Serum Troponin I Assessments in 5- to 30-Year-Olds After BNT162b2 Vaccination

Authors: Timothy E. Albertson, MD, MPH, PhD,[1] Caitlin Hansen, MD, MPH,[2] Smiti Bihari, BM, MSc, MRCPCH,[3] Juleen Gayed, MBBS,[3] Xia Xu, PhD,[4] J. Abraham Simón-Campos, MD,[5] Michael E. Dever, MD,[6] Jose F. Cardona, MD,[7] Essack Mitha, MBChB,[8] Jeffrey B. Baker, MD,[9] Georgina Keep, BSc,[3] Islamiat Oladipupo, MBBS, MPH, PhD,[2] Federico J. Mensa, MD,[10] Ye Feng, PhD,[2] Hua Ma, PhD,[4] Kenneth Koury, PhD,[2] Susan Mather, MD,[11] Claudia Ana Ianos, MD,[12] Annaliesa S. Anderson, PhD,[2] Özlem Türeci, MD,[10] Uğur Şahin, MD,[10] William C. Gruber, MD,[2] Alejandra Gurtman, MD,[2] Charu Sabharwal, MD, MPH,[2] Nicholas Kitchin, MD,[3] on behalf of the C4591031 and C4591007 Clinical Trial Groups

Affiliations: [1]UC Davis Medical Center, Sacramento, CA, USA; [2]Vaccine Research and Development, Pfizer Inc, Pearl River, NY, USA; [3]Vaccine Research and Development, Pfizer Ltd, Hurley, UK; [4]Vaccine Research and Development, Pfizer Inc, Collegeville, PA, USA; [5]Köhler and Milstein Research/Autonomous University of Yucatan, Faculty of Medicine, Mérida, Yucatan, Mexico; [6]Clinical Neuroscience Solutions, Orlando, FL, USA; [7]Indago Research & Health Center, Inc, Hialeah, FL, USA; [8]Newtown Clinical Research, Johannesburg, South Africa; [9]Clinical Research Prime, Idaho Falls, ID, USA; [10]BioNTech, Mainz, Germany; [11]Worldwide Safety, Safety Surveillance and Risk Management, Pfizer Inc, Collegeville, PA, USA; [12]Worldwide Medical and Safety, Pfizer AG, Zurich, Switzerland

Corresponding author:
Juleen Gayed, MBBS
Vaccine Research and Development
Pfizer Ltd
Hurley, UK
Phone: (+44) 07795 486225
Email: Juleen.Gayed@pfizer.com

List of Independent Ethics Committees or Institutional Review Boards

Name	Location
Study C4591031 Substudy B	
Ethik-Kommission bei der Landesärztekammer Hessen	Frankfurt am Main, Germany
Pharma-Ethics Independent Research Ethics Committee	Centurion, Guateng, South Africa
Pharma Ethics (Pty) Ltd	Lyttelton Manor, Guateng, South Africa
WCG IRB	Puyallup, WA, USA
Cincinnati Children's Hospital Medical Center Institutional Review Board	Cincinnati, OH, USA
Study C4591007	
Comité de Bioseguridad del Hospital La Misión S.A. de C.V. Comité de Ética en Investigación del Hospital La Misión Comite de Investigación del Hospital La Misión S.A. de C.V.	Monterrey, Mexico
Comité de Ética de Investigación Clínica del HOSPITAL UNIVERSITARIO 12 DE OCTUBRE	Madrid, Spain
WCG IRB	Puyallup, WA, USA

Eligibility Criteria

C4591031 Substudy B (Participants 12–30 Years of Age)

The substudy included healthy participants who had received 2 or 3 prior doses of 30 µg BNT162b2 (with the first 2 doses 19 to 60 days apart), with the last dose being at least 4 months (120 days) before study vaccination. Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, could be included.

