Vaccines and Related Biological Products Advisory Committee Meeting

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U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of the Effectiveness and Safety of Pfizer-BioNTech COVID-19 Vaccine in Children 6 Months through 4 Years of Age *Emergency Use Authorization Amendment*

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Outline

Background

Study Design

Immunogenicity Data

Descriptive Efficacy Data

Safety Data

Summary of Benefits and Risks

Pharmacovigilance

Pfizer-BioNTech COVID-19 Vaccine

Vaccine Composition

- SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA
- Formulated in lipid particles

Pfizer-BioNTech COVID-19 Vaccine

Primary Series by Age Group

Age Group	Dose mRNA	Regimen	Authorized	Approved
≥16 years*	30 µg (0.3 mL)	2 doses (0, 3 weeks)	December 2020	August 2021
12-15 years*	30 µg (0.3 mL)	2 doses (0, 3 weeks)	May 2021	--
5-11 years*	10 µg (0.2 mL)	2 doses (0, 3 weeks)	October 2021	--
6 months through 4 years	**3 µg (0.2 mL)**	**3 doses (0, 3, ≥8 weeks after Dose 2)**	--	--

*Third primary series dose authorized for certain immune compromised populations

Pediatric EUAs - Pfizer

	5-11 years	12-15 years
Dose/regimen:	10 µg Two doses (0, 3 weeks)	30 µg Two doses (0, 3 weeks)
Safety Endpoints: Solicited local and systemic ARs, unsolicited, SAEs	✓	✓
Immunobridging approach: GMT ratio and seroresponse 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	✓	✓
Safety database (vaccine recipients)	3109	1134
Percentage of participants with ≥2 months follow up	95%	58%

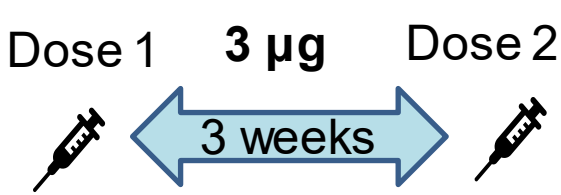
Study Design

- Phase 1 Dose Selection
- Phase 2/3 Study Design
  - Immunobridging Analyses
  - Descriptive Efficacy Analyses

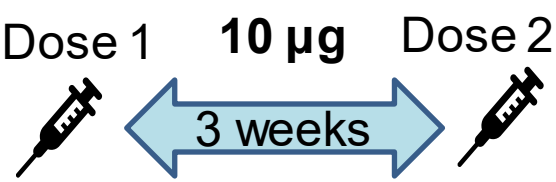
C4591007: Phase 1 Dose Selection

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

2 through 4 (2-4) years of age

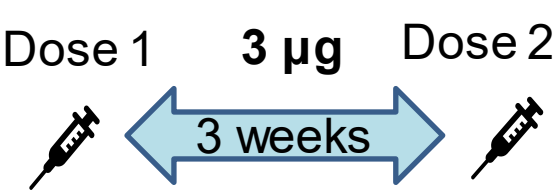


(n=16)



(n=32)

6 through 23 (6-23) months of age



(n=16)

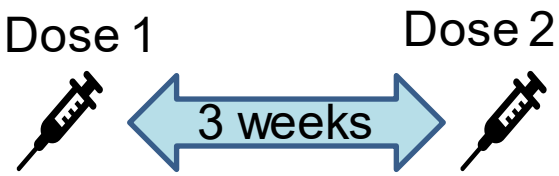
3-µg dose selected for further development (6 months to 4 years of age)

