. Study C4591001 included a phase 1 component for candidate and dose selection, allowing progression to a large placebo-controlled phase 2/3 safety, immunogenicity and efficacy study conducted in the US, Argentina, Brazil, South Africa, Turkey and Germany. While these studies continue, the available clinical evidence demonstrates induction of strong immune responses and high VE, suggesting the vaccine confers protection against COVID-19 in individuals ≥16 years of age. This evidence supported the granting of an EUA.

The observed safety profile in clinical trials to date shows mostly mild reactogenicity, low incidence of severe or serious events, and no clinically concerning safety observations. The vaccine appears to be safe and well-tolerated across the safety population and within demographic subgroups based on age, sex, race/ethnicity, country, and baseline SARS-CoV-2 status. The preponderance of severe cases of COVID-19 in the placebo group relative to the BNT162b2 group (9 of 10) suggests no evidence of vaccine-associated enhanced disease (VAED).

Vaccine efficacy was high, ≥95% for participants without prior evidence of SARS-CoV-2 infection and >94% for those with and without prior infection, in the planned interim and final analyses. Observed VE was >93% across subgroups identified by age, sex, race/ethnicity, and country with the exception of "all others" race group (89.3% VE) and Brazil (87.7% VE).

10. PLANNED PEDIATRIC CLINICAL STUDIES

10.1. Pediatric Pharmacokinetic Studies

Not applicable.

10.2. Clinical Effectiveness and Safety Studies Planned

10.2.1. Ongoing Pediatric Clinical Study

10.2.1.1. Study C4591001: Ages 12 Through 17 Years

Approximately 600 individuals 16 through 17 years of age have been enrolled within the Phase 3 C4591001 study. Data analyses to be submitted will examine safety and effectiveness endpoints.

Approximately 2000 individuals 12 through 15 years of age have been enrolled in the Phase 3 C4591001 study. Data analyses to be submitted will examine safety and effectiveness endpoints to support an indication for use in individuals 12 through 15 years of age.

10.2.2. Proposed Pediatric Clinical Studies

10.2.2.1. Study C4591007: 6 months to <12 years of age

Study C4591007 is a dose-finding, age de-escalating safety and effectiveness study in children 6 months to <12 years of age.

10.2.2.2. Study C4591023: Less than 6 months of age

Study C4591023 is a dose-finding safety and effectiveness study in infants less than 6 months of age.

11. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN

1. Formulation Development: Not applicable.

2. Nonclinical Studies: None.

3. Clinical Studies:

   PK Study: Not applicable.

   Safety and Effectiveness Study: C4591007 (6 months to <12 years of age)

   Protocol submission date: 8 February 2021

   Study initiation date: 24 March 2021

   Estimated study completion date: 31 October 2023

   Estimated final report submission date: 31 March 2024

   Safety and Effectiveness Study: C4591023 (< 6 months)

   Estimated protocol submission date: 31 January 2022

   Estimated study initiation date: 31 April 2022

   Estimated study completion date: 31 July 2024

   Estimated final report submission date: 31 October 2024

4. Target Date for submission of supplemental BLA is October 2021.

   Target Date for submission of supplemental BLA for <12 years of age is to be determined.

12. AGREEMENTS FOR PEDIATRIC STUDIES WITH OTHER REGULATORY AUTHORITIES

BioNTech received approval from the European Medicines Agency for the Paediatric Investigation Plan on 27 November 2020 (EMA Decision P/0480/2020). A deferral is granted for studies from birth to less than 18 years of age.

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