Key exclusion criteria included:

- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s)
- Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 nucleic acid amplification test result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection
- Pregnant or breastfeeding
- Individuals receiving treatment with radiotherapy or immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids
- Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies from 60 days before study intervention administration or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study
- Prior receipt of any COVID-19 vaccine other than BNT162b2 or receipt of medications to prevent COVID-19

Study C4591007 (Participants 5–15 Years of Age)

Healthy participants with preexisting stable disease, defined as disease not requiring significant change in the therapy or hospitalization for worsening disease during the 6 weeks before enrollment, could be included.

Key exclusion criteria included:

- Previous or current diagnosis of multisystem inflammatory syndrome in children
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s)
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination
- Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic lupus erythematosus (stable type 1 diabetes and hypothyroidism were permitted)

- Bleeding diathesis or condition associated with prolonged bleeding that would contraindicate intramuscular injection.
- Pregnant or breastfeeding
- Individuals receiving treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids
- Receipt of blood/plasma products, immunoglobulin, or monoclonal antibodies from 60 days before study intervention administration or receipt of any passive antibody therapy specific to COVID-19 from 90 days before study intervention administration, or planned receipt throughout the study

Timing of Troponin I Analyses in Study C4591007

At Baseline and Postvaccination in Participants 5–<12 Years of Age and 12–15 Years of Age

Troponin I levels in participants 5–<12 years of age and 12–15 years of age were assessed at baseline and 4 days after dose 2 of BNT162b2 or placebo (if 5–<12 years of age). As a result of the 2-dose primary series emergency use authorization issued by the US Food and Drug Administration in 2021 for BNT162b2 10 µg for individuals 5–<12 years of age,[1] participants were unblinded before the original protocol-specified timeframe of 6 months after dose 2 in this age group. The protocol was amended and participants who originally received placebo were offered the opportunity to receive BNT162b2 and did not have an additional blood draw after dose 2. However, with the emergence of the Omicron variant and adult clinical trial data showing an improved response to the Omicron variant after dose 3,[2] a third dose was added for all study participants in 2022. Collection of a blood sample for troponin I level analysis was included for the troponin group 4 days after dose 3 for participants 5–<12 years of age who originally received active vaccine and for all participants 12–15 years of age.

[1] Woodworth K, Moulia D, Collins J, et al. *MMWR Morb Mortal Wkly Rep* 2021;70:1579–1583.

[2] Muñoz FM, Sher LD, Sabharwal C, et al. *N Engl J Med* 2023;388:621–634.

Table S1. Participants with elevated troponin I results after each vaccination by vaccine sequence in C4591031 Substudy B (participants 12–30 years of age)

Vaccination	Sampling time point[a]	Vaccine sequence			
		Sequence 1 (BNT162b2→placebo)		Sequence 2 (placebo→BNT162b2)	
		n/N	% (95% CI)	n/N	% (95% CI)
1	Before	5/751	0.7 (0.2, 1.5)	4/730	0.5 (0.1, 1.4)
	4 Days	7/719	1.0 (0.4, 2.0)	4/693	0.6 (0.2, 1.5)
2	Before	7/628	1.1 (0.4, 2.3)	2/600	0.3 (0.0, 1.2)
	4 Days	10/667	1.5 (0.7, 2.7)	2/634	0.3 (0.0, 1.1)
	1 Month	5/676	0.7 (0.2, 1.7)	2/645	0.3 (0.0, 1.1)

CI, confidence interval.

[a]Protocol-specified time frames for blood sample collection were 4 days (2–5 days) after vaccinations 1 and 2 and 1 month (28–35 days) after vaccinations 1 and 2. Before vaccination 2 was 1 month after vaccination 1. For participants who received an incorrect vaccine at vaccination 2, the troponin results after vaccination 2 were not included in the postvaccination summary for vaccination 2.

N=number of participants for the vaccine sequence with nonmissing troponin I results within the protocol-specified window at the specified time point; this value is the denominator for the percentage calculations.

n=number of participants with elevated troponin I results; an elevated troponin I result is defined as >35 ng/L in males and >17 ng/L in females.

Exact 2-sided CIs were based on the Clopper and Pearson method.