C4591007: Phase 2/3 Study Design

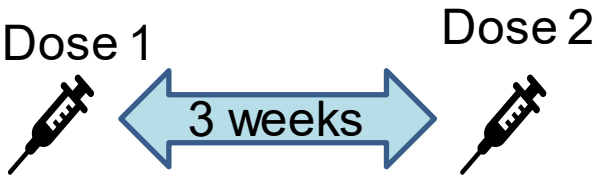
6-23 months of age
2-4 years of age

Randomized 2:1

BNT162b2



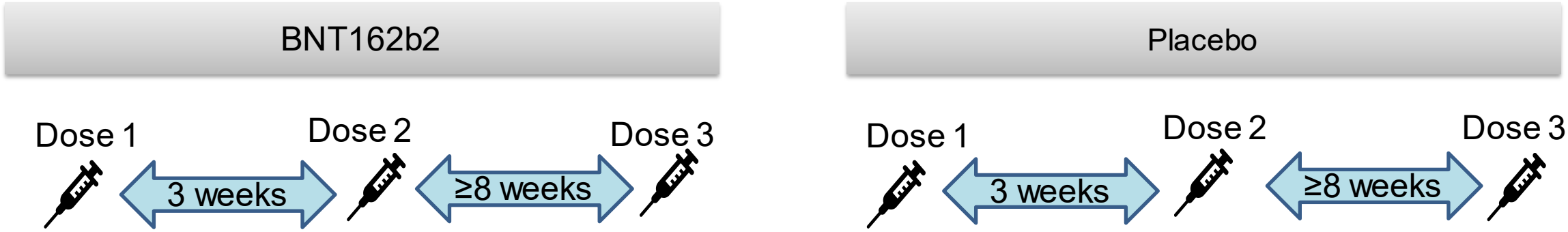
Placebo



C4591007: Amended Phase 2/3 Study Design

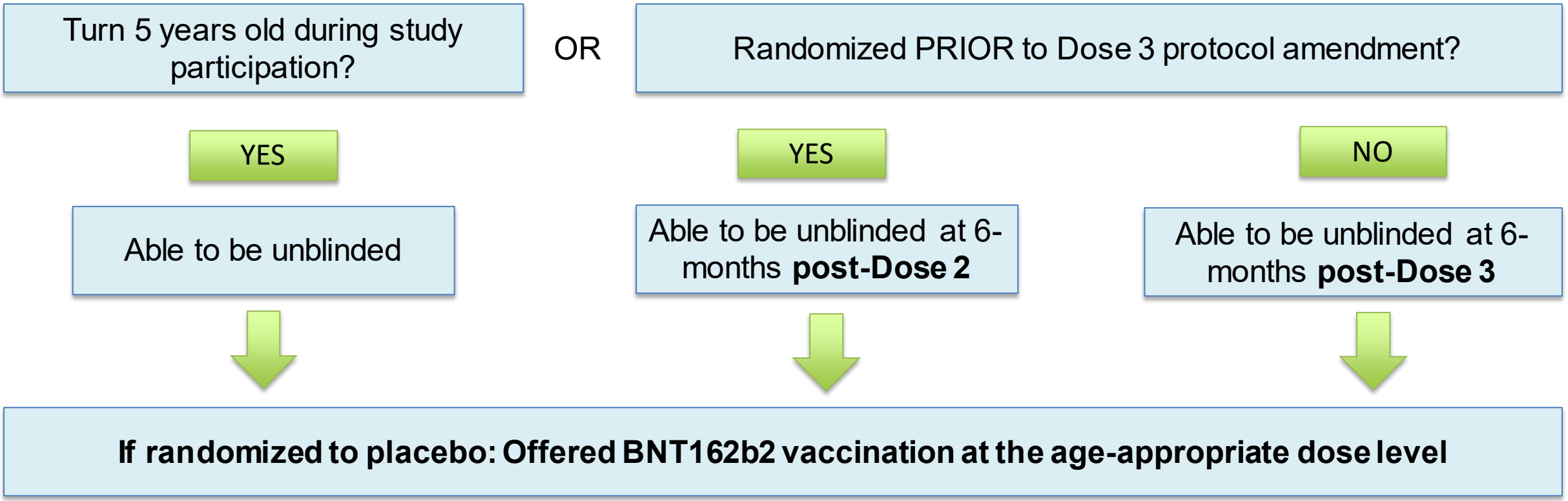
6-23 months of age (n= 1776)
2-4 years of age (n= 2750)

Randomized 2:1



Following analysis of the post-Dose 2 safety and effectiveness data, a third dose was added for all participants 6 months through 4 years of age at least 8 weeks after Dose 2.

C4591007: Unblinding procedures



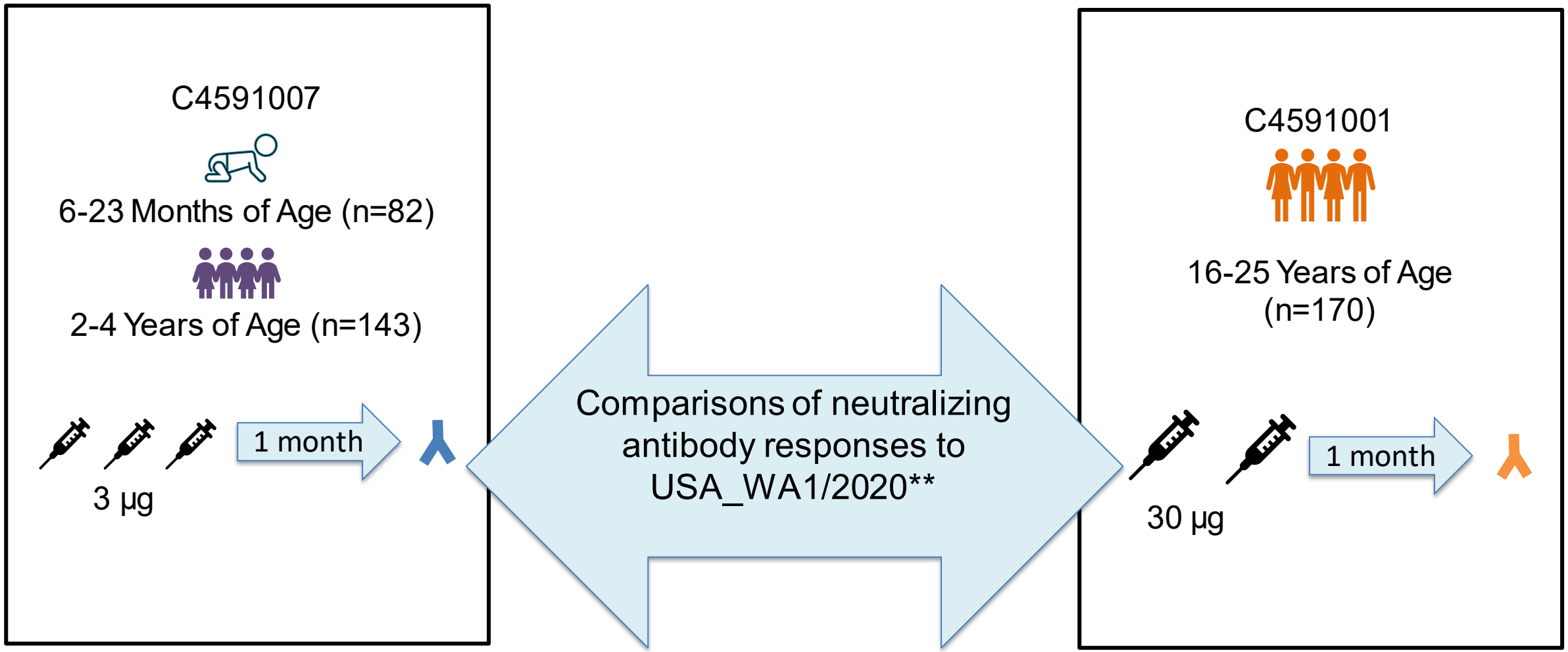
C4591007: Study Objectives/Endpoints

Study Objectives/Endpoints
Immunogenicity data 1 month post Dose 3, for immunobridging analyses (primary endpoints, tested sequentially) • GMTs in 6-23 months and 2-4 years versus GMTs in 16-25 years • Seroresponse in 6-23 months and 2-4 years versus seroresponse in 16-25 years
Efficacy data from accrued COVID-19 cases from all participants (descriptive secondary endpoint)
Safety data from all participants who received study intervention

