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1	Draft manuscript shell sent by Emily to Developer	05/08/2023
2	Draft manuscript completed by developer	12/1/2023
3	Draft manuscript sent to BRAVATO WG for 2-week preliminary peer review process	12/20/2023
4	Emily sends reviewed manuscript to developer	1/11/2024
5	Developer incorporates BRAVATO peer review comments and produces final draft	2/5/2024
6	Emily posts final draft manuscript to BC website for 2-week general peer review	
7	Emily sends final comments to developer who finalizes manuscript	
8	Emily submits manuscript to Vaccine Journal	

A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Comirnaty COVID-19 mRNA vaccine to prevent disease caused by SARS-CoV-2 viruses

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For the Benefit-Risk Assessment of VAccines by TechnolOgy Working Group (BRAVATO; ex-V3SWG) [1]

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1. See Acknowledgement for other BRAVATO members.

Keywords:

COVID-19 Vaccine, Vaccine Safety, Vaccine Benefit/Risk, Coronavirus, SARS-CoV-2

1 Abstract

The Brighton Collaboration Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group evaluates the safety and other key features of new platform technology vaccines, including nucleic acid (RNA and DNA) vaccines. This manuscript uses the BRAVATO template to report the key considerations for a benefit-risk assessment of the coronavirus disease 2019 (COVID-19) mRNA-based vaccine BNT162b2 (COMIRNATY®, or Pfizer-BioNTech COVID-19 vaccine) including the subsequent Original/Omicron BA.1, Original/Omicron BA.4-5 and Comirnaty Omicron XBB.1.5 variant-adapted vaccines developed by BioNTech and Pfizer to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Initial Emergency Use Authorizations or conditional Marketing Authorizations for the original BNT162b2 vaccine were granted based upon safety, immunogenicity, and efficacy data from a placebo-controlled, randomized pivotal trial with 43,548 participants, which found the vaccine to be safe and 95% effective against COVID-19 from 7 days post dose 2. Approval in adolescents was based upon data from 2,260 adolescents randomized 1:1 to receive BNT162b2 or placebo. A full Biologics License Application was later approved by the Food & Drug Administration on 23 August 2021. Similarly, the initial conditional Marketing Authorization granted in the European Union in December 2020 was converted to a full Marketing Authorization in September 2022.

2 Introduction

The Brighton Collaboration (www.brightoncollaboration.org) Viral Vector Vaccine Safety Working Group (V3SWG) was formed in 2008 in recognition of the increasing importance of viral vectors for the development of new vaccines and the need to understand their associated safety issues [1]. To better meet the needs of platform technologies used to develop vaccines to prevent COVID-19, beyond those using viral vectors, the V3SWG was renamed the Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group in July 2020. The BRAVATO WG has developed standardized templates to describe the key characteristics of several major vaccine platform technologies, including nucleic acid vaccines [2]. Usually completed in a partnership between BRAVATO WG and the vaccine developer, the BRAVATO template helps answer important questions on the essential safety and benefit-risk issues associated with the intrinsic properties of the candidate vaccine to facilitate scientific discourse among key stakeholders [3]. The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety has endorsed the use of the template "as it is a structured approach to vaccine safety" [4].

This paper uses a BRAVATO nucleic acid vaccine template to review the features of Pfizer-BioNTech's COVID-19 mRNA Vaccine, Comirnaty (BNT162b2, international non-proprietary name tozinameran), which prevents disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses and was the first prophylactic messenger ribonucleic acid (mRNA) vaccine to be approved. It includes analysis of the variant-adapted vaccines Comirnaty Bivalent Original/Omicron BA.1 (tozinameran/riltozinameran), Comirnaty Bivalent Original/Omicron BA.4-5 (tozinameran/famtozinameran) and Comirnaty Omicron XBB.1.5 (raxtozinameran) in adults and children.

2.1 Background

The first cases of SARS-CoV-2 were reported in December 2019; by March of 2020 the WHO had declared a pandemic, thus triggering a global demand for prophylactic vaccines. Regulatory authorities offered guidance regarding emergency use and expedited pathways for the development and approval of COVID-19 vaccines, while emphasizing the requirement for long-term safety monitoring [5].

mRNA vaccine platforms were well-suited to meet the global demand for preventive vaccines, having already accrued clinical experience in different settings: proof of concept for mRNA prophylactic vaccines was first established in 1993 by Martinon and colleagues in an animal model [6], and the first clinical trial of mRNA vaccines was initiated in 2009, investigating therapeutic vaccines for the potential treatment of cancer [7].

The technology used to develop BNT162b2 was in place at the start of the pandemic as BioNTech had already been developing infectious disease vaccines [8,9], as well as mRNA-based therapeutic cancer vaccines [10,11], including personalized cancer vaccines [12]. In particular, the development of fully individualized mRNA cancer vaccines, where genomic sequencing of tumor samples is used to identify immunogenic mutations and design a therapeutic vaccine tailored to the mutational composition of individual tumor genomes (mutanomes), requires rapid on-demand vaccine design and manufacturing [12,13] and thus depends upon implementation of platform technology approaches. Similar principles were adopted for COVID-19 vaccines, with platform-based nonclinical toxicology studies [14] and extrapolation of immunogenicity and safety information across different vaccine candidates using the same platform used to support the rapid start of first-in-human trials [5] and, later, the licensure of variant-adapted vaccines.

In response to the COVID-19 pandemic, the intrinsic characteristics of mRNA vaccines were instrumental in supporting the rapid development of safe and effective vaccines: mRNA does not integrate into the genome, is degraded by physiological pathways, and results in transient expression of the encoded protein [11,15,16]. mRNA vaccines are molecularly well-defined and can be efficiently synthesized from DNA templates by *in vitro* transcription , facilitating a fast and scalable manufacturing process, leading to rapid vaccine development and supply in the event of a pandemic [17,18]. Additionally, they can be individualized based on the type of mRNA used to elicit an immune response [19]. In light of the emergence of the SARS-CoV-2 Omicron variants, the mRNA vaccine platform was adapted to encode new or modified antigens in response to evolving epidemiological landscapes; leading to the development of the Original/Omicron BA.1 and BA.4-5 bivalent adapted vaccines.

More recently, a vaccine adapted to the Omicron XBB.1.5 variant, based on the BNT162 platform, and the 2023 vaccine composition guidance issued by regulators, was approved in the European Union (EU), Japan, United Kingdom (UK), United States (US), Japan, Singapore, South Korea and others. Based on the currently available information, the benefit-risk profile of the monovalent XBB vaccine is positive and comparable with BNT162b2 and the Original/Omicron BA.1 and BA.4-5 bivalent adapted vaccines.

