Safety and Immunogenicity of the BNT162b2 Vaccine Coadministered With Seasonal Inactivated Influenza Vaccine in Adults

Authors: Louise Murdoch, MBBS,[1] Karen Quan, BSc, MBBS, DPM,[2] James A. Baber, MBChB, MPH,[2] Agnes W.Y. Ho, MS, MMSc,[3] Ying Zhang, PhD,[3] Xia Xu, PhD,[3] Claire Lu, PhD,[4] David Cooper, PhD,[4] Kenneth Koury, PhD,[4] Stephen P. Lockhart, DM,[5] Annaliesa S. Anderson, PhD,[4] Özlem Türeci, MD,[6] Uğur Şahin, MD,[6] Kena A. Swanson, PhD,[4] William C. Gruber, MD,[4] Nicholas Kitchin, MD,[5] on behalf of the C4591030 Clinical Trial Group

Affiliations: [1]Emeritus Research, Camberwell, VIC, Australia; [2]Vaccine Clinical Research and Development, Pfizer Australia Pty Ltd, Sydney, NSW, Australia; [3]Vaccine Research and Development, Pfizer Inc, Collegeville, PA, USA; [4]Vaccine Research and Development, Pfizer Inc, Pearl River, NY, USA; [5]Vaccine Research and Development, Pfizer Ltd, Hurley, UK; [6]BioNTech, Mainz, Germany

Corresponding author:

Karen Quan, BSc, MB, BS, DPM

Vaccine Clinical Research and Development, Pfizer

Sydney, NSW Australia

Telephone: +61 2 9850 3848

Email: Karen.Quan@pfizer.com

Personal classification: Vaccines

SUPPLEMENTARY MATERIAL

List of Investigators*

Name	Institution	Location
Arya, Mark (Ktut)	Australian Clinical Research Network	Sydney, NSW, Australia
Athan, Eugene	Barwon Health	Geelong, VIC, Australia
Blackmore, Timothy (previously Balm, Michelle)	Capital, Coast and Hutt Valley District - Wellington Regional Hospital	Wellington, New Zealand
Bull, Sheetal	Paratus Clinical Research Brisbane	Albion, QLD, Australia
Edwards, Andrew	P3 Research - Kapiti	Paraparaumu, New Zealand
Esquilant, Emma	P3 Research – Hawke`s Bay	Havelock North, New Zealand
Finlay, Joanne (previously Carson, Simon)	Pacific Clinical Research Network – Forte	Christchurch, New Zealand
Hamilton, Paul	New Zealand Clinical Research (Auckland)	Auckland, New Zealand
Hemi, Tiwini	Lakeland Clinical Trials Waikato	Hamilton, New Zealand
Humphrey, Timothy	Lakeland Clinical Trials Wellington	Upper Hutt, New Zealand
Kamerbeek, Jackie	P3 Research - Tauranga	Tauranga, New Zealand
Kerr, Jane	New Zealand Clinical Research (Christchurch)	Christchurch, New Zealand
Kok, Jen	Westmead Hospital	Westmead, NSW, Australia
McGirr, Anthony	Northern Beaches Clinical Research	Brookvale, NSW, Australia
Montgomery, Barnaby	Optimal Clinical Trials	Auckland, New Zealand
Murdoch, Louise	Emeritus Research	Camberwell, VIC, Australia
Neville, A Munro	AusTrials – Wellers Hill	Wellers Hill, QLD, Australia
Quinn, Dean	P3 Research - Wellington	Wellington, New Zealand
Sheahan, Davitt	Lakeland Clinical Trials Culloden	Papamoa Beach, New Zealand
Smith, Susan	Southern Clinical Trials Waitemata Ltd	Auckland, New Zealand
Stubbs, Richard	P3 Research - Palmerston North	Palmerston North, New Zealand
Tagelagi, Maelen (previously King, Craig)	Southern Clinical Trials Totara	Auckland, New Zealand
Thurlow, Claire	Southern Clinical Trials Tasman	Nelson, New Zealand
Williams, Michael	Pacific Clinical Research Network – Rotorua	Rotorua, New Zealand
Wojciechowska, Joanna	Aotearoa Clinical Trials	Auckland, New Zealand

*Investigators who randomized participants.