Table S2. Difference in percentages of participants with elevated troponin I results from before vaccination to subsequent time points after vaccination by vaccine group in C4591031 Substudy B (participants 12–30 years of age)

Sampling time point[a]	Vaccine group							
	BNT162b2				Placebo			
	N	Before vaccination n (%) [95% CI[b]]	After vaccination n (%) [95% CI[b]]	Difference % [95% CI[d]]	N	Before vaccination n (%) [95% CI[b]]	After vaccination n (%) [95% CI[b]]	Difference[c] % [95% CI[d]]
4 Days	1273	7 (0.5) [0.2, 1.1]	9 (0.7) [0.3, 1.3]	0.2 [–0.4, 0.7]	1274	10 (0.8) [0.4, 1.4]	13 (1.0) [0.5, 1.7]	0.2 [–0.3, 0.7]
1 Month	1184	6 (0.5) [0.2, 1.1]	9 (0.8) [0.3, 1.4]	0.3 [–0.4, 0.9]	1179	8 (0.7) [0.3, 1.3]	6 (0.5) [0.2, 1.1]	–0.2 [–0.7, 0.3]

CI, confidence interval.

[a]Protocol-specified time point for blood sample collection. The protocol-specified windows are 4 days (2–5 days) after vaccinations 1 and 2 and 1 month (28–35 days) after vaccinations 1 and 2. For participants who did not receive vaccination 2 or who received an incorrect vaccine at vaccination 2, the troponin results 1 month after vaccination 1 were included in the 1-month summary for vaccination 1 and not included in the prevaccination summary for vaccination 2. The troponin results after vaccination 2 for participants who received an incorrect vaccine at vaccination 2 were also not included in the postvaccination summary for vaccination 2. This analysis is limited to participants with troponin I level measurements within the protocol-specified window at both time points (before vaccination and 4 days or 1 month after vaccination).

[b]Exact 2-sided CIs were based on the Clopper and Pearson method.

[c]Difference in percentage of participants with elevated troponin I levels from before to 4 days after or from before to 1 month after BNT162b2 or placebo (after vaccination – before vaccination).

[d]Adjusted Wald 2-sided CI, based on the Agresti and Min method for the difference in result, expressed as a percentage.

n=Number of participants with elevated troponin I results (ie, >35 ng/L in males and >17 ng/L in females).

N=number of participants for the vaccine group with nonmissing troponin I results within the protocol-specified window at both before vaccination and the specified time point; this value is the denominator for the percentage calculations.

Table S3. Participants with elevated troponin I results by sex and troponin value range in Study C4591007 (participants 5–15 years of age)

Participants 5–<12 years of age													
Time point	**Troponin value range, ng/L**	**BNT162b2 10 µg**						**Placebo**					
		Male		**Female**		**Total**		**Male**		**Female**		**Total**	
		n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
Dose 1	*N*	*265*		*251*		*516*		*139*		*118*		*257*	
prevaccination	Any abnormality	0	0 (0.0, 1.4)	1	0.4 (0.0, 2.2)	1	0.2 (0.0, 1.1)	0	0 (0.0, 2.6)	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
	>17–35		NA	1	0.4 (0.0, 2.2)	1	0.2 (0.0, 1.1)		NA	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
	>35–50	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 2.6)	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
	>50–100	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 2.6)	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
	>100–200	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 2.6)	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
	>200	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 2.6)	0	0 (0.0, 3.1)	0	0 (0.0, 1.4)
Dose 2	*N*	*259*		*244*		*503*		*36*		*31*		*67*	
Day 4	Any abnormality	1	0.4 (0.0, 2.1)	1	0.4 (0.0, 2.3)	2	0.4 (0.0, 1.4)	0	0 (0.0, 9.7)	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
	>17–35		NA	1	0.4 (0.0, 2.3)	1	0.2 (0.0, 1.1)		NA	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
	>35–50	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 9.7)	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
	>50–100	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 9.7)	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
	>100–200	0	0 (0.0, 1.4)	0	0 (0.0, 1.5)	0	0 (0.0, 0.7)	0	0 (0.0, 9.7)	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
	>200	1	0.4 (0.0, 2.1)	0	0 (0.0, 1.5)	1	0.2 (0.0, 1.1)	0	0 (0.0, 9.7)	0	0 (0.0, 11.2)	0	0 (0.0, 5.4)
Dose 3	*N*	*213*		*199*		*412*			*NA*		*NA*		*NA*
Day 4	Any abnormality	1	0.5 (0.0, 2.6)	0	0 (0.0, 1.8)	1	0.2 (0.0, 1.3)						
	>17–35		NA	0	0 (0.0, 1.8)	0	0 (0.0, 0.9)						
	>35–50	0	0 (0.0, 1.7)	0	0 (0.0, 1.8)	0	0 (0.0, 0.9)						
	>50–100	1	0.5 (0.0, 2.6)	0	0 (0.0, 1.8)	1	0.2 (0.0, 1.3)						
	>100–200	0	0 (0.0, 1.7)	0	0 (0.0, 1.8)	0	0 (0.0, 0.9)						
	>200	0	0 (0.0, 1.7)	0	0 (0.0, 1.8)	0	0 (0.0, 0.9)						