C4591007: Phase 2/3 Safety Analyses

Solicited reactogenicity	7 days (Day 1 through Day 7) after each vaccination in an e-diary.
Unsolicited adverse events	• Within 30 minutes after each dose • Dose 1 through 1 month after each dose
Serious adverse events	From Dose 1 to 6 months after Dose 3 or the data cutoff date (April 29, 2021)

C4591007: Immunobridging Analysis



*n= evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection
** NT_{50}, SARS-CoV-2 mNG microneutralization assay

C4591007: Immunobridging Analysis Geometric Mean Titer

Endpoint: Geometric mean neutralizing 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 pediatric age group (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

C4591007: Immunobridging Analysis Seroresponse

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

% (pediatric age group) with ≥4-fold rise from baseline GMT to 1-month post-Dose 3

MINUS

% (16-25 years) with ≥4-fold rise from baseline GMT to 1-month post-Dose 2

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

*Seroresponse is defined as ≥4-fold rise from baseline (before Dose 1). If the baseline measurement is below LLOQ, the postvaccination measure of ≥4 × LLOQ is considered seroresponse. 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.

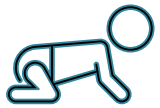
C4591007: Descriptive Efficacy Analysis
Case definitions

Symptomatic	Severe
Presence of at least one of the following symptoms and a positive SARS-CoV-2 nucleic acid amplification test within 4 days of the symptomatic period: • 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 • Vomiting • Inability to eat/poor feeding	Confirmed COVID-19 case with at least one of the following: • Clinical signs at rest indicative of severe systemic illness (RR and HR, by age, $SpO_2 \leq 93\%$ on room air at sea level, or PaO_2/FiO_2 <300 mm Hg) • Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation) • Evidence of shock (systolic blood pressure by age, or requiring vasopressors) • Significant acute renal, hepatic, or neurologic dysfunction • Admission to an ICU • Death

Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-8.

C4591007: Phase 2/3 Pediatric Analysis Populations

Population	Description	6-23 months	2-4 years
Safety/Dose 1 All available efficacy	All participants who receive at least 1 dose of the study intervention.	1178 (BNT162b2) 598 (placebo)	1835 (BNT162b2) 915 (placebo)
	Received 3 doses (prior to unblinding)	386 (BNT162b2) 184 (placebo)	606 (BNT162b2) 280 (placebo)
All-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after vaccination.	146	73
Dose 3 Evaluable immunogenicity	All eligible randomized participants who receive three doses of the vaccine to which they are randomized with Dose 2 received within the predefined window, Dose 3 received at least 60 days after Dose 2, have at least 1 valid and determinate immunogenicity result from the blood sample collected within an appropriate window, and no other important protocol deviations as determined by the clinician.	132	204
Dose 3 Evaluable immunogenicity for primary endpoint analysis	Without evidence of SARS CoV-2 infection up to 1 month after Dose 3	82	143
Evaluable efficacy (Dose 3)	All randomized participants who receive all vaccinations as randomized, with Doses 2 and 3 received within the predefined windows and have no other important protocol deviations as determined by the clinician.	376 (BNT162b2) 179 (placebo)	589 (BNT162b2) 271 (placebo)



C4591007: Demographics and Baseline Characteristics Ph 2/3 Safety Population 6-23 Months

Characteristic	BNT162b2 N=1178	Placebo N=598
Sex	50% female	51% female
Median age	16 months	16 months
% Baseline Positive SARS-CoV-2 status	8%	7%
Race/Ethnicity	78% White, 10% Multiracial, 8% Asian, 4% African American; 14% Hispanic	80% White, 8% Multiracial; 7% Asian, 4% African American; 11% Hispanic
Countries	US (81%), Finland, Spain and Poland (19% combined)	US (81%), Finland, Spain and Poland (19% combined)
Co-morbidities	4%	6%

C4591007: Demographics and Baseline Characteristics Ph 2/3 Safety Population months 2-4 Years

Characteristic	BNT162b2 N=1835	Placebo N=915
Sex	51% female	49% female
Median age	3.0 years	3.0 years
% Baseline Negative SARS-CoV-2 status	13%	14%
Race/Ethnicity	80% White, 7% Multiracial, 7% Asian, 5% African American; 14% Hispanic	79% White, 8% Multiracial; 8% Asian, 5% African American; 13% Hispanic
Countries	US (81%), Finland, Spain and Poland (19% combined)	US (81%), Finland, Spain and Poland (19% combined)
Co-morbidities	12%	14%
Obese	7%	4%

Phase 2/3 Immunogenicity Data

Immunobridging Based on GMT Ratio 6-23 Months

SARS-CoV-2 Neutralizing GMTs (NT_{50})* and GMT Ratio
BNT162b2 Recipients 6-23 Months (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection (Phase 2/3 Evaluable Immunogenicity Populations)

6-23 Months Study C4591007 N=82 GMT (95% CI)	**16-25 Years Study C4591001 N=170 GMT (95% CI)**	**GMT Ratio (6-23 months of Age / 16-25 Years of Age) (95% CI)**
1406.5 (1211.3, 1633.1)	1180.0 (1066.6, 1305.4)	**1.19 (1.00, 1.42)**

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

Subgroup Analyses of GMT 6-23 Months, by Baseline SARS-CoV-2 Serostatus

SARS-CoV-2 Neutralizing GMTs (NT_{50})*
BNT162b2 Recipients 6-23 Months (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2), by Baseline Serostatus
(Phase 2/3 All-Available Immunogenicity Populations)

Baseline SARS-CoV-2 Serostatus	6-23 Months Study C4591007 GMT (n)	16-25 Years Study C4591001 GMT (n)
Positive	3794.8 (6)	2507.9 (8)
Negative	1633.6 (139)	1178.1 (184)

*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 Seroresponse 6-23 Months

Seroresponse Rates
BNT162b2 Recipients 6-23 Months (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection (Phase 2/3 Evaluable Immunogenicity Populations)

6-23 Months Study C4591007 N=80 GMT (95% CI)	**16-25 Years Study C4591001 N=170 GMT (95% CI)**	**% Difference in Seroresponse Rate (Age Group 6-23 months minus Age Group 16-25 Years) (95% CI)**
100 (95.5, 100.0)	98.8 (95.8, 99.9)	**1.2 (-3.4, 4.2)**

Success criteria met as the lower bound of the 95% CI for the difference in seroresponse rate greater than the prespecified margin of -10%.