2.2 Candidate selection

Early COVID-19 clinical vaccine candidates, including BNT162b1 and BNT162b2, were developed using multiple mRNA formats [20-24]. Following their initial clinical evaluation in the BNT162-01 trial in Germany (NCT04380701), two candidates, both lipid

nanoparticle–formulated nucleoside modified RNAs (modRNA), were further evaluated in the Phase 1 portion of the C4591001 clinical trial in the US in younger and older adults (NCT04368728): BNT162b1 [21,22], which encodes a trimerized, secreted version of the receptor-binding domain of the SARS-CoV-2 spike (S) protein, and BNT162b2 [23], which encodes the full-length S protein. Both vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing titers, with titers equal or greater than that of a panel of SARS-CoV-2 convalescent serum samples. BNT162b2 showed a more favorable immunogenicity and tolerability profile [22,23,25], and was therefore selected as the lead candidate for Phase 2/3 trials on the basis of the totality of data obtained in the two Phase 1 trials, and challenge studies in non-human primates (NHPs) [26]. T-cell recognition of epitopes spread across the entire length of the S protein was a further reason to favor BNT162b2 over BNT162b1, as it was expected to mitigate the risk of immune escape of new variant strains [23].

BNT162b2 encodes the SARS-CoV-2 *Wuhan-Hu-1* (GenBank MN908947.3) strain full-length S protein [23], which mediates viral attachment and entry into host cells and is a key target of elicited virus-neutralizing antibodies [27]. The substitution of two residues to proline (K986P/V987P) in the vaccine-encoded S protein serve to lock it in the prefusion conformation [26] so as to better mimic the receptor-unbound state of the S protein [28]. The mRNA contains the modified nucleoside, N1-methyl-pseudouridine (m1Ψ); the nucleotide-modRNA intended to reduce an innate immune response via pathogen-associated molecular pattern (PAMP) receptor activation [29]. This modification also improves stability and translational capacity [30], elements further supported with additional pharmacological optimization of non-coding sequence elements [31,32].

The non-infectious SARS-CoV-2 S protein encoding mRNA is packaged into lipid nanoparticles (LNPs) that protect against degradation by RNases and facilitate delivery of the mRNA to antigen-presenting cells at draining lymph nodes, following intramuscular (IM) injection, to elicit an adaptive humoral and cellular immune response [24,33,34].

2.3 Preclinical development

The nonclinical safety, immunogenicity, and efficacy of BNT162b2 was assessed in rodents and NHPs. Preclinical characterization of BNT162b2 confirmed that intramuscular (IM) vaccination elicited a substantial SARS-CoV-2 S-specific antibody response in mice, with high virus-neutralizing titers and strong T-helper-1 CD4+ and IFNγ+CD8+ T-cell responses [26] which induced an anti-viral protective effect in hACE2 transgenic mice [35]. Prime-boost vaccination of rhesus macaques elicited SARS-CoV-2-neutralizing titers significantly higher than that of a panel of SARS-CoV-2-convalescent human sera and protected macaques against challenge with SARS-CoV-2, with evidence of protection of the lower respiratory tract against viral infection and no evidence of enhanced disease [26]. In independent repeat-dose toxicity studies, rats were treated with doses of up to 100 µg BNT162b2 every three weeks, demonstrating a safety profile in line with the anticipated immune and transient inflammatory responses [14]. Treatment of female rats with two 30 µg doses – reflecting the full human primary series dosing regimen with BNT162b2 – prior to mating and on gestation days 9 and 20 in an International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-compliant, nonclinical developmental and reproductive toxicity study did not affect female mating performance, fertility, or any ovarian or uterine parameters. Embryo-fetal or

postnatal survival, growth, and physical/neurofunctional development in the offspring through the end of lactation were also unaffected [36].

2.4 Clinical development and approval

The candidate selection and dose-finding Phase 1 trials showed that BNT162b2 induces adaptive immune responses in humans at the selected primary two-dose schedule of 30 μg doses administered 21 days apart [23,37]; additionally, neutralizing titers of sera drawn one week post second dose were more than three times greater than that of a panel of convalescent sera. Poly-specific CD4+ and CD8+ T-cell immune responses were detectable in most participants assayed [23]. In both trials, local reactions were mild to moderate (grades 1 and 2, predominantly injection site pain); fatigue, headache, and muscle and joint pain were the most common systemic adverse events (AEs), predominantly mild (grade 1) but with moderate to severe events (grade 2-3) reported; and most reactogenic events resolved within seven days after vaccination. No serious AEs or grade 4 reactogenicity events were reported from either Phase 1 trial [23,25]. The observed elicited strong immune responses and favorable safety and reactogenicity profile indicated that the vaccine has a positive benefit-risk profile [25].

The Phase 2/3 pivotal trial (NCT04368728) was a placebo-controlled, observer-blinded, multinational, efficacy trial that randomized participants 1:1 to receive two doses, 21 days apart, of 30 μg BNT162b2 or placebo; the trial recruited approximately 43,500 participants and generated data while the wild-type SARS-CoV-2 virus was predominant in circulation [20]. 49% of participants were female, and the trial recruited predominantly White (83%, of which 28% self-identified as Hispanic or Latinx), Black or African American (9%), and Asian (4%)

participants. Individuals were recruited with risk factors for complications from COVID-19: 35% of participants were obese (defined as a body mass index of ≥ 30.0), 21% had at least one underlying medical condition, and 42% were over 55 years of age [20]. Initial data from an analysis after 170 evaluable COVID-19 cases, with two months of follow-up after vaccination, pointed to 95% vaccine efficacy in preventing COVID-19 in persons 16 years of age or older; the trial therefore met its primary objective. Sub-group analyses indicated that vaccine efficacy was consistent across subgroups defined by age, sex, obesity, and presence of a coexisting condition (including hypertension, analyzed separately)[38]. The safety and reactogenicity profile of BNT162b2 in 43,448 participants aged 16-years or older was in line with that observed in the Phase 1 trials and the interim analysis, and characterized by short-term, mild to moderate pain at the injection site (> 80%), fatigue (> 60%), headache (> 50%) myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia, and injection site swelling (both > 10%) [34]. Serious AEs were reported at similar rates in those vaccinated with BNT162b2 versus placebo; few participants had severe AEs or AEs leading to study withdrawal [20]. There were two deaths in the BNT162b2 arm and four in the placebo group, none of which were reported as related to vaccine or placebo [20]. A longer term, 6-month follow-up analyzed data from 44,060 participants aged 16 years or older and 2,260 participants aged 12-15 years (data cut off, March 13, 2021). Among participants aged 16 years or older, 22,030 received at least one dose of BNT162b2 and 22,030 received at least one dose of placebo. Among participants aged 12-15 years, 1,131 and 1,129 received at least one dose of BNT162b2 or placebo. Vaccine efficacy against COVID-19 among, 42,094 participants 12 years of age or older, was 91.3% (95% CI 89.0–93.2) irrespective of previous SARS-CoV-2 infection, and vaccine efficacy against severe disease was 96.7% (95% CI 80.3–99.9) [39]. A reduction of vaccine efficacy to 90% within 2 to 4 months and to 84% within 4 to 6 months was

noted after the second dose [20,39]. Severe disease was based on the US Food & Drug Administration (FDA) definition and defined as confirmed COVID-19 and the presence of one or more of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, $SpO_2 \leq 93\%$ on room air at sea level, or $PaO_2/FiO_2 < 300$ mmHg); respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure) [40]. In the longer follow-up study 55% of the participants vaccinated with BNT162b2 were followed up for 6 months or longer after the second dose and demonstrated a reactogenicity profile similar to that in the previous study, with most of the systemic events being reported as mild to moderate and few severe AEs reported [20,39]. No new safety signals were identified and the only new AEs attributable to BNT162b2 were decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis. There was a similarly low incidence of serious AEs in the BNT162b2 and placebo groups, with no new serious AEs related to BNT162b2 reported, and few serious AEs or AEs leading to study withdrawal. The number of deaths was similar for BNT162b2 and placebo recipients, and no deaths were reported as related to the vaccine [39].