Participants 12–15 years of age							
Time point	**Troponin value range, ng/L**	**BNT162b2 30 µg**					
		Male		**Female**		**Total**	
		n	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**
Dose 1	*N*	*270*		*216*		*486*	
prevaccination	Any abnormality	2	0.7 (0.1, 2.7)	0	0 (0.0, 1.7)	2	0.4 (0.0, 1.5)
	>17–35		NA	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
	>35–50	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
	>50–100	2	0.7 (0.1, 2.7)	0	0 (0.0, 1.7)	2	0.4 (0.0, 1.5)
	>100–200	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
	>200	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
Dose 2	*N*	*256*		*209*		*465*	
Day 4	Any abnormality	1	0.4 (0.0, 2.2)	1	0.5 (0.0, 2.6)	2	0.4 (0.1, 1.5)
	>17–35		NA	1	0.5 (0.0, 2.6)	1	0.2 (0.0, 1.2)
	>35–50	1	0.4 (0.0, 2.2)	0	0 (0.0, 1.7)	1	0.2 (0.0, 1.2)
	>50–100	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
	>100–200	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
	>200	0	0 (0.0, 1.4)	0	0 (0.0, 1.7)	0	0 (0.0, 0.8)
Dose 3	*N*	*235*		*188*		*423*	
Day 4	Any abnormality	2	0.9 (0.1, 3.0)	1	0.5 (0.0, 2.9)	3	0.7 (0.1, 2.1)
	>17–35		NA	0	0 (0.0, 1.9)	0	0 (0.0, 0.9)
	>35–50	1	0.4 (0.0, 2.3)	1	0.5 (0.0, 2.9)	2	0.5 (0.1, 1.7)
	>50–100	1	0.4 (0.0, 2.3)	0	0 (0.0, 1.9)	1	0.2 (0.0, 1.3)
	>100–200	0	0 (0.0, 1.6)	0	0 (0.0, 1.9)	0	0 (0.0, 0.9)
	>200	0	0 (0.0, 1.6)	0	0 (0.0, 1.9)	0	0 (0.0, 0.9)