Additional Eligibility Criteria

Participants were also excluded from the study if any of the following criteria applied:

- Other medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior, or laboratory abnormality that may increase the risk of study participation
- Allergy to egg proteins (egg or egg products) or chicken proteins
- Bleeding diathesis or condition associated with prolonged bleeding that would contraindicate intramuscular injection
- Individuals who receive treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids (if systemic corticosteroids are administered for ≥14 days at a dose of ≥20 mg/day of prednisone or equivalent), eg, for chronic obstructive pulmonary disease, or planned receipt throughout the study. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted
- Receipt of blood/plasma products or immunoglobulin from 60 days before study vaccine administration or planned receipt throughout the study
- Receipt of any passive antibody therapy specific to COVID-19 from 90 days before study vaccine administration or planned receipt throughout the study

Vaccination Temporary Delay Criteria

The following conditions were considered temporary or self-limiting and a participant could be vaccinated once the condition(s) resolved and no other exclusion criteria were met. Participants meeting these criteria at Vaccination 1 were considered screen failures if enrollment had closed once the condition(s) resolved.

- Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before study vaccine administration. This included a positive SARS-CoV-2 test result (NAAT or rapid antigen test) within 28 days.
- Receipt of any nonstudy vaccine within 28 days before study vaccine administration.
- Anticipated receipt of any nonstudy vaccine within 28 days after study vaccine administration.

- Receipt of short-term (<14 days) systemic corticosteroids. Study vaccine administration was to be delayed until systemic corticosteroid use had been discontinued for ≥28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.

Prohibited Medications, Treatments, and Vaccines During the Study

In addition to those outlined in the exclusion criteria, receipt of the following vaccines and medications during the time periods listed below may have excluded a participant from the per-protocol analysis from that point onward and may have required vaccinations to be discontinued in that participant; however, the participant would not necessarily be withdrawn from the study:

- Unless considered medically necessary, no vaccines other than the study vaccine were to be administered within 28 days before and 28 days after each study vaccination
- Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study
- Receipt of any other (nonstudy) COVID-19 vaccine at any time during study participation
- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study vaccine administration (however, if a participant was taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it was not to be withheld before administration of study vaccine; additionally, antipyretics and other pain medication to treat symptoms associated with study vaccine administration were permitted)

Sample Size Determination

The sample size calculation was based on the primary immunogenicity estimands and corresponding endpoints (ie, full-length S-binding immunoglobulin G (IgG) levels and strain-specific hemagglutination inhibition assay titers). The following table presents the power to demonstrate noninferiority of the immune responses elicited by BNT162b2 and the seasonal inactivated influenza vaccine from the coadministration group to the separate-administration group.

Endpoint	NI margin	SD in natural log scale[a]	Power Assumed GMR=0.9 N=450 evaluable/group
SARS-CoV-2 full-length S-binding IgG	1.5-fold	1.05	98.8%
HAI titers			
A/H1N1	1.5-fold	1.05	98.8%
A/H3N2	1.5-fold	1.07	98.5%
B/Brisbane	1.5-fold	1.13	97.4%
B/Massachusetts	1.5-fold	1.16	96.8%
All[b]			90.7%

GMR=geometric mean ratio; HAI=hemagglutination inhibition assay; IgG=immunoglobulin G; NI=noninferiority; S-binding=spike protein–binding; SD=standard deviation.
[a]Assay SDs for SARS-CoV-2 full-length S-binding IgG were based on the 1 month after dose 2 immunogenicity results from the C4591020 study (NCT04816669; 18–55 years of age), and the C4591001 study (NCT04368728; 56–85 years of age); assay SDs for HAI endpoints were based on results for Afluria Quad.[1]
[b]All=overall power to demonstrate noninferiority for all endpoints.