During the 6-month safety follow-up, Bell's palsy (facial paralysis) occurred in four participants treated with BNT162b2 versus two participants treated with placebo. There was insufficient information to determine a causal relationship with the vaccine [34]. No notable patterns or numerical imbalances were otherwise detected between treatment groups for specific categories of serious or non-serious AEs, including other neurologic or neuro-inflammatory, and thrombotic events that would suggest a causal relationship to BNT162b2, both during blinded placebo-controlled follow-up and during unblinded follow-up [34].

In a Phase 2 clinical trial conducted in China by Fosun pharma, BioNTech's partner for China, Hong-Kong, Taiwan and Macau, 720 adults of Han ethnicity aged 18 to 85 were vaccinated with one or more doses of BNT162b2 and 239 with placebo. A similar safety profile was observed in this population for up to 6 months post dose 2 as that seen in the population recruited to the pivotal Phase 3 trial for BNT162b2. Reactogenicity was mild to moderate and typically resolved a few days after onset, and there was a low incidence of serious AEs [41]. No vaccine related serious AEs were observed. Vaccination induced robust SARS-CoV-2 neutralizing antibody and SARS-CoV-2-specific T-cell responses [41]. In a Phase 1/2 trial, 160 healthy Japanese individuals were randomized 3:1 to receive two doses of BNT162b2 or placebo 21 days apart. With BNT162b2, local reactions and systemic events were generally transient and mild to moderate. No serious AEs were recorded, and severe AEs were uncommon. BNT162b2 vaccination induced a robust immune response and was well tolerated in Japanese adults aged 20 to 85 [42]. COVID-19 infection rates were not assessed in either the Han or Japanese studies.

2.5 Adolescent and pediatric clinical development

The pivotal Phase 2/3 clinical trial NCT04368728 recruited individuals aged 12 to 15 years to characterize the safety, immunogenicity, and efficacy of BNT162b2 in adolescents.
Long-term safety follow-up of 2,260 adolescents (1,131 received BNT162b2; 1,129 received placebo), including 1,559 adolescents that were followed for at least 4 months after the second dose, revealed a similar safety profile for BNT162b2 to that seen in adults. The most frequent adverse reactions in adolescents that received two doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%) [34]. An

analysis of all unsolicited AEs reported during blinded follow-up from dose 1 through one month after dose 2 identified lymphadenopathy (9 versus 2), and nausea (5 versus 1) as adverse reactions.

Few serious AEs were observed, and none were vaccine related. Adolescents developed a stronger immunological response to the vaccine, with a 1.76-fold (95% confidence interval [CI], 1.47 to 2.10) increased SARS-CoV-2 neutralizing geometric mean titer one month after dose 2, relative to participants aged 16 to 25 years.

Vaccine efficacy against COVID-19 among 1,983 participants aged 12 to15 years was 100% (95% CI, 75.3 to 100) for those who did not have evidence of previous SARS-CoV-2 infection [43].

Data from NCT04816643, a Phase 1 dose-finding trial and Phase 2–3 randomized trial showed that a primary two-dose series of 10 μg Comirnaty administered 21 days apart is safe, immunogenic, and efficacious in children aged 5 to 11 years. In the pivotal trial, children were randomized 2:1 to receive either BNT162b2 or placebo. Data from children treated with BNT162b2 (n=1,517) or placebo (n=751) with a median follow-up of 2.3 months showed that BNT162b2 had a favorable safety profile, in line with other age groups [44]. As was observed in the adult trial, injection site pain and fatigue and headache were the most common local and systemic events. While predominantly mild to moderate, severe injection site pain, fatigue, and headache events were reported by 0.6%, 0.9%, and 0.3% of BNT162b2 recipients, reported after the first or second dose. No vaccine related serious AEs or deaths were recorded. Neutralizing titers were of a similar magnitude to that induced in 16- to 25-year-olds (geometric mean ratio 1.04, 95% CI 0.93–1.18), and vaccine efficiency was 90.7% (95% CI 67.7–98.3).

Following a Phase 1 dose-finding trial, 1,178 children aged 6 months to 2 years of age and 1,835 children aged 2 to –4 years were treated with a two-dose primary series of 3 μg BNT162b2 [45]. A

third 3 μg dose (at least 8 weeks after dose 2) was administered after preliminary immunogenicity results starting in January 2022, which coincided with the emergence of the B.1.1.529 (Omicron) variant. Immunobridging success criteria 1 month post dose 3 were met for both age groups following the addition of a third dose to the primary series. Seroresponse was 100%, and neutralizing titers were 1.19-fold higher for children aged 6 months to 2 years and 1.3-fold higher for those aged 2 to 4 years when compared with the neutralizing titers observed in those aged 16 to 25 years 1 month post primary series dosing. Overall vaccine efficacy against symptomatic COVID-19 in children aged 6 months to 4 years was 73.2% (95% CI 43.8–87.6) [45]. Reactogenicity was mostly mild to moderate, with no grade 4 events reported. Similarly low rates of fever were reported after vaccination with BNT162b2 as for children in the above age groups treated with placebo [45]. However, six BNT162b2 recipients recorded a temperature of over 40 degrees, while only one placebo participant did [45]. Tenderness was the predominant local reaction in children aged 6 months to 2 years, while pain was the most frequent local reaction in children aged 2 to 4 years. Irritability was the most frequent systemic event among children aged 6 months to 2 years, while fatigue was the most frequent among children aged 2 to 4 years. AEs occurred at similar frequencies for BNT162b2 recipients and placebo recipients in both age groups. The dosing scheme, 3 μg, three dose schedule (second dose 3 weeks after the first dose and third dose at least 8 weeks after the second dose), was therefore considered to be safe, immunogenic, and efficacious in this age group.

2.6 Data supporting booster dosing

The safety and efficacy of a third dose of BNT162b2 was assessed in NCT04955626, a placebo-controlled, randomized, Phase 3 trial that assigned participants who had received two 30 μg doses of BNT162b2 at least 6 months earlier to be vaccinated with a third dose of BNT162b2 (n = 5,081) or placebo (N = 5,044). Local and systemic reactogenicity events from the third dose were generally of low grade, and no new safety signals were identified. Three serious AEs related to the vaccine were reported, with two participants experiencing increased hepatic enzyme levels and a third who experienced tachycardia. Vaccine efficacy was 95.3% (95% CI 89.5–98.3) [46]. The trial also assessed the safety and efficacy of a fourth dose of BNT162b2 in participants triple-vaccinated with BNT162b2 (N=305); the safety profile was similar to that of the third dose in adults aged over 55 years [47].

The safety of booster dosing of Comirnaty in participants aged 12 to 15 years and older is inferred from safety data from studies of a booster dose of Comirnaty in participants 16 years of age and older [34].