*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 GMT Ratio 2-4 Years

SARS-CoV-2 Neutralizing GMTs (NT_{50})* and GMT Ratio
BNT162b2 Recipients 2-4 Years (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection (Phase 2/3 Evaluable Immunogenicity Populations)

2-4 Years Study C4591007 N=143 GMT (95% CI)	**16-25 Years Study C4591001 N=170 GMT (95% CI)**	**GMT Ratio (2-4 Years / 16-25 Years) (95% CI)**
1535.2 (1388.2, 1697.8)	1180.0 (1066.6, 1305.4)	**1.30 (1.13, 1.50)**

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

Subgroup Analyses of GMT 2-4 Years, by Baseline SARS-CoV-2 Serostatus

SARS-CoV-2 Neutralizing GMTs (NT_{50})*
BNT162b2 Recipients 2-4 Years (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2), by Baseline Serostatus
(Phase 2/3 All-Available Immunogenicity Populations)

Baseline SARS-CoV-2 Serostatus	**2-4 Years Study C4591007 GMT (n)**	**16-25 Years Study C4591001 GMT (n)**
Positive	3574.5 (13)	2507.9 (8)
Negative	1572.8 (204)	1178.1 (184)

*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 Seroresponse 2-4 Years

Seroresponse Rates
BNT162b2 Recipients 2-4 Years (1 Month After Dose 3) and 16-25 Years (1 Month After Dose 2) Without Evidence of SARS-CoV-2 Infection (Phase 2/3 Evaluable Immunogenicity Populations)

2-4 Years Study C4591007 N=141 % (95% CI)	**16-25 Years Study C4591001 N=170 % (95% CI)**	**% Difference in Seroresponse Rate (Age Group 2-4 Years minus Age Group 16-25 Years) (95% CI)**
100.0 (97.4, 100.0)	98.8 (95.8, 99.9)	**1.2 (-1.5, 4.2)**

Success criteria met as the lower bound of the 95% CI for the difference in seroresponse rate greater than the prespecified margin of -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 Immunogenicity Analyses Omicron and Delta Variants

Geometric Mean Fold Rises (GMFRs) of SARS-CoV-2 Neutralizing GMTs
BNT162b2 Recipients 6 Months-4 Years (1 Month after Dose 3)
Without Evidence of Prior SARS-CoV-2 Infection (Phase 2/3 Evaluable Immunogenicity Population Subsets)

Assay Target	C4591007 6-23 Months BNT162b2 3 µg N=32	C4591007 2-4 Years BNT162b2 3 µg N=34
USA_WA1/2020 (Reference strain)		
Post-Dose 3 GMT (95% CI)	640.0 (502.6, 815.0)	471.4 (344.6, 644.8)
GMFR (95% CI)	**6.2 (4.7, 8.2)**	**6.7 (5.1, 8.9)**
B.1.617.2 (Delta variant)		
Post-Dose 3 GMT (95% CI)	606.3 (455.5, 806.9)	471.4 (341.2, 651.1)
GMFR (95% CI)	**6.4 (4.6, 9.1)**	**6.9 (4.9, 9.8)**
B.1.1.529 (Omicron variant)		
Post-Dose 3 GMT (95% CI)	127.5 (90.2, 180.1)	82.5 (55.4, 122.9)
GMFR (95% CI)	**7.8 (6.0, 10.2)**	**5.9 (3.9, 9.0)**

SARS-CoV-2 fluorescent focus reduction neutralization test (FFRNT) is a non-validated assay was used to generate data against the SARS-CoV-2 strains, including recombinant USA_WA1/2020 (reference), B.1.617.2 (Delta), and BA.1 (Omicron).

GMFR=GMT at 1 month post-Dose 3/GMT pre-Dose 3

Phase 2/3 Descriptive Efficacy Data

Follow Up Time: Efficacy Population

Follow-up Time After Dose 3 – Blinded Follow-Up Period

6-23 Months– Dose 3 All-Available Efficacy Population

	BNT162b2 (3 µg) (N=386) %	Placebo (N=184) %	Total (N=570) %
Time from Dose 3 to cutoff date			
<1 Month	16.6	15.8	16.3
≥1 to <2 Months	50.8	54.3	51.9
≥2 to <3 Months	22.3	19.6	21.4
≥3 Months	10.4	10.3	10.4

2-4 Years– Dose 3 All-Available Efficacy Population

	BNT162b2 (3 µg) (N=606) %	Placebo (N=280) %	Total (N=886) %
Time from Dose 3 to cutoff date			
<1 Month	23.6	22.9	23.4
≥1 to <2 Months	41.6	41.8	41.6
≥2 to <3 Months	19.0	22.1	20.0
≥3 Months	15.8	13.2	15.0

Preliminary Efficacy Analysis 6-23 Months (Data accrued through April 29, 2022)

Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 Blinded Follow-Up Period
Phase 2/3, Participants 6 -23 months with and without evidence of infection prior to 7 days after Dose 3
(Dose 3 Evaluable Efficacy Population)

	BNT162b2 (3 µg) (N=376) n1/n2 Surveillance Time	**Placebo (N=179) n1/n2 Surveillance Time**	**Vaccine Efficacy (95% CI)**
First COVID-19 occurrence from 7 days after Dose 3	1/269 0.029	2/134 0.014	**75.6%** **(-369.1, 99.6)**

N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
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.
n2 = Number of participants at risk for the endpoint.

