CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 30 SEPTEMBER 2021 IN INDIVIDUALS AGED BETWEEN 12 AND 15 YEARS OF AGE

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LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AER	adverse event report
BC	Brighton Collaboration
COVID-19	coronavirus disease 2019
HLT	(MedDRA) high level term
LLT	lower level term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
MC	medically confirmed
PT	(MedDRA) preferred term
PM	post-marketing
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	(MedDRA) system organ class
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease

1. METHODOLOGY

Pfizer is responsible for the management post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of AERs does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

2. RESULTS

2.1. Safety Database

2.1.1. General Overview

Cumulatively, out of the 629,525[1] total reports received through 30 September 2021, there was a total of 3320 post-marketing reports containing 10,050 events occurred in paediatric individuals aged between 12 and 15 years of age.

Table 1 and Table 2 presents the main characteristics of the 12-15 year of age cases.

[1] Using the RMP search criteria.

Table 1. Selected Case Characteristics of Post-Marketing Reports Involving Individuals 12 – 15 Years of Age Received Cumulatively through 30 September 2021

Characteristics		No. of Cases N (%)
No. of Cases		3320
Gender	Female	1601 (48.2)
	Male	1619 (48.8)
	Unknown/No Data	100 (3.0)
Age (years)	N	3320[a]
	Min-Max	12 – 15
	Mean	13.6
	Median	14
Country of occurrence (≥2% of all cases)	United States (US)	1606 (48.4)
	France	214 (6.4)
	Italy	206 (6.2)
	Japan	160 (4.8)
	Denmark	154 (4.6)
	Canada	142 (4.3)
	Germany	103 (3.1)
	Netherlands	99 (3.0)
	Spain	97 (2.9)
Case Seriousness	Serious	1215 (36.6)
	Non-serious	2105 (63.4)
Case Outcome	Resolved/Resolving	557 (16.8)
	Resolved with sequelae	19 (0.6)
	Not resolved	693 (20.9)
	Fatal	18 (0.5)
	Unknown	1211 (36.5)
Medically Confirmed	Yes	1490 (44.9)
	No	1830 (55.1)

a. There were 813 reports in individuals aged 12 years (24.49%), 739 report in individuals aged 13 years (22.26%), 839 reports in individuals aged 14 years (25.27%), and 929 reports in individuals aged 15 years (27.98%).

Table 2. Medical History and Co-Suspect Medications of Post-Marketing Reports Involving Individuals 12 – 15 Years of Age Received Cumulatively through 30 September 2021

Medical history was available in 976 cases; the most frequently reported (≥2%) medical history SOCs included: Immune system disorders (368), Respiratory, thoracic and mediastinal disorders (228), Infections and infestations (198), Psychiatric disorders (188), Nervous system disorders (143), Congenital, familial and genetic disorders (90), Skin and subcutaneous tissue disorders (89) and Surgical and medical procedures (67). Regardless the SOC, the most frequently (>40 occurrences) reported PTs included Asthma (161), COVID-19 (110), Food allergy (82), Seasonal allergy (74), Drug hypersensitivity (64), Hypersensitivity (63), Attention deficit hyperactivity disorder (59).
Co-suspect medications were reported in 47 cases; those reported at least twice, included: COVID-19 Moderna (mRNA 1273) vaccine (8), Sodium chloride (6), adalimumab (5), Human papillomavirus vaccine and Johnson & Johnson vaccine (3 each), ciprofloxacin, COVID-19 AstraZeneca vaccine and fluoxetine (2 each).

Figure 1 shows the events grouped by SOCs; the SOCs that contained the greatest number (≥5%) of events included General disorders and administration site conditions (2545 AEs), Nervous system disorders (1606), Injury, poisoning and procedural complications (1131), Gastrointestinal disorders (830), Skin and subcutaneous tissue disorders (599), Musculoskeletal and connective tissue disorders (584), Respiratory, thoracic and mediastinal disorders (495), Cardiac disorders (362), Investigation (350), Infections and infestations (229), Psychiatric disorders (188) and Vascular disorders (167).

Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness

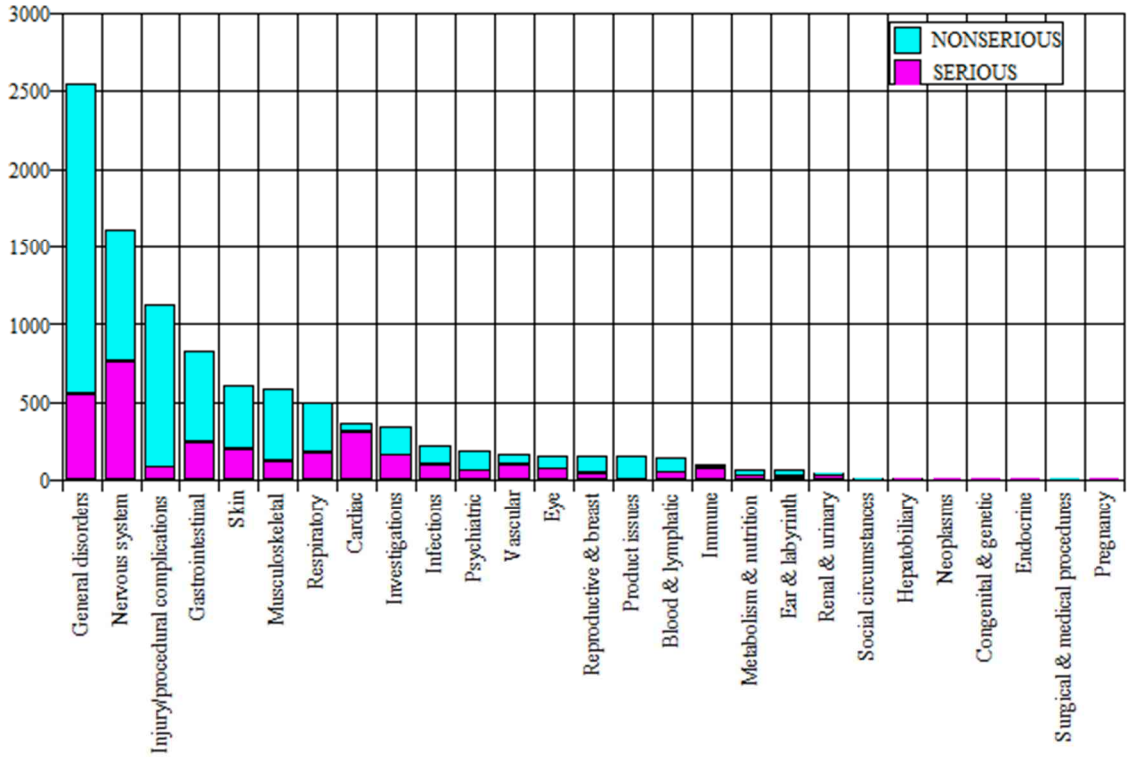

Table 3 shows the most commonly (≥2%) reported MedDRA (v. 24.0) PTs.

Table 3. Adverse Events Reported in ≥2% Cases in 12-15 Years of Age

MedDRA SOC	MedDRA PT	Cumulatively through 30 September 2021 n (%[a])
Blood and lymphatic system disorders	Lymphadenopathy	90 (2.71)
Cardiac disorders	Myocarditis	154 (4.64)
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	269 (8.1) 196 (5.9) 82 (2.47)

Table 3. Adverse Events Reported in ≥2% Cases in 12-15 Years of Age

MedDRA SOC	MedDRA PT	Cumulatively through 30 September 2021 n (%[a])
General disorders and administration site conditions		
	Pyrexia	578 (17.41)
	Fatigue	346 (10.42)
	Malaise	190 (5.72)
	Chest pain	178 (5.39)
	Chills	164 (4.94)
	Vaccination site pain	158 (4.76)
	Pain	146 (4.4)
	Asthenia	98 (2.95)
Injury, poisoning and procedural complications		
	Poor quality product administered	274 (8.25)
	Overdose	81 (2.44)
	Product preparation error	80 (2.41)
	Expired product administered	77 (2.32)
	Off label use	76 (2.29)
	Product storage error	71 (2.14)
Musculoskeletal and connective tissue disorders		
	Pain in extremity	227 (6.84)
	Myalgia	93 (2.8)
Nervous system disorders		
	Headache	520 (15.66)
	Dizziness	184 (5.54)
	Syncope	148 (4.46)
	Loss of consciousness	100 (3.1)
Product issues		
	Product temperature excursion issue	140 (4.22)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	118 (3.55)
	Oropharyngeal pain	70 (2.11)
Skin and subcutaneous tissue disorders		
	Rash	127 (3.83)
	Urticaria	117 (3.52)
Total number of events		**10050**

a. Adverse Event Reporting Proportion: n/N*100; n: number of Adverse Events; N: Number of Cases

2.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan

Table 4. Safety Concerns[a]

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 Use in Paediatric Individuals <5 Years of Age Vaccine Effectiveness

a. According to BLA US-PVP version 1.2.