A third 10 μg dose in children aged 5 to 11 years of age boosted the magnitude and breadth of the antibody response to both the SARS-CoV-2 ancestral strain and the Omicron BA.1 and BA.4/BA.5 sub-lineages in 401 children who had previously been vaccinated with a primary two-dose series in the NCT04816643 trial. The third dose was administered at least 5 months (range 5 to 9 months) after the primary series; one month post dose 3, 98.5% of participants achieved seroresponse compared with 77.6% before dose 3.. Comparisons of neutralizing titers 1 month post doses 2 and 3 revealed that a booster dose increased neutralizing antibody activity, with a geometric mean ratio of 2.17. The third dose increased neutralizing titers against the wild-type strain 5-fold, and 12-fold for the BA.5 variant. The safety/tolerability profile was acceptable, with a similar safety profile to the primary two-dose series. AEs were reported by 9%

of participants, up to one month post dose 3, and no AEs led to withdrawal. No serious AEs or deaths were recorded, and no cases of myocarditis/pericarditis or anaphylaxis were observed. Fifteen participants (3.7%) reported lymphadenopathy, including lymph-node pain in one participant. Of these, 14 cases were considered vaccine related; most cases resolved within one week [48].

2.7 Post-marketing data

As of December 2022, over 4.3 billion doses of BNT162b2 have been distributed globally [49]. After authorization of BNT162b2, passive and active surveillance systems have been used worldwide to capture safety data from a global population, which is far more heterogenous than any clinical trial participant population.

AEs of special interest (AESIs) are pre-identified and pre-defined serious or non-serious events of scientific and medical interest that are often identified through safety surveillance systems or based on known occurrence patterns within the population. For BNT162b2, selected AESIs are closely monitored, both in clinical trials and during post-marketing safety surveillance, to evaluate whether any of the events occur in temporal relation to vaccine administration, and with a potential causal relationship to it.

An AESI initially detected in clinical trials with BNT162b2 before being observed during mass vaccination campaigns is acute peripheral facial paralysis, or Bell's palsy [50]. This event has been reported as an AE with BNT162b2 vaccination and has been included in the product information, even though a direct causal relationship has not been established [34,50-53]. Another AESI that was monitored, and consequently added to the product information, was anaphylaxis. During

post-marketing surveillance of BNT162b2, anaphylaxis was one of the first safety signals to be detected. However, despite increasing exposure, the cumulative number of cases remained small:[54] after administration of approximately 1.9 million first doses of BNT162b2, the rate of anaphylaxis was estimated to be 11.1 cases per million doses; subsequently, after administration of approximately 9.9 million doses, it was estimated to be 4.7 cases per million doses [55,56].

An elevated risk of myocarditis and pericarditis following vaccination was detected from post-marketing safety surveillance, which has also been characterized as an AESI [34]. Usually developing within 14 days of vaccination, myocarditis and pericarditis have been observed more frequently after the second dose of BNT162b2 and in young males [34]. Data suggest that the majority of cases recover; however intensive care support has been required for some cases, and fatal cases have been seen [34]. In an analysis conducted by the Vaccine Safety Datalink in the US, an estimated 3.2 excess cases per million first doses and 22.4 excess cases per million second doses of BNT162b2 were detected among males aged 18 to 39 years during the 0- to 7-day risk interval post-vaccination versus 22- to 42-days post-vaccination [57]. Safety monitoring later identified an increased risk in children aged 12 to 17 years, with no myocarditis or pericarditis signals detected in younger children (aged 5−11 years) [58]. Consequently, myocarditis and pericarditis are classified and listed as an 'Important Identified Risk' in the EU-Risk Management Plan (EU-RMP) and continue to be closely monitored. No other important potential or identified risks are currently included in the EU-RMP [59].

Real world data has also been used to inform usage of BNT162b2 in special populations. As pregnant people are not usually included in early clinical trials, data regarding vaccine use in this population is usually obtained post-authorization. In the EU, in February 2022, language on the use of the BNT162b2 during pregnancy and breast feeding was updated in the BNT162b2 label

following a review of available data, including real world evidence from early vaccination campaigns and literature [60]. For example, in a single center retrospective cohort study including 4,399 women who gave birth between January and June 2021, 913 of whom were vaccinated, prenatal maternal vaccination was shown to have no adverse effects on pregnancy course or outcome [61]. Similarly, in another study using data from a multicenter retrospective computerized database, in 713 women vaccinated twice with BNT162b2 compared with 1,063 women who were unvaccinated, vaccination was not associated with adverse maternal outcomes and led to a reduction in risk for adverse neonatal outcomes [62].

The regulators also relied on available literature references to support the introduction of a three-dose primary series regimen in immunocompromised individuals. In a trial by Kamar et al. in 101 solid organ transplant recipients (including kidney, liver, lung, heart, and pancreas recipients), a third dose of BNT162b2 significantly improved vaccine immunogenicity, with 68% of vaccine recipients seropositive 4 weeks after the third dose versus 40% prior to administration of the third dose [63]. Based on these data, updates were made to the US Emergency Use Authorization Factsheets and in the EU Product Information (approval 4 October 2021) [64].

Other AEs reported from post-marketing surveillance of BNT162b2, evaluated by health authorities and the manufacturer as signals, and consequently added to the product information due to a possible causal relationship to the vaccine, included gastrointestinal disorders (diarrhea [very common, ≥1/10], vomiting [common, ≥1/100 to <1/10]); dizziness (uncommon, ≥1/1000 to <100); extensive swelling of vaccinated limb, facial swelling, paresthesia, hypoaesthesia, and erythema multiforme (all, frequency not known) [34]. It is not recommended to report the frequency of adverse reactions based on spontaneous reporting because the number quickly

becomes outdated; instead, clinical trials where the reaction could have been observed should be reviewed and used to categorize frequency [65].

2.8 Development and approval of variant-adapted vaccines

Adapted bivalent vaccines were developed in the face of diminishing vaccine effectiveness against COVID-19 symptomatic disease; factors that lead to the decline in effectiveness include waning immunity, as well as immune evasion by Omicron variant BA.1 (alias B.1.1.529) and its descendants [66]. Adapted bivalent vaccines include: Comirnaty Original/Omicron BA.1, which contains the original BNT162b2 and an Omicron BA.1-adapted version of the vaccine; and Comirnaty Original/Omicron BA.4-5, which contains BNT162b2 and an Omicron BA.4-5-adapted version of the vaccine. Of note, BA.4-5 is so-named because the BA.4 and BA.5 Omicron subvariants share an identical S protein. The Original/Omicron BA.4-5 vaccine was rolled out for persons aged 5 years or older in the US from the 01 September 2022 as a single booster dose at least two months after primary or booster vaccination [67].