Post hoc efficacy, from Dose 1
6-23 Months (Data accrued through April 29, 2022)

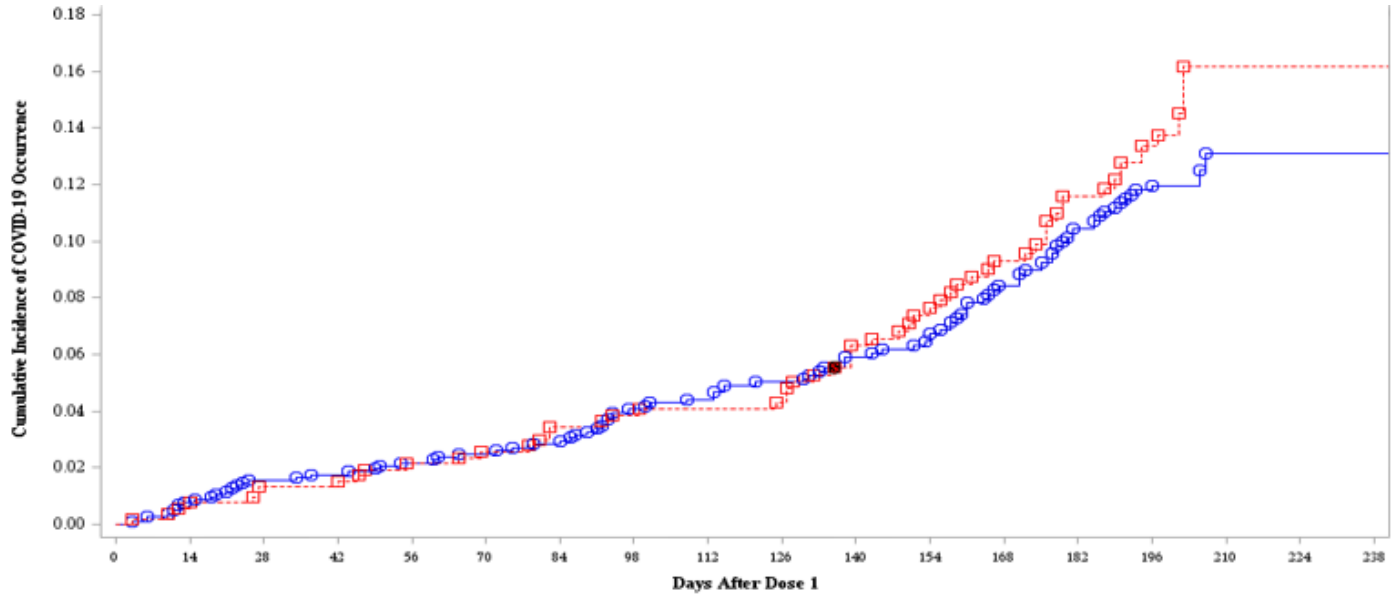
First COVID-19 Occurrence After Dose 1, Blinded Follow-Up Period Participants 6 -23 Months, All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 3 µg (N=1178) Cases, n1/n2 Surveillance Time	Placebo (N=598) Cases, n1/n2 Surveillance Time	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1	98/1027 0.456	58/524 0.232, (524)	14.0 (-21.2, 38.4)
Dose 1 to before Dose 2	13/1027 0.063	5/524 0.032	-29.7 (-364.7, 56.6)
Dose 2 to <7 days after Dose 2	3/1002 0.019	3/517 0.010	48.4 (-285.0, 93.1)
≥7 Days after Dose 2 to before Dose 3	80/998 0.338	48/512 0.173	14.5 (-24.9, 41.0)
Dose 3 to <7 days after Dose 3	1/336 0.006	0/147 0.003	UND (NA, NA)
≥7 Days after Dose 3	1/277 0.030	2/139 0.015	75.5 (-370.1, 99.6)

Abbreviations: NA=not applicable; VE=Vaccine Efficacy; UND=Undefined.
N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
Total surveillance time in 1,000 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 Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
n2 = Number of participants at risk for the endpoint.

Post hoc efficacy, from Dose 1
6-23 Months (Data accrued through April 29, 2022)

Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1
Participants 6-23 Months, All-Available Efficacy Population



Participants at Risk

A:	1027	1019	1009	961	922	896	871	844	795	771	722	677	641	609	540	121	69	29	11	3	0	0
B:	524	521	516	501	473	461	445	438	417	399	365	338	326	309	268	48	27	7	2	1	1	0

Cumulative Number of Events

A:	0	8	16	18	22	25	29	39	42	47	54	60	72	86	96	98	98	98	98	98	98	98
B:	0	4	7	8	11	13	17	19	20	21	29	34	40	48	54	58	58	58	58	58	58	58

A: BNT162b2 3 µg
B: Placebo

Note: "S" indicates participants with severe COVID-19.

Preliminary Efficacy Analysis
2- 4 years (Data accrued through April 29, 2022)

Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3 Blinded Follow-Up Period
Phase 2/3, Participants 2 -4 Years of Age with and without evidence of infection prior to 7 days after Dose 3
(Dose 3 Evaluable Efficacy Population)

	BNT162b2 (3 µg) (N=589) n1/n2 Surveillance Time	**Placebo (N=271) n1/n2 Surveillance Time**	**Vaccine Efficacy (95% CI)**
First COVID-19 occurrence from 7 days after Dose 3	2/466 0.054	5/202 0.024	**82.4%** **(-7.6, 98.3)**

N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
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.
n2 = Number of participants at risk for the endpoint.

