

**Vaccines and Related Biological Products
Advisory Committee October 26, 2021
Meeting Presentation**

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Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety of Pfizer-BioNTech COVID-19 Vaccine in Children 5 through 11 Years of Age *Emergency Use Authorization Amendment*

Leslie Ball, M.D.







FDA/CBER

Office of Vaccines Research and Review

Division of Vaccines and Related Products Applications

October 26, 2021

Outline

-  Background
-  Study Design
-  Immunogenicity Data
-  Efficacy data
-  Safety Data
-  Summary

Outline



Background



Pfizer-BioNTech COVID-19 vaccine, mRNA

EUA request for use of Pfizer-BioNTech COVID-19 vaccine as a 2-dose (primary) series, administered 3 weeks apart, in children 5-11 years of age

- Each dose contains 10 µg mRNA (0.2 mL)
- Vaccine Composition
 - SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA
 - Formulated in lipid particles
- Pfizer-BioNTech COVID-19 vaccine is authorized for use as a primary series in individuals 12 years of age and older (with and without certain compromised immune systems) and as a booster dose. Each dose contains 30 µg mRNA (0.3 mL).
- In August 2021, FDA approved the BNT162b2 vaccine under the proprietary name COMIRNATY in individuals 16 years of age and older. Each dose contains 30 µg mRNA (0.3 mL).

A circular icon with a light blue gradient and a shadow, containing a white outline of a document with a pencil, representing study design or research.

Study Design



C4591007: Study Overview

Ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled immunogenicity, efficacy, and safety study

Phase 1: dosing finding

5 through 11 (5-11) years of age: BNT162b2 dose levels 10, 20, 30 μg

Safety and immunogenicity data

Phase 2/3:

Final dose level for 5-11 years of age: 10 μg



C4591007: Study Design



Phase 2/3


5-11 years of age
(only this age group included in aEUA)


Randomized
2:1


Dose 1

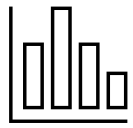
Dose 2

 
← 3 weeks →
○ BNT162b2 10 μ g (n=3109)
○ Saline placebo (n= 1538)

 Immunogenicity data for immunobridging analysis (n= 322)

 Efficacy data from accrued COVID-19 cases

 Safety data (Cohorts 1 and 2)



C4591007: Phase 2/3 Cohorts for Safety Analyses



**Cohort 1: Safety data includes reactogenicity, unsolicited AEs
(non-serious, serious, AEs of clinical interest)**

Enrollment initiated June 7, 2021

Data cut-off September 6



95% with ≥ 2 months safety data post Dose 2



BNT162b2 (10 μ g) n= 1518
Placebo n= 750

**Cohort 2: Additional safety data submitted during the EUA review
process (especially SAEs, AESIs)**

Enrollment initiated August 26, 2021

Data cut-off October 8



71% with ≥ 2 weeks safety data post Dose 2



BNT162b2 (10 μ g) n= 1591
Placebo n= 778



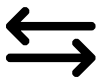
Comparator for immunobridging analysis

C4591001: Ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled safety, immunogenicity, and efficacy study