If the geometric mean ratio of the coadministration group to the separate-administration group was 0.9 for SARS-CoV-2 full-length S-binding IgG levels and for HAI titers of each influenza strain, with assumed standard deviations for each endpoint, a sample size of 450 evaluable participants per group was estimated to provide an overall power of 90.7% to declare noninferiority for all coprimary endpoints. Assuming a nonevaluable rate of 20%, the study was to randomize approximately 1126 participants to achieve 450 evaluable participants in each group.

[1] Treanor JT et al. *Vaccine* 2017;35:1856-1864.

Table S1. Study populations

Population	Definition
Enrolled	All participants who provided informed consent
Randomized	All participants assigned a randomization number
Evaluable BNT162b2 immunogenicity	All eligible, randomized participants who received all vaccinations at Visit 1 as randomized (coadministration group) or received all vaccinations at Visit 1 and Visit 2 as randomized (separate-administration group), had ≥1 valid and determinate full-length S-binding IgG result from the blood sample collected within the predefined window (within 28–42 days after receipt of BNT162b2) at Visit 2 (coadministration group) or at Visit 3 (separate-administration group), had no reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and through 1 month after BNT162b2 vaccination (Visit 2 for the coadministration group and Visit 3 for the separate administration group), and had no other important protocol deviations as determined by the clinician
Evaluable SIIV immunogenicity	All eligible randomized participants who received all vaccinations at Visit 1 as randomized, had ≥1 valid and determinate HAI titer result from the blood sample collected within the predefined window at Visit 2 (within 28–42 days after receipt of SIIV), and had no other important protocol deviations as determined by the clinician
Safety	All participants who received any of the study vaccines

HAI=hemagglutination inhibition assay; IgG=immunoglobulin G; SIIV=seasonal inactivated influenza vaccine.

Table S2. Immunogenicity populations

	Coadministration group (BNT162b2 + SIIV)/placebo n[a] (%)	Separate-administration group (Placebo + SIIV)/BNT162b2 n[a] (%)	Total N[a] (%)
Randomized[b]	568 (100.0)	566 (100.0)	1134 (100.0)
Evaluable BNT162b2 immunogenicity population	499 (87.9)	413 (73.0)	912 (80.4)
Excluded from evaluable BNT162b2 immunogenicity population	69 (12.1)	153 (27.0)	222 (19.6)
Reason for exclusion[c]			
Did not receive all vaccinations at Visit 1 as randomized for coadministration group or did not receive all vaccinations at Visit 1 and Visit 2 as randomized for separate administration group	4 (0.7)	9 (1.6)	13 (1.1)
Had reported COVID-19 or new SARS-CoV-2 infection after Visit 1 and through 1 month after BNT162b2 vaccination[d]	53 (9.3)	122 (21.6)	175 (15.4)
Did not have ≥1 valid and determinate full-length S-binding IgG result within 28–42 days after BNT162b2 vaccination	45 (7.9)	41 (7.2)	86 (7.6)
Had important protocol deviation as determined by the clinician	6 (1.1)	6 (1.1)	12 (1.1)
Evaluable SIIV immunogenicity population	520 (91.5)	496 (87.6)	1016 (89.6)
Excluded from the evaluable SIIV immunogenicity population	48 (8.5)	70 (12.4)	118 (10.4)
Reason for exclusion[c]			
Did not receive all vaccinations at Visit 1	4 (0.7)	2 (0.4)	6 (0.5)
Did not have ≥1 valid and determinate HAI assay result within 28–42 days after SIIV vaccination	45 (7.9)	69 (12.2)	114 (10.1)
Had important protocol deviation as determined by the clinician	4 (0.7)	4 (0.7)	8 (0.7)

HAI=hemagglutination inhibition assay; IgG=immunoglobulin G; N-binding=SARS-CoV-2 nucleoprotein–binding; S=spike protein; SIIV=seasonal inactivated influenza vaccine.

[a]Number of participants with the specified characteristic.

[b]These values are the denominators for the percentage calculations.

[c]Participants may have been excluded for more than 1 reason.

[d]1 month after BNT162b2 vaccination was Visit 2 for the coadministration group and Visit 3 for the separate-administration group.