Post hoc efficacy, from Dose 1
2-4 Years (Data accrued through April 29, 2022)

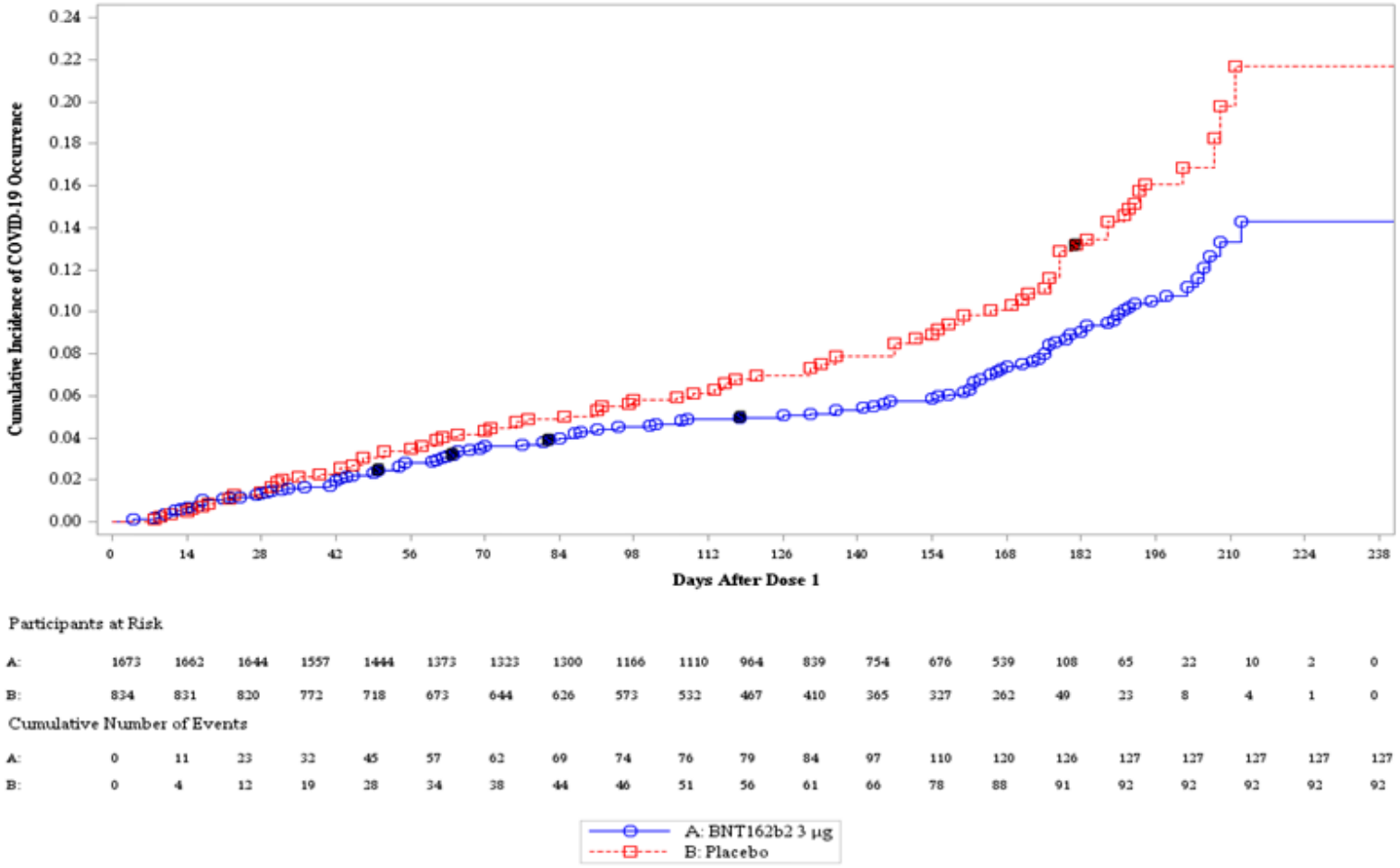
First COVID-19 Occurrence After Dose 1, Blinded Follow Up Period
Participants 2-4 Years of Age, All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 3 µg (N=1178) Cases, n1/n2 Surveillance Time	Placebo (N=598) Cases, n1/n2 Surveillance Time	Vaccine Efficacy % (95% CI)
First COVID-19 occurrence after Dose 1	127/1673 0.661	92/834 0.323	32.6 (10.8, 48.8)
Dose 1 to before Dose 2	21/1673 0.100	8/834 0.050	-32.1 (-244.8, 43.8)
Dose 2 to <7 days after Dose 2	4/1639 0.031	5/819 0.016	60.1 (-85.6, 92.1)
≥7 Days after Dose 2 to before Dose 3	100/1630 0.464	74/814 0.228	33.6 (9.1, 51.3)
Dose 3 to <7 days after Dose 3	0/553 0.010	0/222 0.004	NE
≥7 Days after Dose 3	2/481 0.056	5/209 0.025	82.3 (-8.0, 98.3)

Abbreviations: NE=not estimable; VE=Vaccine Efficacy; UND=Undefined.
N = number of participants in the specified group.
n1 = Number of participants meeting the endpoint definition.
Total surveillance time in 1,000 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 Dose 1 to the end of the surveillance period for the overall row and from start to the end of range stated for each interval.
n2 = Number of participants at risk for the endpoint.

Post hoc efficacy, from Dose 1
2-4 Years (Data accrued through April 29, 2022)

Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1
Participants 2-4 Years, All-Available Efficacy Population



Note: "S" indicates participants with severe COVID-19.