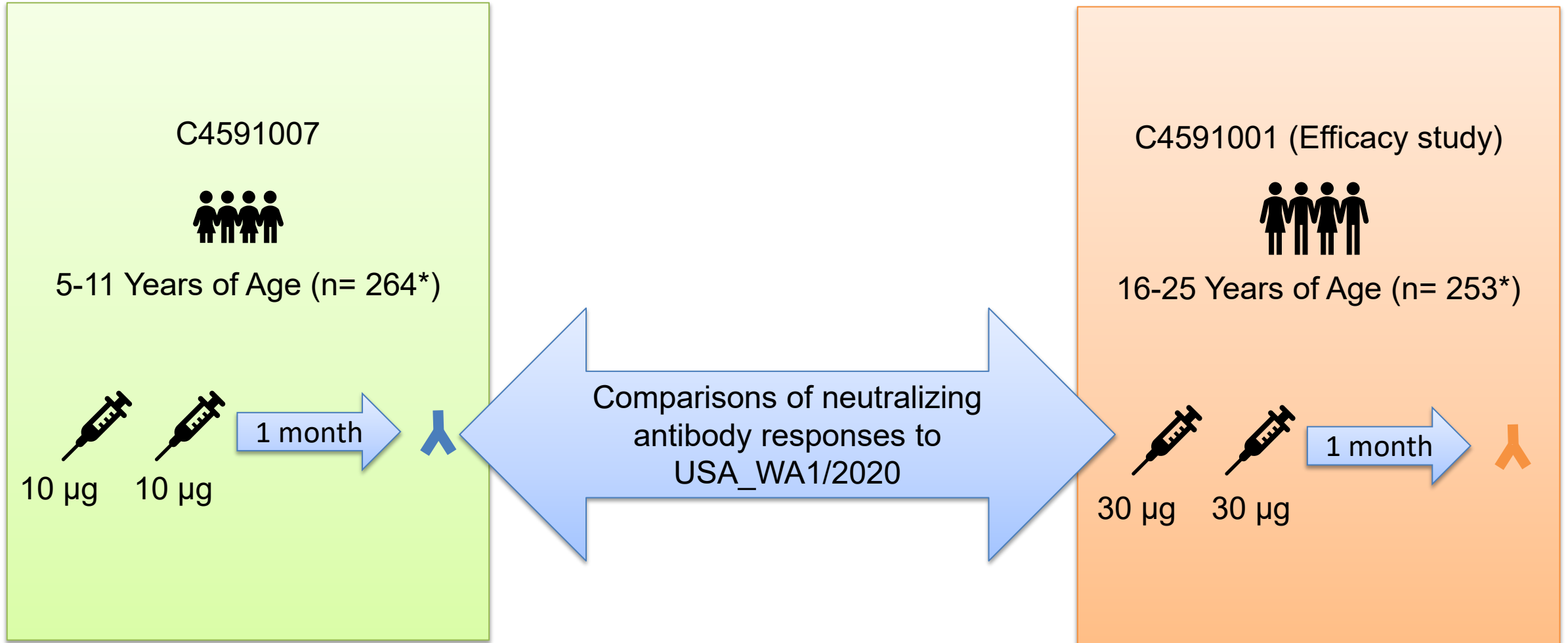


Efficacy in age group 16- 55 years was 91.2%

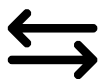
↔ Immunogenicity data from 300 randomly selected participants 16 through 25 (16-25) years of age used for immunobridging analysis



Immunobridging Analysis



*n= evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection



Immunobridging Analysis: Geometric Mean Titer



Endpoint: Geometric mean neutralizing antibody titer (GMT) 1 Month Post-Primary Series based on SARS-CoV-2 Microneutralization Assay-NT50 against USA_WA1/2020

GMT ratio of SARS-CoV-2 neutralizing titers

GMT 5-11 years (C4591007) 

GMT 16-25 years (C4591001) 

Immunobridging success criteria:

- lower limit of the 2-sided 95% CI for GMT ratio >0.67
- point estimate of GMT ratio ≥ 1.0



Immunobridging Analysis: Seroresponse



Percentage difference between seroresponse

% 



MINUS

% 






Immunobridging success criterion:
lower limit of the 95% CI for the difference in % of participants with seroresponse is > -10%

*The lower limit of quantitation (LLOQ) is defined as the lowest sample concentration that can be measured by the assay with acceptable accuracy, linearity and precision.



Analysis Populations: Disposition



	C4591007 Phase 2/3: 5-11 years Placebo 	C4591007 Phase 2/3: 5-11 years BNT162b2 10 µg 	C4591001 Phase 2/3: 16-25 years BNT162b2 30 µg 
Safety population (Cohort 1)	750	1518	-
Safety population (Cohort 2)	788	1591	-
Immunobridging subset*	-	322	300
Evaluable immunogenicity population without evidence of infection	-	264	253
Evaluable efficacy population without evidence of infection	663	1305	-

Without evidence of infection=Participants who had no serological or virological evidence (prior to the 1-month post-Dose 2 blood sample collection) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and Visit 4 (C4591007) or Visit 3 (C4591001), SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2, and negative NAAT [nasal swab] result at any unscheduled visit prior to the 1-month post-Dose 2 blood sample collection) and had no medical history of COVID-19 were included in the analysis.