Unlike for the Original/Omicron BA.1 bivalent vaccine, no clinical data were available at the time of the initial approval for the Original/Omicron BA.4-5 bivalent vaccine. Regulatory approval in this case was therefore based on nonclinical immunogenicity data for the Original/Omicron BA.4-5 bivalent and Original/Omicron BA.1 bivalent vaccines [68]; as well as clinical safety and immunogenicity data for the Original/Omicron BA.1 bivalent vaccine and an Omicron BA.1 monovalent vaccine, which demonstrated a noninferior seroresponse against BA.1 and showed a similar safety and reactogenicity profile to BNT162b2 original [69,70]. Previous clinical and nonclinical experience across multiple BNT162-based variant-adapted vaccine

candidates was taken into consideration by the regulators in the review of the Original/Omicron BA.4-5 vaccine, in addition to the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices recommendations which evaluated the safety and effectiveness data for the monovalent mRNA COVID vaccines [69].

Clinical immunogenicity and safety data for the BA.4-5 adapted vaccine were subsequently generated in adults previously triple-vaccinated with the original BNT162b2 vaccine (NCT05472038, [71]) and submitted to the regulators as a post-approval commitment to confirm the benefit-risk profile of the Omicron-adapted bivalent vaccine.

Multiple real world evidence cohort studies have been released for the Pfizer-BioNTech Comirnaty/BNT162b2 and Moderna's mRNA-1273 COVID-19 bivalent Original/Omicron BA.4-5 vaccines that indicate that a booster is effective in preventing severe disease and death. A large cohort study monitored severe disease with Omicron BA.4.6, BA.5, BQ.1, and BQ.1.1 over 99 days when the monovalent mRNA vaccines BNT162b2 and Spikevax (previously known as COVID-19 Vaccine Moderna), INN elasomeran, were administered (n= 292,659, May – August 2022) and 99 days where the two Original/Omicron BA.4-5 bivalent vaccines were administered (n = 1,070,136, September – December 2022). Vaccine effectiveness against severe infection resulting in hospitalization or death was 24.9% for a monovalent booster and 61.8% for a bivalent booster, yielding a relative vaccine effectiveness of 36.9% [72]. Extended follow-up showed that effectiveness against severe infection resulting in hospitalization or death waned over time, from 67.4% after two weeks to 38.4% after 20 weeks [73].

A further retrospective population-based cohort study from Israel estimated the association between vaccination with a BioNTech/Pfizer bivalent vaccine and COVID-19 outcomes while adjusting for demographic factors and coexisting illnesses in all adults aged 65 years or older of

Clalit Health Services eligible for a bivalent booster vaccination. 134,215 were boosted with a BA.4/5-adapted vaccine and 435,304 not boosted. Adjusted hazard ratio (HR) for hospitalization due to COVID-19 was 0.28 (95% CI 0.19–0.40). The absolute risk reduction for hospitalizations due to COVID-19 in bivalent mRNA booster recipients versus non-recipients was 0.089% (95% CI 0.075–0.101). Adjusted HR for death due to COVID-19 was 0.32, 95% CI 0.18–0.58, p=0.0002). Vaccine effectiveness was calculated as 72% (95% CI 60–81) for hospitalization due to COVID-19 and 68% (95% CI 42–82) for death due to COVID-19. The study did not evaluate AEs and safety data [74].

Since its emergence, the SARS-CoV-2 Omicron variant has continued to evolve rapidly, demonstrating antigenic shift and drift, with significant mutational changes noted in late 2022 and resulting in a fast-changing epidemiological landscape. This evolution has given rise to the XBB variants, derived from a recombination between Omicron BA.2.75 and BA.2.10.1 [75-78]. A real world evidence study evaluating the effectiveness of bivalent vaccines – including the bivalent Original/Omicron BA.4-5 vaccine – in preventing hospitalization in adults, during circulation of XBB.1 and related sub-lineages, found that bivalent vaccines demonstrated ~60–70% vaccine effectiveness [79,80]. However, vaccine effectiveness appeared to wane 2–6 months after vaccination [79,80].

In response, vaccine manufacturers were advised by regulatory and public health authorities to revise the currently authorized COVID-19 vaccines. The WHO recommended updating COVID-19 vaccines with an XBB.1 descendant lineage antigen, such as XBB.1.5 or XBB.1.16, in a monovalent formulation [81]. This recommendation was based on the observed antigenic shift away from the original virus; the low or undetectable levels of neutralizing antibody titers induced against XBB.1 sub-lineages by antigens targeting the original virus; and the potential

impact on the magnitude of the induced immune response by multi- or bivalent vaccines versus a monovalent vaccine [81]. Concurrent guidance was subsequently issued by the European Medicines Association (EMA) and the US FDA, advocating for the use of XBB-containing vaccines, with a preference for XBB.1.5 expressed by the US FDA [82,83]

BioNTech and Pfizer have developed a monovalent XBB.1.5 variant-adapted vaccine which is supported by murine preclinical data. The monovalent XBB.1.5 vaccine demonstrated higher pan-XBB neutralizing antibody responses versus the bivalent Original/BA.4-5 vaccine in a booster setting in mice [84]. A stronger response was also noted against the recently emerged variant BA.2.86, with nonclinical immunogenicity data demonstrating a 3-fold increase in titers following vaccination with the monovalent XBB.1.5 vaccine compared with the bivalent BA.4-5 vaccine [85]. Additionally, when used as a primary series in mice, the monovalent XBB.1.5 vaccine elicited a higher neutralizing antibody response against XBB.1.5, XBB.1.16, XBB.2.3 and EG.5.1 (20- to 64-fold higher) versus those elicited by a bivalent BA.4-5 vaccine [84,85].

In 2023, a simplified dosing regimen was implemented for all BioNTech-Pfizer COVID-19 vaccines, reducing the regimen down to receipt of a single dose for adults and children aged 5 years and over, regardless of prior COVID-19 vaccination history, and in infants from 6 months to 4 years of age that have previously completed primary series or had prior COVID-19 infection [34].

Given the large amount of real world evidence available for evaluating the safety and effectiveness of BNT162b2, a systematic literature survey was not performed which is a

potential limitation of this review. This review has also not considered the circulating variants at the time of each study.

3 Conclusion

Comirnaty and the variant-adapted vaccines have shown a consistent safety and immunogenicity profile in the populations in which they are approved for use. Since then, over 4.3 billion doses of these vaccines have been distributed worldwide to treat people in 80 countries [49]. Thorough safety and vaccine efficacy surveillance via multiple networks is being conducted worldwide, facilitating the safe and effective use of BNT162b2 and the subsequent variant-adapted vaccines globally. Post-marketing surveillance has been used to assess and minimize the risk of AESIs associated with vaccine administration, such as anaphylaxis, Bell's palsy, and myocarditis and pericarditis, as well as risks associated with its administration in special populations. Based on all available safety and efficacy/effectiveness data for BNT162b2 and the variant-adapted vaccines, the benefit/risk balance remains positive when considering the severity of COVID-19 disease and its associated comorbidities and potential outcomes.

The benefit-risk balance of BNT162b2 and the variant-adapted vaccines continues to be evaluated in ongoing clinical trials and post-marketing surveillance systems.

4 Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the authors. They do not necessarily represent the official positions of any

participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

5 Acknowledgements

The development of the Comirnaty COVID-19 vaccine has been funded by BioNTech SE and Pfizer. We would like to thank the other BRAVATO members and participants (current list found at https://brightoncollaboration.us/bravato/) for their support and helpful comments. We thank all volunteers who participated in the clinical trials; all BioNTech SE and Pfizer colleagues who contributed to the development of these vaccines: Annette Vogel and Andreas Kuhn (both BioNTech SE) for review of the manuscript, and Madeleine Nowak (BioNTech SE) for editorial assistance.