Table S3. Participants with HAI titer seroprotection before and 1 month after vaccination and seroconversion at 1 month after vaccination

		Coadministration group (BNT162b2 + SIIV)/placebo			Separate-administration group (placebo + SIIV)/BNT162b2		
Influenza strain	**Response**	**N[a]**	**n[b] (%)**	**95% CI**	**N[a]**	**n[b] (%)**	**95% CI**
H1N1 A/Victoria	Seroprotection: Before SIIV	509	340 (66.8)	62.5, 70.9	478	323 (67.6)	63.2, 71.8
	Seroprotection: 1 month after SIIV	516	504 (97.7)	96.0, 98.8	492	483 (98.2)	96.6, 99.2
	Seroconversion: 1 month after SIIV	508	254 (50.0)	45.6, 54.4	478	266 (55.6)	51.1, 60.2
H3N2 A/Darwin	Seroprotection: Before SIIV	514	365 (71.0)	66.9, 74.9	482	328 (68.0)	63.7, 72.2
	Seroprotection: 1 month after SIIV	519	498 (96.0)	93.9, 97.5	491	480 (97.8)	96.0, 98.9
	Seroconversion: 1 month after SIIV	514	315 (61.3)	56.9, 65.5	482	297 (61.6)	57.1, 66.0
B/Austria	Seroprotection: Before SIIV	515	129 (25.0)	21.4, 29.0	483	111 (23.0)	19.3, 27.0
	Seroprotection: 1 month after SIIV	514	385 (74.9)	70.9, 78.6	491	374 (76.2)	72.1, 79.9
	Seroconversion: 1 month after SIIV	511	273 (53.4)	49.0, 57.8	480	277 (57.7)	53.1, 62.2
B/Phuket	Seroprotection: Before SIIV	515	260 (50.5)	46.1, 54.9	484	230 (47.5)	43.0, 52.1
	Seroprotection: 1 month after SIIV	520	441 (84.8)	81.4, 87.8	496	418 (84.3)	80.8, 87.4
	Seroconversion: 1 month after SIIV	515	187 (36.3)	32.1, 40.6	484	183 (37.8)	33.5, 42.3

HAI=hemagglutination inhibition assay; SIIV=seasonal inactivated influenza vaccine.

Results are for the evaluable SIIV immunogenicity population. Exact 2-sided 95% CIs were calculated using the Clopper-Pearson method. Baseline was defined as Visit 1. Seroprotection is defined as HAI titer ≥1:40. Seroconversion is defined as ≥4-fold rise from before to after receipt of SIIV if the HAI titer is ≥1:10 before SIIV, or if the HAI titer is ≥1:40 after SIIV when the titer was <1:10 before SIIV.

[a] Number of participants in the specified group with valid and determinate assay results for the specified assay at the specified sampling timepoint (and also at baseline for seroconversion). These values are the denominator for the percentage calculations.

[b] Number of participants meeting seroprotection or seroconversion definition.

Table S4. Severity scale for local reactions and systemic events

	Mild	Moderate	Severe	Grade 4
Local reactions				
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	ED visit or hospitalization for severe pain
Redness	>2.0–5.0 cm (5–10 measuring device units)	>5.0–10.0 cm (11–20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0–5.0 cm (5–10 measuring device units)	>5.0–10.0 cm (11–20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis
Systemic events				
Fever	38.0°C–38.4°C	>38.4°C–38.9°C	>38.9°C–40.0°C	>40.0°C
Vomiting	1–2 times in 24 h	>2 times in 24 h	Requires IV hydration	ED visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools in 24 h	4–5 loose stools in 24 h	≥6 loose stools in 24 h	ED visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ED visit or hospitalization for severe headache
Fatigue/tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ED visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ED visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ED visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ED visit or hospitalization for severe new or worsened joint pain

ED=emergency department; IV=intravenous.