*Immunobridging subset from C4591007 and randomly selected subset from C4591001

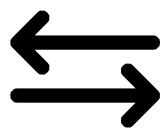


Demographics and Baseline Characteristics (C4591007 Ph 2/3 Safety Population Cohort 1)



- 52% males and 48% females, median age 8 years
- 91% without evidence of prior COVID-19 infection
- Race: 78% White, 6% African American, 6% Asian, 21% Hispanic
- Enrolled in 4 countries: US (71%), Finland, Spain and Poland (29% combined)
- Approximately 20% of subjects had comorbidities:
 - Obesity ~12%
 - Asthma ~8%
 - Neurologic disorders ~1%
 - Congenital heart disease ~<1%

Immunogenicity Data



Immunobridging Based on GMT Ratio (USA_WA1/2020)

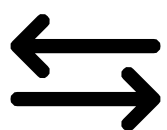


SARS-CoV-2 Neutralizing GMTs at 1 Month Post-Primary Series
Evaluable Immunogenicity Population without Evidence of Infection

GMT (95% CI) 5 -11 Years of Age Study C4591007 N = 264	GMT (95% CI) 16-25 Years of Age Study C4591001 N = 253	GMT Ratio (95% CI) (5-11 Years of Age / 16-25 Years of Age)
<p>1197.6 (1106.1, 1296.6)</p>	<p>1146.5 (1045.5, 1257.2)</p>	<p>1.04 (0.93, 1.18)</p>

Success criteria met as the lower bound of the 2-sided 95% CI for the GMT ratio was >0.67 and the point estimate of the GMT ratio was ≥1.0.

Assay: SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer



Immunobridging Based on Seroreponse Rate (USA_WA1/2020)



Seroreponse Rates at 1 Month Post-Primary Series at 1 Month Post-Primary
Evaluable Immunogenicity Population without Evidence of Infection

Seroreponse 5 -11 Years of Age Study C4591007 % (95% CI) N= 264	Seroreponse 16-25 Years of Age Study C4591001 % (95% CI) N= 253	% Difference in Seroreponse Rate (5 -11 Years minus 16- 25 Years) (95% CI)
99.2 (97.3, 99.9)	99.2 (97.2, 99.9)	0 (-2.0, 2.2)

Success criterion met as the lower limit of the 95% CI for the difference in percentages of participants with seroreponse was greater than -10%.

Assay: SARS-CoV-2 mNeonGreen virus microneutralization assay (SARS-CoV-2 mNG NT), reference strain: recombinant USA_WA1/2020. NT50= 50% neutralizing titer



Exploratory Analysis: Geometric Mean Titer (Delta Variant and USA_WA1/2020 Strain)



Participants Without Evidence of Infection up to 1 Month After Dose 2, Phase 2/3 – 5-11 Years of Age, Subset of Evaluable Immunogenicity Population

Assay* Target	Time Point	BNT162b2 10 µg N=34 GMT (95% CI)	Placebo N=4 GMT (95% CI)
USA_WA1/2020	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
USA_WA1/2020	1 month post-Dose 2	365.3 (279.0, 478.4)	10.0 (10.0, 10.0)
B.1.617.2 (Delta)	Pre-Dose 1	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)
B.1.617.2 (Delta)	1 month post-Dose 2	294.0 (214.6, 405.3)	10.0 (10.0, 10.0)

*SARS-CoV-2 plaque-reduction neutralization (PRNT) assay

Assay not yet validated; Analyses not verified by FDA

Outline

 Efficacy data



Supportive Efficacy Analysis: Case definitions

COVID-19

Presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test), which triggered a potential COVID-19 illness visit:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea as defined by ≥ 3 loose stools/day
- Vomiting



Severe COVID-19

Confirmed COVID-19 plus at least one of the following symptoms:

- Clinical signs at rest indicative of severe systemic illness:
 - Respiratory rate and heart rate outside normal range
 - $SpO_2 \leq 92\%$ on room air, $>50\%$ FiO_2 to maintain $\geq 92\%$, or $PaO_2/FiO_2 < 300$ mm Hg
- Respiratory failure: defined as needing high-flow oxygen, including CPaP, BiPaP, noninvasive ventilation, mechanical ventilation, or ECMO
- Evidence of shock or cardiac failure:
 - SBP (mm Hg); $<70 + (\text{age in years} \times 2)$ for age up to 10 years, <90 for age ≥ 10 years
 - Requiring vasoactive drugs to maintain blood pressure in the normal range
- Significant acute renal failure (serum creatinine ≥ 2 times ULN for age or 2-fold increase in baseline creatinine)
- Significant gastrointestinal/hepatic failure (total bilirubin ≥ 4 mg/dL or ALT 2 times ULN for age)
- Significant neurological dysfunction (Glasgow Coma Scale score ≤ 11 , or acute change in mental status with a decrease in Glasgow Coma Scale score ≥ 3 points from abnormal baseline)
- ICU admission
- Death



Supportive Efficacy Analysis

(Data accrued through October 8, 2021)



Vaccine Efficacy in Participants **Without** Evidence of Infection Prior to 7 Days After Dose 2
(5-11 Years of Age Evaluable Efficacy Population)

	BNT162b2 10 µg (N^a=1305) n1^b Surveillance Time^c (n2^d)	Placebo (N^a=663) n1^b Surveillance Time^c (n2^d)	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence from 7 days after Dose 2	3 0.322 (1273)	16 0.159 (637)	90.7 (67.7, 98.3)

- a. N = number of participants in the specified group.
- b. n1 = Number of participants meeting the endpoint definition.
- c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
- d. n2 = Number of participants at risk for the endpoint.



Supportive Efficacy Analysis

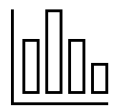
(Data accrued through October 8, 2021)

- Most cases occurred in July-August 2021.
- No severe COVID-19 cases or hospitalizations.
- Only one case in a child with underlying comorbidities (asthma).
- All COVID-19 cases in US, except for one case in Spain.
- No virus sequence analyses were available.
- Asymptomatic disease and transmission were not assessed.

Outline



Safety Data



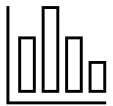
Follow Up Time (C4591007 Safety Population Cohorts 1 and 2)



Follow-up Time After Dose 2
Phase 2/3 – 5-11 Years of Age

Time from Dose 2 to cutoff date (September 6, 2021)	Cohort 1 BNT162b2 10 µg N=1518 n (%)	Cohort 1 Placebo N=750 n (%)
<1 month	7 (0.5)	4 (0.5)
≥1 month to <2 months	74 (4.4)	32 (4.4)
≥2 months to <3 months	1444 (95.1)	714 (95.2)
≥3 months	0	0

Time from Dose 2 to cutoff date (October 8, 2021)	Cohort 2 BNT162b2 10 µg N=1591 n (%)	Cohort 2 Placebo N=788 n (%)
<1 week	21 (1.3)	15 (1.9)
≥1 week to <2 weeks	448 (28.2)	200 (25.4)
≥2 weeks to <3 weeks	779 (49.0)	397 (50.4)
≥3 weeks to <4 weeks	343 (21.6)	176 (22.3)



Safety Analyses: C4591007 Phase 2/3

Local Reactions



Frequency of Solicited Local Reactions Within 7 Days After Each Dose, in Phase 2/3
Participants 5-11 Years of Age, Cohort 1 Safety Population

Event	BNT162b2 Dose 1 N=1511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1501 %	Placebo Dose 2 N=741 %
Any pain at the injection site	74.1	31.3	71.0	29.5
Severe	0.3	0.0	0.3	0.0
Any redness	14.7	5.7	18.5	5.4
Severe	0.0	0.0	0.2	0.0
Any swelling	10.5	2.7	15.3	2.7
Severe	0.1	0.0	0.0	0.0

Any local reaction= any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site.

Pain: Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.

Redness/swelling: Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.