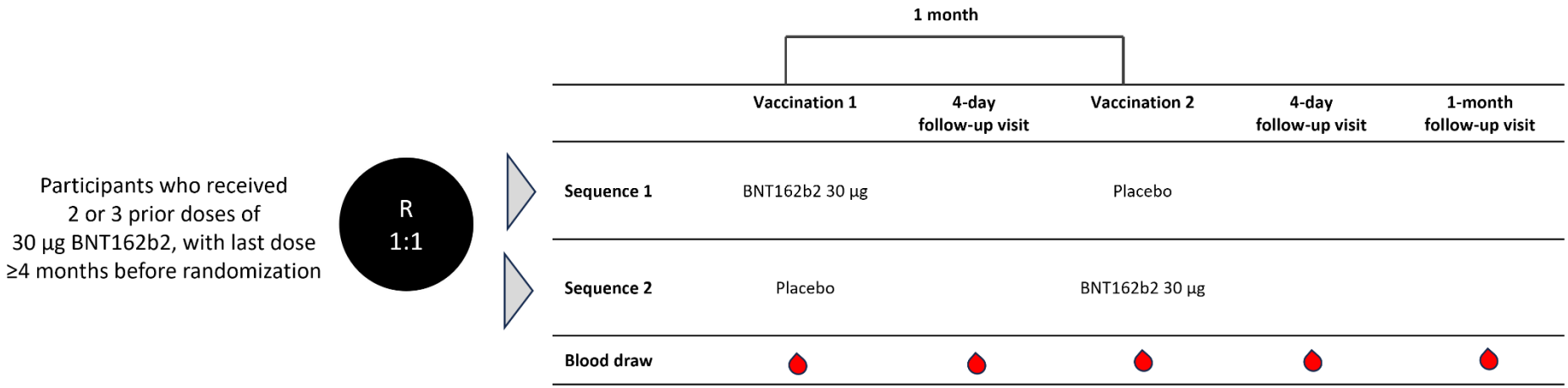
CI, confidence interval; NA, not applicable; n, number of participants with an elevated troponin I result (ie, >35 ng/L in males and >17 ng/L in females); N, number of participants with troponin I test results in the specified group (these values are the denominators for the percentage calculations.
Exact 2-sided CI was based on the Clopper and Pearson method.

Table S4. Number of participants with adverse events of special interest in C4591031 Substudy B (participants 12–30 years of age)

System organ class Preferred term	BNT162b2 (N=1453) n (%)	Placebo (N=1463) n (%)
Any event	41 (2.8)	45 (3.1)
Blood and lymphatic system disorders	0	1 (<0.1)
Increased tendency to bruise	0	1 (<0.1)
Cardiac disorders	1 (<0.1)	0
Tachycardia	1 (<0.1)	0
Endocrine disorders	1 (<0.1)	0
Hypothyroidism	1 (<0.1)	0
Gastrointestinal disorders	0	1 (<0.1)
Hematochezia	0	1 (<0.1)
General disorders and administration site conditions	4 (0.3)	3 (0.2)
Pyrexia	1 (<0.1)	2 (0.1)
Chest discomfort	1 (<0.1)	1 (<0.1)
Chest pain	2 (0.1)	0
Infections and infestations	11 (0.8)	5 (0.3)
COVID-19	8 (0.6)	2 (0.1)
Suspected COVID-19	2 (0.1)	2 (0.1)
Bronchitis	0	1 (<0.1)
Herpes zoster	1 (<0.1)	0
Injury, poisoning, and procedural complications	0	1 (<0.1)
Contusion	0	1 (<0.1)
Investigations	18 (1.2)	26 (1.8)
SARS-CoV-2 test positive	18 (1.2)	26 (1.8)
Musculoskeletal and connective tissue disorders	0	1 (<0.1)
Arthralgia	0	1 (<0.1)
Nervous system disorders	0	1 (<0.1)
Ageusia	0	1 (<0.1)
Anosmia	0	1 (<0.1)
Reproductive system and breast disorders	0	1 (<0.1)
Heavy menstrual bleeding	0	1 (<0.1)
Respiratory, thoracic, and mediastinal disorders	9 (0.6)	5 (0.3)
Cough	6 (0.4)	4 (0.3)
Dyspnea	2 (0.1)	0
Asthma	0	1 (<0.1)
Respiratory disorder	1 (<0.1)	0
Skin and subcutaneous tissue disorders	1 (<0.1)	2 (0.1)
Rash	1 (<0.1)	1 (<0.1)
Urticaria	0	1 (<0.1)

Medical Dictionary for Regulatory Activities (MedDRA, v25.1) was applied.

Figure S1. Design of C4591031 Substudy B



R, randomization.

Figure S2. Participants in C4591031 Substudy B (12–30 years of age) with elevated troponin I levels by troponin value range

The exact 2-sided 95% confidence interval (CI) was based on the Clopper-Pearson method.