5.1 Declaration of interests

The Brighton Collaboration BRAVATO authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. BioNTech authors are current employees of BioNTech, a for-profit organization, who may own stock or hold stock options. AM is an inventor on patents and/or patent applications related to RNA technology and COVID-19 vaccines.

5.2 Funding

Funding for BNT162b2 (COMIRNATY®, or Pfizer-BioNTech COVID-19 vaccine) was supported by a grant from the German Federal Ministry of Education and Research and up to €100 million in debt financing from the European Investment Bank. Writing of the manuscript

was funded by BioNTech SE. The BRAVATO Working Group is partially supported by the Coalition for Epidemic Preparedness Innovations (CEPI) under a service order entitled Safety Platform for Emergency vACcines (SPEAC) Project with the Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA.

Brighton Collaboration Standardized Template for Collection of Key Information for Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
1. Authorship	**Information**	**Comments/Concerns**
1.1 Author(s) and affiliation(s)	Shanti Pather[a], Nicola Charpentier[a], Frank van den Ouweland[a], Ruben Rizzi[a], Andrew Finlayson[a], Nadine Salisch[a], Alexander Muik[a], Claudia Lindemann[a], Ruzwana Khanim[a], Sultan Abduljawad[a], Emily R. Smith[b]*, Marc Gurwith[b], Robert T. Chen[b] [a] BioNTech SE, Mainz, Germany [b] Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA, USA	
1.2. Date completed/updated	[To be updated]	
2. Basic Vaccine information	**Information**	**Comments/Concerns**
2.1 Vaccine name	**Original vaccines** Comirnaty 30 micrograms/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty 30 micrograms/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty 10 micrograms/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty 3 micrograms/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. **Original/Omicron BA.1 vaccines** Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. **Original/Omicron BA.4-5 vaccines** Comirnaty Original/Omicron BA.4-5 (15/15 micrograms)/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34].	BNT162b2 (tozinameran) is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA template, encoding the viral spike (S) protein of SARS-CoV-2 [34]. Comirnaty Original/Omicron BA.1 (tozinameran/riltozinameran) is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1) [34]. Comirnaty Original/Omicron BA.4-5 (tozinameran/famtozinameran) is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein

	Comirnaty Original/Omicron BA.4-5 (5/5 micrograms)/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty Original/Omicron BA.4-5 (1.5/1.5 micrograms) dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. **Omicron XBB.1.5 vaccines** Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty Omicron XBB.1.5 10 microgram/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty Omicron XBB.1.5 10 micrograms/dose dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34]. Comirnaty Omicron XBB.1.5 3 microgram/dose concentrate for dispersion for injection COVID-19 mRNA Vaccine (nucleoside modified) [34].	of SARS-CoV-2 (Omicron BA.4-5) [34]. Comirnaty Omicron XBB.1.5 (raxtozinameran) is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA template, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5) [34].
2.2 Nucleic Acid Type: DNA, RNA, self-amplifying RNA	COVID-19 mRNA vaccine: Nucleoside modified messenger RNA is formulated in lipids, the combination of which forms LNPs [34].	
2.3 Adjuvant (if applicable)	The vaccine does not contain any adjuvants, however, the mRNA and the lipid components of the LNP have an adjuvant-like effect [59,86].	
2.4 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g. complexing with polymers, encapsulation within microparticles, liposomes)	Beyond the active substances, the vaccines contain [34,59]: *Excipients for Comirnaty 30 micrograms/dose concentrate for dispersion for injection (PBS-Sucrose)* - ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315) (LNP component) - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) (LNP component) - 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) (LNP component) - cholesterol (LNP component) - potassium chloride - potassium dihydrogen phosphate - sodium chloride - disodium phosphate dihydrate - sucrose	The Tris-sucrose formulation was based on the PBS-Sucrose concentrate for dispersion for injection formulation, except that the formulation buffer was changed from phosphate buffered saline to Tris buffer, without sodium chloride and potassium chloride, while maintaining the same target pH [34,59].

	- water for injections - sodium hydroxide (for pH adjustment) - hydrochloric acid (for pH adjustment) *Excipients for Comirnaty Tris-sucrose formulations for Original, Original/Omicron BA.1, Original/Omicron BA.4-5 and Omicron XBB.1.5 vaccines:* - ALC-0315 - ALC-0159 - DSPC - cholesterol - trometamol - trometamol hydrochloride - sucrose - water for injections	
2.5 Route and method of delivery (e.g. IM injection, gene gun, electroporation)	The vaccine is delivered via IM injection [34].	
3. Target Pathogen and Population	**Information**	**Comments/Concerns**
3.1 What is the target pathogen?	The target pathogen is SARS-CoV-2 which causes the coronavirus disease of 2019 (COVID-19) [34].	
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:	The clinical manifestations of COVID-19 vary widely, from asymptomatic infection (approximately 17–45%, across age groups) to severe illness and death [87-90]. The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection versus household transmission or other healthcare facilities [90]. Almost half of infections in children are asymptomatic [90].	
● In healthy people	The most common symptoms of COVID-19 are fever (42-80%), shortness of breath (35-71%), fatigue (33-56%), cough (32-77%), chills (63%), myalgias (63%), headache (59%), and diarrhea (5-33%) [91-93]. Patients with COVID-19 also commonly experience gustatory disorders (44%) and olfactory disorders (53%) [94]. Between 7 and 40% of those hospitalized with COVID-19 experience severe symptoms, necessitating intensive care [91,95,96]. Between 26 January 2020 and 27 February 2021, the CDC estimated that 75-88% of excess deaths across the US were associated with COVID-19 [97]. In the UK, the overall reported mortality among hospitalized patients with COVID-19 was between 17% and 27% [98,99]. Complications associated with COVID-19 can affect many different organs and organ systems including the heart, brain, lung, liver, kidney, and coagulation system [100,101]. In a meta-analysis including 42 studies, the risk of thromboembolism was 21% overall and 31% in the intensive care	