Table 5. Important Identified Risk Anaphylaxis – Post-Marketing Reports Received Cumulatively through 30 September 2021 on 12 – 15 Years of Age Individuals

- Search criteria: MedDRA PTs Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**46 (100)**	**46 (100)**	**15 (32.6)**	**0**	**32 (69.6)**	**0**	**2 (4.3)**	**12 (26.1)**
Anaphylactic reaction	41 (89.1)	41 (100)	14 (34.1)	0	29 (70.7)	0	1 (2.4)	11 (26.8)
Anaphylactic shock	4 (8.7)	4 (100)	1 (25)	0	3 (75)	0	1 (25)	0
Anaphylactoid reaction	1 (2.2)	1 (100)	0	0	0	0	0	1 (100)

*For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

- Number of relevant cases: 43 (1.3% of 3320 cases, the total 12-15 years old PM dataset).
- Medically Confirmed (MC) cases (33), Non-MC cases (10).
- Country of incidence: Japan (18), US (8), Belgium (3), France, Germany and UK (2 each), Brazil, Denmark, Finland, Ireland, Israel, Italy, Portugal and Romania (1 each).
- Subjects' gender: female (25), male (18).
- Subjects' age in years (n = 43), range: 12-15, mean 13.5, median 13.
- Time to event onset (n = 43), range:<24 hours to 7 days.
  - <24 hours: 37 events;
  - 1 day: 3 events;
  - 2-7 days: 3 events.
- Duration of relevant event (n = 12 out of 32 occurrences with outcome of resolved/resolved with sequelae).
  - <24 hours: 10 events;
  - 1 day: 0 events;
  - 2 days: 2 events.

Table 6. Important Identified Risk Myocarditis and Pericarditis – Post-Marketing Reports Received Cumulatively through 30 September 2021 on 12 – 15 Years of Age Individuals

Overall, there were 180 potentially relevant cases of Myocarditis and Pericarditis; 154 cases reported myocarditis and 61 cases reported pericarditis (in 35 of these cases, the subjects developed both myocarditis and pericarditis).

Myocarditis

- Search criteria: MedDRA PTs Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis.
- Number of relevant cases: 154 (4.6% of 3320 cases, the total 12-15 years old PM dataset).
- These 154 cases were individually reviewed and assessed according to Brighton Collaboration (BC) Myocarditis Case Definition and Level of Certainty Classification (version 1.5.0, 16 July 2021), as per table below:

Brighton Collaboration Level	Number of cases
BC 1	14
BC 2	9
BC 3	0
BC 4	130
BC 5	1
Total	*154*

Level 1 indicates a definitive case with the highest level of diagnostic certainty of myocarditis, level 2 indicates a probable case, and level 3 indicates a possible case. Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**154 (100)**	**153 (99.4)**	**111 (72.1)**	**0**	**79 (51.3)**	**0**	**17 (11)**	**58 (37.7)**
Myocarditis	154 (100)	153 (99.4)	111 (72.1)	0	79 (51.3)	0	17 (11)	58 (37.7)

*For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

- MC cases (128), Non-MC cases (26).
- Country of incidence: Hong Kong (39), US (26), Germany (18), France (17), Italy (8), Israel (7), Austria and Spain (6 each), Denmark and Japan (5 each), Canada (3), Czech Republic and Latvia (2 each) and 1 case each from 10 other countries.
- Subjects' gender: female (20), male (131) and unknown (3).
- Subjects' age in years (n = 154), range: 12-15, mean 13.9, median 14.
- Relevant cardiac medical history: Arrhythmia (2), Aortic dilatation, Atrial fibrillation, Heart disease congenital, Marfan's syndrome, Myocardial infarction, Myocardial ischaemia, Myocarditis, Palpitations, Ventricular tachycardia (1 each).
- COVID-19 medical history: COVID-19 (6), Asymptomatic COVID-19 and SARS-CoV-2 test positive (1 each).

Table 6. Important Identified Risk Myocarditis and Pericarditis – Post-Marketing Reports Received Cumulatively through 30 September 2021 on 12 – 15 Years of Age Individuals

- Myocarditis was reported:
  - after the 1st dose in 36 cases;
  - after the 2nd dose in 106 cases;
  - in 12 cases it was unknown after which dose myocarditis occurred.
- Time to event onset (n = 108), range:<24 hours to 42 days.
  - <24 hours: 6 events;
  - 1 day: 30 events;
  - 2-4 days: 54 events;
  - 5-14 days: 11 events;
  - 15-30 days: 5 events;
  - 31-42 days: 2 events.
- Duration of relevant event (n = 8 out of 34 occurrences with outcome of resolved/resolved with sequelae).
  - 1-2 days: 4 events;
  - 5-6 days: 4 events.