Safety Analyses: C4591007 Phase 2/3

Systemic Reactions



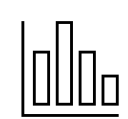
Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, by Severity, in Phase 2/3
 Participants 5-11 Years of Age, Cohort 1 Safety Population

Event	BNT162b2 Dose 1 N=1511 %	Placebo Dose 1 N=749 %	BNT162b2 Dose 2 N=1501 %	Placebo Dose 2 N=741 %
Fever				
≥38.0°C	2.5	1.3	6.5	1.2
≥38.0°C to 38.4°C	1.5	0.5	3.4	0.7
>38.4°C to 38.9°C	0.8	0.7	2.5	0.4
>38.9°C to 40.0°C	0.2	0.1	0.5	0.1
>40.0°C	0.0	0.0	0.1	0.0
Any fatigue	33.6	31.3	39.4	24.3
Severe	0.3	0.1	0.7	0.1
Any headache	22.4	24.1	28.0	18.6
Severe	0.1	0.5	0.2	0.0
Any new or worsened muscle pain	9.1	6.8	11.7	7.4
Severe	0.1	0.0	0.1	0.0
Any diarrhea	5.9	4.1	5.3	4.7
Severe	0.0	0.0	0.0	0.0
Any chills	4.6	4.7	9.8	4.3
Severe	0.0	0.0	0.1	0.1
Any new or worsened joint pain	3.3	5.5	5.2	3.6
Severe	0.0	0.0	0.0	0.0
Any vomiting	2.2	1.5	1.9	0.8
Severe	0.0	0.0	0.0	0.0
Use of antipyretic or pain medication	14.4	8.3	19.7	8.1

Fatigue/Headache/Chills/Muscle pain/Joint pain: Mild: does not interfere with activity; Moderate: some interference with activity; Severe: prevents daily activity.

Vomiting: Mild: 1 to 2 times in 24 hours; Moderate: >2 times in 24 hours; Severe: requires intravenous hydration.

Diarrhea: Mild: 2 to 3 loose stools in 24 hours; Moderate: 4 to 5 loose stools in 24 hours; Severe: 6 or more loose stools in 24 hours.

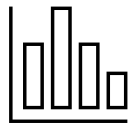


Safety Analyses: C4591007 Phase 2/3

Solicited Reactions



	BNT162b2 10 µg Dose 1	Placebo Dose 1	BNT162b2 10 µg Dose 2	Placebo Dose 2
Any solicited local reaction				
Day of onset: median (min, max)	1.0 (1, 6)	1.0 (1, 6)	1.0 (1, 7)	1.0 (1, 7)
Duration: median (min, max)	2.0 (1, 10)	1.0 (1, 10)	2.0 (1, 11)	1.0 (1, 12)
Persisted beyond 7 days n/N (%)	11/1511 (0.7)	9/749 (1.2)	8/1501 (0.5)	5/741 (0.7)
Any solicited systemic reaction				
Day of onset: median (min, max)	2.0 (1, 7)	1.0 (1, 7)	2.0 (1, 7)	2.0 (1, 7)
Duration: median (min, max)	1.0 (1, 22)	1.0 (1, 19)	1.0 (1, 51)	1.0 (1, 10)
Persisted beyond 7 days n/N (%)	29/1511 (1.9)	15/749 (2.0)	30/1501 (2.0)	13/741 (1.8)

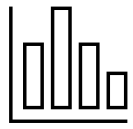


Safety Analyses: C4591007 Phase 2/3

Unsolicited Adverse Events



- Cohort 1: The most common unsolicited AE was lymphadenopathy (n=13 [0.9%] in the BNT162b2 group and n= 1 [0.1%] in the placebo group).
- Cohort 2: Lymphadenopathy was reported in 6 (0.4%) vaccine recipients and 3 placebo recipients (0.4%).
- Withdrawals due to AEs: One participant in the BNT162b2 group (Cohort 2) was withdrawn due to AEs of fever 2 days after Dose 1 and worsening of neutropenia (medical history: benign transient neutropenia).



Safety Analyses: C4591007 Phase 2/3

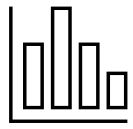
Adverse Events of Special Interest



FDA conducted Standardized MedDRA Queries (SMQs) to evaluate for constellations of unsolicited AEs

SMQ analyses with imbalances	Cohort 1	Cohort 2
Hypersensitivity (primarily skin and subcutaneous disorders including rash and dermatitis)	n= 14 BNT162b2 group (0.92%) n= 4 in the placebo group (0.53%)	n= 9 BNT162b2 group (0.57%) n= 4 in the placebo group (0.51%)
Angioedema (angioedema, face swelling, and urticaria)	n= 4 BNT162b2 group (0.26%) n= 3 in the placebo group (0.40%)	n= 3 BNT162b2 group (0.19%) n= 1 in the placebo group (0.13%)

- One participant, a 6-year-old female in the BNT162b2 group, reported Henoch-Schönlein purpura (HSP) which was diagnosed 21 days after Dose 1 and was considered non-serious. As of the data cut-off, Dose 2 had not been administered.
- All but 1 event of angioedema (rash on torso with onset at 11 days post-Dose 2) were considered resolved.
- Chest pain reported in Cohorts 1 and 2: n= 6 in the BNT162b2 group and n= 6 in the placebo group, all resolved without intervention, and all considered to be noncardiac in origin.