	unit (ICU), with the pooled odds of mortality being 74% higher among those who experienced thromboembolism versus those who did not.[102]. COVID-19 symptoms can persist weeks or months beyond the acute infection [103,104]. A meta-analysis including 31 studies of adult patients with COVID-19 found that symptoms persisted for between 14 days and 3 months after infection and included a broad range of symptoms. For example, persistent fatigue (39-73%), breathlessness (39-74%), decrease in quality of life (44-69%), reduced pulmonary function, abnormal CT findings (39-83%), evidence of myocarditis (3-26%), and changes in brain integrity with neurological symptoms (55%) [105]. Symptoms of the variant Omicron BA.1 may differ from those of prior strains [106]. Omicron was confirmed as present in all EU/EEA countries in January 2022 [107]. Notably, patients infected Omicron were significantly younger versus those infected with earlier variants, such as Alpha or Delta [108]. Evidence suggests that the risk of severe disease with BA.4 and BA.5 is comparable to earlier Omicron sub-lineages, and the risk of reinfection with these Omicron variants in individuals that have previously been infected with variants that emerged before Omicron may be higher [109-111]. During the first week that Omicron was identified in the US (December 1-8, 2021) 93% of cases reported were symptomatic, with the initial signs and symptoms including a cough (89%), fatigue (65%), nasal congestion/runny nose (59%), fever (38%), nausea/vomiting (22%), shortness of breath/difficulty breathing (16%), diarrhea (11%), and loss of taste/smell (8%)[112]. In a study comparing COVID-19 cases from the Omicron period with cases from the delta period, the prevalence of self-reported loss of taste significantly decreased during the Omicron period (26.9% versus 57.4%, $p<0.001$) [113]. Additionally, in a study conducted in France, in patients, most of whom had received at least one dose of vaccination, the majority of early Omicron cases were symptomatic (89%), reporting mild symptoms that lasted a median of 4 days [114]. Additionally, Omicron XBB.1.5 and other XBB variants are not thought to have a significant impact on disease severity [76]. In a large US-based cohort study, conducted across five hospitals, no association was found between XBB.1.5 and an increased risk of hospital admission or the need for supplemental oxygen versus other Omicron subvariants [115]. A study conducted in India, which sequenced 1,141 positive COVID-19 samples, approximately 20% of which were an XBB variant, suggested that XBB variants were causing only mild disease [116]. The post-acute sequelae of SARS-CoV-2 infection (PASC), or long-COVID, encompasses a wide range of signs and symptoms that may be persistent, worse, or new after the acute phase of the infection [117]. PASC may affect multiple organ systems, including cardiovascular, mental, metabolic, and renal [117]. In the US, as of June 2023, approximately 28% of adults that have been infected with COVID-19 are thought to experience post-COVID conditions [118].	
● In immunocompromised people	An immunocompromised condition may be associated with an increased risk for breakthrough infection, severe illness or death due to COVID-19 [119-123]. Severe illness means that a person with COVID-19 may need: require hospitalization, intensive care, or a ventilator to help them breathe [124]	

	Humoral immunity may be weaker in people who are immunocompromised, reducing their ability to produce antibodies against COVID-19 infection or vaccination [125,126]. Immune responses to vaccination against COVID-19 may differ among people with different immunocompromising conditions. For example, among people living with HIV, vaccine response may depend on CD4+ T-cell count; while in patients with chronic inflammatory disease undergoing B-cell depletion therapy, while there is a T-cell mediated immune response to the vaccine, the humoral response may be diminished [127]. Additionally, among patients with inborn errors of immunity, cellular and humoral responses to COVID-19 vaccination have been shown to differ [127].	
● In neonates, infants, children	Among symptomatic, non-hospitalized children under 18 years of age with laboratory-confirmed COVID-19, 89% experienced one or more typical symptoms of COVID, including fever, cough, shortness of breath, and 22% experienced all three [92]. People of all ages, including children, can develop serious illness from COVID-19 [128,129]. For the period January 1- March 31, 2021, across 14 states, the CDC's COVID-NET database recorded 204 adolescents aged 12 to 17 who were hospitalized for likely primarily COVID-19-related reasons [130]. In the COVID-NET database, between January and August 2023, 54% of children under 18 years that had COVID-19 associated hospitalizations had no underlying medical conditions; underlying medical conditions were more likely in children aged 5 years or older versus those under 5 years [131]. A study of 1,945,831 individuals aged 0 to 18 recorded in the Premier Healthcare Database between January and October 2020 included 20,714 pediatric cases of COVID-19; the authors reported that COVID-19 cases 12 to 18 years were more likely to develop serious illness than those aged 2 to 11 [132]. A report of hospitalizations among children aged 5 to 11 years between March 2020 and February 2022 in the COVID-NET database found that severe COVID-19 (ICU admission, invasive mechanical ventilation or death) was associated with underlying medical conditions including diabetes and obesity [133]. In a meta-analysis of 42 studies investigating the impact of comorbidities in children with COVID-19 (N=28,5004 children), the risk of severe disease was higher in children with versus without comorbidities [134]. In a study including data from the Premier Healthcare Database Special COVID-19 Release database (PHD-SR), including 2,430 children hospitalized with COVID-19, 31% of children experienced severe disease that necessitated intensive care or invasive ventilation, or resulted in death [132]. Risk factors for severe COVID-19 in hospitalized children included presence of a comorbid condition, younger age, and male sex [132]. In particular, childhood obesity has been associated with two to three times the risk of severe disease or hospitalization [135,136]. In a population-level analysis of hospitalization after COVID-19 infection, in children under 18 years in England, including data collected between February 2020 and January 2022, 10,540 children were hospitalized due to COVID-19 while 1,125,010 emergency hospitalizations were made due to other causes over the same time period; risk of hospitalization for severe disease among children was therefore low [137]. Additionally, pediatric intensive care admissions due to COVID-19 were low and declined with the emergence of newer variants (Alpha, Delta and Omicron) [137].	

	Children infected with COVID-19 are at risk of subsequent multisystem inflammatory syndrome (MIS-C) and may develop a rash following resolution of COVID-19 [138,139]. Symptoms of MIS-C can include a fever with some of the following: a rash, abdominal pain, bloodshot eyes, diarrhea, low blood pressure, vomiting, and hypotension or shock [140,141]. Patients with MIS-C may also develop myocarditis and cardiac dysfunction [140]. With the emergence of Omicron infection rates in children and hospitalization became more frequent due to greater viral transmissibility [142,143]. In the US, the mean weekly COVID-19-associated hospitalization rate for infants less than six months was higher during the Omicron BA.2/BA.5 period (13.7) than during the delta period (8.3) (RR = 1.6; 95% CI 1.4–1.8) [144]. At the start of the COVID-19 pandemic children appeared to be less susceptible to COVID-19 disease [145]. Although the clinical picture in childhood is often distinct from that in adults, in both age groups chronic underlying medical problems, immunodeficiency and virus virulence can predispose to severe disease [142-144,146,147].	
● During pregnancy and in the fetus	Pregnant women and breast feeding mothers may need to take extra precautions against COVID-19 due to increased risk for severe illness [148]. Risk factors for severe COVID-19 infection during pregnancy include advanced maternal age, high body mass index, and chronic medical conditions (such as hypertension and diabetes)[149]. In an analysis of data collected in the US between January and October 2020, among approximately 400,000 women aged 15 to 44 with symptomatic COVID-19, pregnant women were more likely to require ICU admission, invasive ventilation, extracorporeal membrane oxygenation, and die versus women who were not pregnant [150]. Furthermore, in a meta-analysis including data from 33 countries and territories, and almost 22,000 COVID-19 cases in pregnant or postpartum women, risk of severe COVID-19 or adverse pregnancy outcomes was higher in women with comorbidities including cardiovascular disease, hypertension and diabetes, compared with those without [151]. Additionally, other identified risk factors included anemia, HIV infection and being underweight prior to pregnancy [151].	
● In elderly	Risk for severe or fatal COVID-19 disease has been shown to increase with older age [152]. Immunosenescence and inflammation predispose frail and elderly people to viral infections; with regards to COVID-19, the decline in immune function due to aging can lead to the development of more severe disease and increase the likelihood of complications or death compared with younger people [153]. In a review of data from 278 papers published between July 2021 and February 2022, among patients with COVID-19, while comorbidity correlated with poorer outcome in any age group, it was particularly notable after the age of 60 [154]. Additionally, the correlation strength increased with increasing number of comorbidities [154]. Data from COVID-NET, a surveillance network in the US, collected between January and August 2023, showed approximately 60% of COVID-19 associated hospitalizations and ICU admissions, and almost 90% of in-hospital deaths associated with COVID-19 were adults aged 65 years or older [155].	