Descriptive Efficacy Analysis (Data accrued through April 29, 2022)

- All post Dose 3 cases occurred from February through April 2022, when Omicron was the predominant circulating variant
- One hospitalization for severe COVID-19 (2yr old vaccine recipient, 99 days after Dose 2)
- Limited by small numbers, short duration of follow-up after Dose 3

Phase 2/3 Safety Data

Follow Up Time: Safety Population

Follow-up Time After Dose 3 – Total Blinded and Open-Label Follow-Up Period

6-23 Months– Dose 3 Safety Population

	BNT162b2 (3 µg) N=758 %	Placebo N=184 %	Total N=942 %
Time from Dose 3 to cutoff date			
<1 Month	13.3	15.2	13.7
≥1 to <2 Months	25.9	47.8	30.1
≥2 to <3 Months	51.2	25.0	46.1
≥3 Months	9.6	12.0	10.1

2-4 Years of Age – Dose 3 Safety Population

	BNT162b2 (3 µg) N=1041 %	Placebo N=280 %	Total N=1321 %
Time from Dose 3 to cutoff date			
<1 Month	16.6	22.5	17.9
≥1 to <2 Months	26.1	40.4	29.1
≥2 to <3 Months	45.1	23.6	40.6
≥3 Months	12.1	13.6	12.4

Safety Analyses: Phase 2/3 Immediate Adverse Events

BNT162b2	**6-23 Months**	**2-4 Years**
Dose 1	n= 3 vomiting, injection site erythema and hematoma (n=1 each)	n= 5 erythema (n= 2), injection site bruising, injury associated with device, and skin abrasion (n=1 each)
Dose 2	n= 3 injection site erythema, injection site swelling and rash (n=1 each)	n= 4 injection site pain, injection site erythema, rash erythematous and urticaria (n=1 each)
Dose 3	n= 0	n= 0

Safety Analyses: Phase 2/3 Local Reactions 6-23 Months

Frequency of Solicited Local Reactions Within 7 Days After Each Dose

Event	BNT162b2 Dose 1 N=1159-1173	Placebo Dose 1 N=591-595	BNT162b2 Dose 2 N=1137-1147	Placebo Dose 2 N=590-591	BNT162b2 Dose 3 N=362-365	Placebo Dose 3 N=170
Tenderness at the injection site, %						
Any	16.6	11.2	15.0	8.5	16.0	11.8
Severe	0	0	0.1	0	0	0
Redness, %						
Any	10.6	7.4	9.3	6.6	7.1	5.3
Severe	0	0	0	0	0.3	0
Swelling, %						
Any	3.9	2.5	3.9	1.5	2.7	1.8
Severe	0	0	0	0	0	0
Any local reaction	23.8	17.5	21.6	13.4	20.5	15.3

Tenderness Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
Redness and swelling Mild: 0.5 to ≤2.0 cm; moderate: 2.0 to ≤7.0 cm; severe: >7.0 cm.
Any local reaction Any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site

Safety Analyses: Phase 2/3 Local Reactions 2-4 Years

Frequency of Solicited Local Reactions Within 7 Days After Each Dose

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
Pain at the injection site, %						
Any	30.8	20.6	31.0	20.3	26.7	13.4
Severe	0	0.1	0	0.1	0	0
Redness, %						
Any	8.8	8.5	11.4	5.7	10.9	3.4
Severe	0.1	0.1	0.1	0	0	0
Swelling, %						
Any	3.7	2.9	5.7	2.1	3.1	1.1
Severe	0	0	0	0	0	0
Any local reaction	35.5	25.2	36.3	23.3	31.5	15.6

Tenderness severe: prevents daily activity.
Redness and swelling severe: >7.0 cm.
Any local reaction Any redness >0.5 cm, any swelling >0.5 cm, or any pain at the injection site

Safety Analyses: Phase 2/3 Systemic Reactions 6-23 Months

Frequency of Systemic Reactions Within 7 Days After Each Dose

Event	BNT162b2 Dose 1 N=1159-1173	Placebo Dose 1 N=591-595	BNT162b2 Dose 2 N=1137-1147	Placebo Dose 2 N=590-591	BNT162b2 Dose 3 N=362-365	Placebo Dose 3 N=170
Fever, %						
≥38.0°C	7.2	7.2	7.4	6.1	6.8	5.9
>38.9°C to 40.0°C	1.6	1.0	2.0	1.2	1.4	0.6
>40.0°C	0.1	0.2	0.1	0	0.3	0
Irritability, %						
Any	51.2	47.2	47.4	40.7	43.6	37.6
Severe	0.6	0	0.6	0.8	0.3	0
Drowsiness, %						
Any	27.0	29.3	23.8	21.2	19.9	12.9
Severe	0.2	0.3	0.4	0.2	0.3	0.6
Decreased Appetite, %						
Any	22.2	21.2	22.2	18.0	20.2	13.5
Severe	0.3	0.2	0.4	0.2	1.1	0
Any systemic event	61.0	58.2	55.8	50.4	51.5	45.3
Use of antipyretic or pain medication, %	24.0	19.7	21.2	18.8	19.2	16.5

Irritability Severe: inconsolable; crying, cannot be comforted
Drowsiness Severe: disabling; not interested in usual daily activity
Appetite Severe: refusal to eat
Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain

Safety Analyses: Phase 2/3 Systemic Reactions 2-4 Years (1)

Frequency of Systemic Reactions Within 7 Days After Each Dose

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
Fever, %						
≥38.0°C	5.2	5.3	4.9	5.2	5.1	4.2
>38.9°C to 40.0°C	0.7	0.9	1.1	0.9	0.7	1.1
>40.0°C	0.1	0	0.1	0	0	0
Fatigue, %						
Any	29.7	30.6	25.7	22.9	24.5	21.8
Severe	0.3	0.6	0.5	0.3	0.4	0
Headache, %						
Any	4.5	4.9	4.6	4.1	4.9	4.2
Severe	0	0.1	0	0.1	0	0
Chills, %						
Any	2.3	2.4	3.0	2.6	3.3	2.7
Severe	0.2	0	0	0	0.2	0

Fatigue, headache, chills Severe: prevents daily activity; Any= any fever ≥38.0°C, any fatigue, headache, or chills
Any systemic event: any vomiting, diarrhea, any headache, new or worsened muscle pain, or new or worsened joint pain

Safety Analyses: Phase 2/3 Systemic Reactions 2-4 Years (2)