Pericarditis

- Search criteria: MedDRA PTs: Autoimmune pericarditis; Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.
- Number of relevant cases 61 (1.2% of 3320 cases, the total 12-15 years old PM dataset).
- These 61 cases were individually reviewed and assessed according to BC Pericarditis Case Definition and Level of Certainty Classification (version 1.0.0, 15 July 2021), as per table below:

Brighton Collaboration Level	Number of cases
BC 1	1
BC 2	4
BC 3	0
BC 4	56
BC 5	0
Total	*61*

Level 1 indicates a definitive case with the highest level of diagnostic certainty of myocarditis, level 2 indicates a probable case, and level 3 indicates a possible case. Level 4 is defined as "reported event of myocarditis with insufficient evidence to meet the case definition" and Level 5 as not a case of myocarditis.

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**61 (100)**	**61 (100)**	**17 (27.9)**	**0**	**18 (29.5)**	**1 (1.6)**	**9 (14.8)**	**33 (54.1)**
Pericarditis	61 (100)	61 (100)	17 (27.9)	0	18 (29.5)	1 (1.6)	9 (14.8)	33 (54.1)

*For the outcome count, the multiple LLTs that code to the same PT within a case or the PTs duplicated during migration from legacy databases (possibly with different outcome), are counted and presented individually. Therefore, for selected PTs the total count of event outcomes may exceed from the total number of events.

Table 6. Important Identified Risk Myocarditis and Pericarditis – Post-Marketing Reports Received Cumulatively through 30 September 2021 on 12 – 15 Years of Age Individuals

- MC cases (52), Non-MC cases (9).
- Country of incidence: Hong Kong (29), Italy (7), France (6), US (4), Canada (3), Australia, Belgium, Germany, Japan (2 each) and 1 case each from 4 other countries.
- Subjects' gender: female (13), male (48).
- Subjects' age in years (n = 61), range: 12-15, mean 14, median 14.
- Relevant cardiac medical history: Aortic valve incompetence, Cardiac aneurysm, Cardiac septal defect repair, DiGeorge's syndrome, Fallot's tetralogy, Heart disease congenital, Pericarditis (1 each).
- COVID-19 medical history: COVID-19 (3).
- Pericarditis was reported:
  - after the 1st dose in 14 cases;
  - after the 2nd dose in 38 cases;
  - in 9 cases it was unknown after which dose pericarditis occurred.
- Time to event onset (n = 32), range:<24 hours to 31 days.
  - <24 hours: 1 event;
  - 1 day: 6 events;
  - 2-4 days: 16 events;
  - 5-14 days: 5 events;
  - 15-31 days: 4 events.
- Duration of relevant event (n = 2 out of 12 occurrences with outcome of resolved/resolved with sequelae); 1 event resolved after 3 days and 3 hours and the second one after 6 days.

Table 7. Important Potential Risk Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD) - Post-Marketing Reports Received Cumulatively through 30 September 2021 on 12 – 15 Years of Age Individuals

- Search criteria:
  - PT=Vaccine associated enhanced respiratory disease; Vaccine associated enhanced disease OR
  - Standard Decreased Therapeutic Response Search (Drug ineffective OR Vaccination failure) AND 1 among the following PTs: Dyspnoea; Tachypnoea; Hypoxia; COVID-19 pneumonia; Respiratory failure; Acute respiratory distress syndrome; Cardiac failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.
- Number of cases 2 (0.06% of 3320 cases, the total 12-15 years old PM dataset).
- MC cases (2), Non-MC cases (0).

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Event by Outcome* N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	**6 (100)**	**6 (100)**	**6 (100)**	**0**	**4 (66.7)**	**0**	**0**	**2 (33.3)**
Diarrhoea	1 (16.7)	1 (100)	1 (100)	0	1 (100)	0	0	0
Drug ineffective	1 (16.7)	1 (100)	1 (100)	0	0	0	0	1 (100)
Multisystem inflammatory syndrome in children	1 (16.7)	1 (100)	1 (100)	0	1 (100)	0	0	0
Seizure	1 (16.7)	1 (100)	1 (100)	0	1 (100)	0	0	0
Vaccination failure	1 (16.7)	1 (100)	1 (100)	0	0	0	0	1 (100)
Vomiting	1 (16.7)	1 (100)	1 (100)	0	1 (100)	0	0	0

Of the 2 cases retrieved with the above criteria, both cases were determined to be non-contributory and are not further discussed.