Table S5. Adverse events reported within 1 month after vaccination[a]

System organ class Preferred term	Coadministration group Visit 1 BNT162b2 + SIIV (N[b]=564) n[c] (%)	Coadministration group Visit 2 placebo (N[b]=562) n[c] (%)	Separate-administration group Visit 1 SIIV + placebo (N[b]=564) n[c] (%)	Separate-administration group Visit 2 BNT162b2 (N[b]=557) n[c] (%)
Blood and lymphatic system disorders	3 (0.5)	1 (0.2)	0	0
Lymphadenopathy	3 (0.5)	1 (0.2)	0	0
Cardiac disorders	5 (0.9)	0	0	2 (0.4)
Palpitations	4 (0.7)	0	0	1 (0.2)
Gastrointestinal disorders	6 (1.1)	3 (0.5)	6 (1.1)	7 (1.3)
Vomiting	2 (0.4)	0	1 (0.2)	3 (0.5)
General disorders and administration site conditions	35 (6.2)	12 (2.1)	36 (6.4)	13 (2.3)
Influenza-like illness	9 (1.6)	9 (1.6)	12 (2.1)	7 (1.3)
Injection site pain	16 (2.8)	1 (0.2)	14 (2.5)	1 (0.2)
Injection site erythema	3 (0.5)	0	5 (0.9)	0
Chest pain	3 (0.5)	0	0	2 (0.4)
Infections and infestations	105 (18.6)	123 (21.9)	109 (19.3)	103 (18.5)
COVID-19	46 (8.2)	63 (11.2)	56 (9.9)	48 (8.6)
Upper respiratory tract infection	27 (4.8)	31 (5.5)	24 (4.3)	22 (3.9)
Gastroenteritis	8 (1.4)	6 (1.1)	7 (1.2)	5 (0.9)
Viral upper respiratory tract infection	4 (0.7)	6 (1.1)	6 (1.1)	7 (1.3)
Viral infection	4 (0.7)	2 (0.4)	1 (0.2)	3 (0.5)
Influenza	3 (0.5)	1 (0.2)	2 (0.4)	2 (0.4)
Nasopharyngitis	1 (0.2)	2 (0.4)	4 (0.7)	2 (0.4)
Respiratory tract infection	1 (0.2)	3 (0.5)	2 (0.4)	2 (0.4)
Gastroenteritis viral	1 (0.2)	1 (0.2)	3 (0.5)	2 (0.4)
Urinary tract infection	1 (0.2)	4 (0.7)	0	1 (0.2)
Injury, poisoning and procedural complications	9 (1.6)	6 (1.1)	6 (1.1)	8 (1.4)
Fall	2 (0.4)	3 (0.5)	3 (0.5)	4 (0.7)
Ligament sprain	1 (0.2)	0	3 (0.5)	2 (0.4)
Musculoskeletal and connective tissue disorders	6 (1.1)	6 (1.1)	7 (1.2)	7 (1.3)
Back pain	0	1 (0.2)	3 (0.5)	2 (0.4)
Nervous system disorders	7 (1.2)	3 (0.5)	9 (1.6)	6 (1.1)
Headache	4 (0.7)	2 (0.4)	2 (0.4)	4 (0.7)
Respiratory, thoracic and mediastinal disorders	11 (2.0)	10 (1.8)	8 (1.4)	6 (1.1)
Cough	2 (0.4)	3 (0.5)	4 (0.7)	1 (0.2)
Oropharyngeal pain	1 (0.2)	4 (0.7)	2 (0.4)	2 (0.4)
Rhinorrhea	4 (0.7)	2 (0.4)	1 (0.2)	1 (0.2)

SIIV=seasonal inactivated influenza vaccine.

Results are for the safety population.

[a]Adverse events reported in ≥0.5% of participants in either group or the associated system organ class.

[b]Number of participants in the specified group. This value is the denominator for the percentage calculations.

[c]Number of participants reporting ≥1 occurrence of the specified event category.

Figure S1. GMCs and GMFRs for SARS-CoV-2 full-length S-binding IgG from before vaccination to 1 month after vaccination by baseline SARS-CoV-2 status

Data are for the evaluable BNT162b2 immunogenicity population. Two-sided 95% CIs for GMCs and GMFRs were based on the Student *t* distribution. Baseline SARS-CoV-2 positive was a positive N-binding antibody result at Visit 1 or medical history of SARS-CoV-2 or COVID-19. GMC=geometric mean concentration; GMFR=geometric mean fold rise; IgG=immunoglobulin G.