Frequency of Systemic Reactions Within 7 Days After Each Dose

Event	BNT162b2 Dose 1 N=1813-1825	Placebo Dose 1 N=905-909	BNT162b2 Dose 2 N=1772-1779	Placebo Dose 2 N=877-878	BNT162b2 Dose 3 N=547-552	Placebo Dose 3 N=262
Vomiting, %						
Any	3.0	2.7	3.4	3.3	1.6	3.8
Severe	0	0	0	0	0	0
Diarrhea, %						
Any	7.7	8.0	6.7	7.3	5.1	5.0
Severe	0	0	0.1	0	0	0
New or worsened muscle pain, %						
Any	2.4	1.7	2.6	2.4	2.0	1.5
Severe	0.1	0	0	0	0	0
New or worsened joint pain, %						
Any	0.8	2.0	1.4	1.0	1.3	0.8
Severe	0	0	0	0	0.2	0
Any systemic reaction	38.0	38.9	33.7	32.2	30.8	29.4
Use of antipyretic or pain medication, %	10.8	9.1	9.9	8.4	8.5	6.9

Muscle and joint pain 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.
Any systemic event: any vomiting, diarrhea, any headache, new or worsened muscle pain, or new or worsened joint pain

Safety Analyses: Phase 2/3
Unsolicited Non-serious Adverse Events

Unsolicited Non-serious Adverse Events
Frequency of unsolicited non-serious AEs: • 6-23 Months: 29.1% BNT162b2 vs. 26.3% placebo • 2-4 Years: 18.5% BNT162b2 vs. 18.5% placebo
The most commonly reported AEs were consistent with: • Local and systemic reactogenicity and/or • Events frequently reported in this age group (e.g., infections and injuries) not considered related to study vaccination
Adverse events considered related to BNT162b2 included lymphadenopathy and hypersensitivity

Safety Analyses: Phase 2/3
Adverse Events of Clinical Interest

Lymphadenopathy	Frequency	Considered Related
6-23 Months	2 BNT162b2 recipients and no placebo recipients	Event of left groin node enlargement 2 days after BNT162b2 in left thigh; event of neck swollen lymph node after BNT162b2 Dose 2
2-4 Years	1 BNT162b2 recipient and no placebo recipients	Event of left ear lymphadenopathy 2 days after BNT162b2 Dose 2

Hypersensitivity	Frequency	Comment
6-23 Months	2.1% in BNT162b2 and 2.0% in placebo group	Most were common skin and subcutaneous tissue disorders for this age: rash, eczema/atopic dermatitis, dermatitis, contact dermatitis
2-4 Years	0.9% in BNT162b2 and 0.4% in placebo group	

Anaphylaxis	
6-23 Months	No vaccine-related events of anaphylaxis occurred
2-4 Years	

Safety Analyses: Phase 2/3 Serious Adverse Events

	6-23 Months
Frequency	3.1% in the BNT162b2 group and 2.3% in the placebo group • Most were gastrointestinal or respiratory illnesses/infections that occur commonly in this age group
Related	None

	2-4 Years
Frequency	0.7% in the BNT162b2 group and 0.9% in the placebo group
Related	Pyrexia and pain in extremity (calf pain) considered related by investigator, FDA considered the events to be potentially consistent with symptoms due to an unspecified viral infection, e.g., viral myositis

Pharmacovigilance

Pharmacovigilance Plan

Important identified risks	Anaphylaxis, myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and lactation, vaccine effectiveness, use in pediatric individuals <6 months of age

Surveillance activities	• Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days: Serious adverse events (irrespective of attribution to vaccination); Cases of Multisystem Inflammatory Syndrome in children and adults; Cases of COVID-19 that result in hospitalization or death. Additionally, following approval of Comirnaty 125742/0, the sponsor was also asked to submit reports of myocarditis and pericarditis as 15-day reports to VAERS.
	• The Sponsor will conduct:
	  • Passive and active surveillance activities for continued vaccine safety monitoring
	  • Periodic aggregate review of safety data and submit periodic safety reports
	  • Planned surveillance studies, including active follow-up studies for safety in the US and EU

Surveillance Studies

Post-authorization surveillance studies including children 6 months- 4 years of age

Study C4591009	Non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States • Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised, and persons with a history of COVID-19 within selected data sources participating in the U.S. Sentinel System.
Study C4591021	Post-conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine • Objective: To determine whether an increased risk of prespecified AESI, including myocarditis/pericarditis, exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 Vaccine.
Study C4591021 (substudy)	Substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY • Objective: To describe the clinical course of myocarditis/pericarditis, including treatment, survival, hospitalization, and long-term cardiac outcomes of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least one dose of the Pfizer-BioNTech COVID-19 Vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.
Study C4591036	Prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network [PHN]). • Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis.
Study C4591014	Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California to include vaccine effectiveness analyses among individuals 6 months through 4 years of age

Summary of Benefits and Risks

Summary of Benefits and Risks for 6 Months through 4 Years

Known and Potential Benefits	Uncertainties in Benefits	Known and Potential Risks	Uncertainties in Risks
Prevention of symptomatic COVID-19, based on: • Immunobridging analyses met pre-specified success criteria that allow for inference of vaccine effectiveness for individuals 6 months- 4 years of age • Preliminary evidence of vaccine efficacy against COVID-19 in descriptive analyses • Expectation of greater effectiveness against more severe COVID-19	• Effectiveness against: emerging SARS-CoV-2 variants, long term effects of COVID-19 • Effectiveness in: certain populations at higher risk of severe COVID-19, individuals previously infected with SARS-CoV-2 • Duration of protection	• Local and systemic reactogenicity • Myocarditis/pericarditis • Lymphadenopathy • Anaphylaxis and other hypersensitivity reactions	• Safety in certain subpopulations • Adverse reactions that are uncommon or that require longer follow-up to be detected

Voting Question for VRBPAC

Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine, when administered as a three-dose series (3 mcg each dose), outweigh its risks for use in infants and children 6 months through 4 years of age?

END