Table 8. Description of Missing Information

Topic	Description
Use in Pregnancy and Lactation	• Search criteria: Pregnancy cases are identified as cases where: - Patient Pregnant Flag is "Yes"; - If there is a value for Pregnancy Outcome, Birth Outcome, or Congenital Anomaly; - If Delivery Notes are available; - If any of the valid events on the case contains one of the following:" o SOC Pregnancy, puerperium and perinatal conditions, or HLT Exposures associated with pregnancy, delivery and lactation; Lactation disorders, or PT Exposure via body fluid. • Number of cases: 1 serious case from UK (0.03% of 3320 cases, the total 12-15 years old PM dataset). A 12-year-old was pregnant (gestation week unknown) at the time of first dose; she had miscarriage 2 weeks after vaccine administration. No additional information was available for this case. • There were no cases indicative of breastfeeding.
Use in Paediatric Individuals <5 years of Age	• Number of cases: 56 (0.01% of the 629,525 cases, the total PM dataset). • MC cases (23), Non-MC cases (33). • Country of incidence: UK (14), US (13), Italy (7), South Africa (4), Japan and Spain (3 each), Germany, Lithuania and Netherlands (2 each) and 1 case each from other 6 countries. • Cases Seriousness: serious (14), non-serious (42). • Subjects' gender: female (28), male (24), unknown/no data (4). • Subjects' age in years (n = 55), range: 0.02-4.75, mean 1.8, median 3. • Case outcome: fatal (2)[2], resolved/resolving (23), not resolved (16), and unknown (15). • Of the 172 reported events, those reported more than three times were as follows: Product administered to patient of inappropriate age (21), Off label use (17), Product use issue (15), Pyrexia (11), Fatigue, Headache, Myalgia and Nausea (4 each).
Vaccine Effectiveness	• Number of cases: 29 (0.9 % of the 3320 cases, the total 12-15 years old PM dataset). • MC cases (14), Non-MC cases (15). • Number of lack of efficacy events: 29 [PTs: Drug ineffective (20) and Vaccination failure (9)]. • Country of incidence: US (14), Austria and Brazil (2 each) and 1 case each from other 11 countries.

[2] Both cases contained minimal information with unknown medical history, concomitant medications and clinical course; for both cases it was unknown if an autopsy was performed. The first case, from UK, involved a 5-month-old male boy who received the first dose on 17 April 2021 and died on 02 May 2021. A SARS-CoV-2 test negative was reported on an unknown date. The second case, from Saudi Arabia, involved a 2-year-old girl who had been hospitalized since 14 February 2021 (she may have gotten sick from first shot) and received the second dose on 25 February 2021. The patient died on 03 March 2021.

Table 8. Description of Missing Information

Topic	Description
Vaccine Effectiveness (Cont'd)	• COVID-19 infection was suspected in 3 cases, confirmed in 26 cases (including 1 case of asymptomatic COVID-19). • COVID-19 infection (suspected or confirmed) outcome was reported as resolved/resolving (6), not resolved (1) or unknown (22) at the time of the reporting. **Drug ineffective cases (20)** • Drug ineffective event seriousness: serious (19), non-serious (1). • Lack of efficacy term was reported: o after the 1st dose in 12 cases o after the 2nd dose in 7 cases o in 1 case it was unknown after which dose the lack of efficacy occurred. • Latency of lack of efficacy term reported after the first dose was known for 3 cases: after 5, 13 and 15 days, respectively. • Latency of lack of efficacy term reported after the second dose was known for 2 cases: after 2 and 5 days, respectively. • Latency of lack of efficacy term reported in cases where the number of doses administered was not provided, was known in 1 case: after 5 days. **Vaccination failure cases (9)** • Vaccination failure seriousness: all serious. • Lack of efficacy term was reported in all cases after the 2nd dose. • Latency of lack of efficacy was known for all 9 cases: in 1 case after 10 days and in the other 8 cases between 23 and 92 days. • COVID-19 (8) and Asymptomatic COVID-19 (1) were the reported vaccine preventable infections that occurred in these 9 cases.

3. SUMMARY AND CONCLUSION

Review of the cumulative available post-marketing data in individuals aged between 12 and 15 years, did not identify any additional or unexpected risks associated with for BNT162b2 and confirms the favorable benefit risk balance observed in the clinical study. Post-marketing surveillance activities will continue.