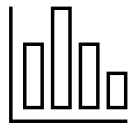


Safety Analyses: C4591007 Phase 2/3

Serious Adverse Events



- In Cohorts 1 and 2, SAEs occurred at a frequency of 0.1% and 0.2%, respectively, in vaccine recipients, and in 0.1% and 0% in placebo recipients, respectively.
- SAEs included common events occurring in this population (arthropod bite, knee infection, traumatic bone fracture) and were considered unrelated to vaccination
- There were no reports of myocarditis/pericarditis or anaphylaxis, and no participant deaths.



Pharmacovigilance

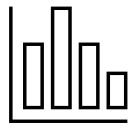


The pharmacovigilance (PV) plan includes monitoring for safety concerns :

Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

Four post-authorization observational studies which will include 5-11 year age group:

- A non-interventional safety study in the United States to assess the occurrence of safety events of interest, including myocarditis and pericarditis.
- Active surveillance study among individuals in Europe to assess the potential increased risk of AESIs, including myocarditis/pericarditis.
- Substudy to describe the natural history of myocarditis and pericarditis.
- Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination.

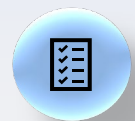


Pediatric EUAs - Pfizer



	EUA 5-11 years	EUA 12-15 years
Dose/regimen	Two 10 µg doses 3 weeks apart	Two 30 µg doses 3 weeks apart
Safety Endpoints	Solicited local and systemic ARs, unsolicited, SAEs, AESIs	Solicited local and systemic ARs, unsolicited, SAEs, AESIs
Immunobridging approach	GMT ratio and seroresponse 1 month post dose 2 compared with young adults 16-25 years of age in C4501001 efficacy study	GMT ratio 1 month post dose 2 compared with young adults 16-25 years of age in C4501001 efficacy study (seroresponse analysis was descriptive only)
Efficacy Endpoints	Secondary descriptive	Secondary descriptive
Safety database (vaccine recipients)	~3000	~1131
Length of follow up	1444 with ≥2 months of follow up	660 with ≥2 months of follow up

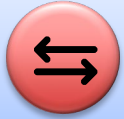
Outline



Summary



Summary: Immunogenicity and Efficacy



Immunobridging success criteria were met for geometric mean neutralizing antibody titers and seroresponse rates at 1 month post-Dose 2 against the USA_WA1/2020 reference strain



Descriptive immunogenicity analyses of neutralizing antibody titers against **B.1.617.2 (Delta)** strain of in a small subset (n= 34 BNT162b2) showed that a 10 µg BNT162b2 primary series elicited PRNT 50% neutralizing titers against the reference strain and B.1.617.2 (Delta)



Supplemental descriptive efficacy analysis showed VE against symptomatic COVID-19 after 7 days post Dose 2 was 90.7% (2-sided 95% CI: 67.4%, 98.3%) in participants 5-11 years of age without prior evidence of SARS-CoV-2 infection



Summary: Safety

- Solicited local and systemic ARs generally occurred more frequently after Dose 2.
 - Most commonly reported solicited ARs were pain at the injection site, fatigue, and headache.
 - Most local and systemic reactions were mild to moderate in severity and resolved within 1 - 2 days
- The most frequently reported unsolicited AE in BNT162b2 recipients was lymphadenopathy, slightly higher than reported in children 12 years old and older.
- More BNT162b2 recipients reported hypersensitivity-related adverse events (primarily pruritic, papular rash and dermatitis) than placebo recipients. No anaphylaxis cases were reported.
- SAEs occurred at a rate of less than 0.2% in vaccine recipients; all reported SAEs were considered to be unrelated to vaccination.
- There were no cases of myocarditis/pericarditis at the time of data cutoff.





END