• In any other special populations	Certain medical conditions are associated with an increased risk for severe illness, including (alphabetical order): cancer, chronic kidney disease, chronic liver disease , chronic lung diseases, cystic fibrosis, dementia or other neurological condition, diabetes (type 1 or type 2), disabilities, heart conditions, HIV infection, immunocompromised condition or weakened immune system, mental health conditions, overweight and obesity, physical inactivity, pregnancy, sickle cell disease or thalassemia, smoking (current or former), solid organ or blood stem cell transplant, stroke or cerebrovascular disease, substance use disorders, and tuberculosis [156].	
3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g., incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio *(*R_0*)*, and spontaneous mutation)?	Studies from early in the pandemic demonstrated that time from onset of illness to acute respiratory distress syndrome was 8-12 days and time from onset of illness to ICU admission was 9.5–12 days [129,157-159]. A person's risk of infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation [160]. People living in long-term care facilities or high-density apartment homes or working in occupations with close proximity to others (e.g., healthcare, transportation), have a higher risk of infection [160,161]. Among children, the primary source of infection is an infected adult living in the same household [162]. For those who develop symptoms, the incubation period varies by variant and is usually between 3 and 6.5 days [163]. A meta-analysis of data gathered between January 1 and August 31, 2020 estimated the basic reproduction number at that time to be 2.69 (95% CI 2.40–2.98), and the case fatality rate to be 2.67 (95% CI 2.25–3.13) [164]. The spontaneous mutation rate of SARS-CoV-2 has been estimated as $1.3 \times 10^6 \pm 0.2 \times 10^6$ per-base per-infection cycle, with a rate five times higher for the S protein [165]. As with other respiratory infections, including influenza, respiratory syncytial virus and other coronaviruses, COVID-19 has shown seasonal patterns, with cases peaking during autumn and winter (between November and April) [166,167]. Similarly, during period, there are increases in hospitalization and death rates [166].	
3.4 What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, lactating women (breast feeding), adult, elderly)?	In a prospective cohort study conducted in New York in 2020, among hospitalized cases with COVID-19 (N=257), approximately 90% were over 40 years old, and 58% were at least 60 years old [95]. Additionally, in a multivariable analysis including data from 2491 patients hospitalized with COVID-19 in the US between March and May 2020, male sex was associated with admission to ICU and in-hospital mortality [168]. In another meta-analysis including 6,653,207 patients with COVID-19 from 88 European cohort studies published before the 12th June 2021, male gender was associated with hospital admission, the need for mechanical ventilation, and ICU mortality [169].Those at high risk of severe disease or death due to COVID-19 are a high priority for vaccination, including boosters, according to the WHO; these include the elderly, those with comorbidities, such as obesity, diabetes lung diseases, heart, liver, and kidney disease, those with moderate to severe immunocompromising conditions, and those who are pregnant [170]. Generally, the disease appears not to be severe among younger persons (age 0–24 years); a report looking at	

	COVID-19 trends in people aged 0-24 years in the US between March and December 2020 found that 2.5% were hospitalized (N=1,202,539), 0.8% admitted were to an intensive care unit (N=254,934), and <0.1% died (N=1,410,280) [171].	
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?	At the time of finalization of this article, no infection- or vaccination-elicited absolute immune correlate of protection against SARS-CoV-2 or COVID-19 (i.e., an immune marker preventing the endpoint at a certain quantifiable threshold) had been identified. This is largely due to variability in endpoint definition, differences in the analytical methods used to quantify immune markers between randomized controlled vaccine efficacy studies, and the lack of broadly applicable standard reagents and controls needed to calibrate absolute marker quantities across assays and SARS-CoV-2 variants. Randomized controlled trials and observational cohort or case/ cohort studies did however identify multiple immune markers as relative correlates of protection (i.e., markers whose magnitude is associated with higher levels of protection in all or a subset of the population) in humans [172-175]. Those exclusively comprised humoral immune mediators and included serum anti-S immunoglobulins – predominantly Immunoglobulin (Ig)G – and SARS-CoV-2 neutralizing antibody titers. Additionally, viral challenge studies in animal models and observational studies in humans identified circulating or mucosal levels of antigen-specific immunoglobulin A and circulating or tissue-resident SARS-CoV-2 antigen-specific T cells to play a supportive role in protection against infection or COVID-19 disease. The operational and analytical complexity of T-cell analyses in large-scale controlled vaccine efficacy trials largely preclude assessing the true protective role of T-cell responses to SARS-CoV-2 S or other proteins in humans, but small observational studies and animal challenge studies support their role in the clearance of SARS-CoV-2 infection and attenuation of COVID-19 disease severity [26,176,177].	
3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk	Evidence suggests the risk of severe disease with the Omicron subvariant of SARS-CoV-2 is reduced compared with the delta subvariant [178]. In a study comparing cumulative deaths in the US during the Omicron and Delta waves (December 2021 to March 2022 and July 2021 to November 2021, respectively) the case fatality ratio was approximately half with Omicron versus Delta, and, when considering unreported infections in addition to confirmed cases, it is believed to have been approximately five times lower with Omicron versus Delta [178]. Additionally, in a prospective cohort study conducted in the UK over a 10 month period, disease severity – measured by the relative risk of the need for fraction inspired oxygen, WHO outcome score, and length of hospital stay – was lower with Omicron versus Delta [179]. However, during the Omicron wave, the risk of hospitalization for children increased versus the delta wave – in South Africa, the fraction of children admitted to hospital increased two-fold with Omicron versus Delta – although this may not have indicated an increase in severe disease [178]. The constant emergence of new strains means that all figures reported here are potentially outdated.	
4. Characteristics of Vaccine Transgene and Expression	**Information**	**Comments/ Concerns**

4.1 Nature of the nucleic acid platform (**DNA** - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; **RNA-** messenger, self-replicating, other)	Nucleoside modified mRNA formulated in LNP that encodes the SARS-CoV-2 spike glycoprotein (S) stabilized in its prefusion conformation [23]. The drug substance is a single-stranded, 5'-capped mRNA produced by *in vitro* transcription from the corresponding DNA template, encoding full-length SARS-CoV-2 S protein [34].	
4.2 Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)	BNT162b2 comprises an mRNA encoding a full-length sequence of the S protein (Genbank: QHD43416.1) from SARS-CoV-2 strain *Wuhan-Hu-1* (GenBank: MN908947.3) containing the two point mutations, K986P and V987P, to ensure that the S protein remains in an antigenically optimal prefusion conformation.[23]. The bivalent vaccines, Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5, comprise two mRNAs encoding two full-length SARS-CoV-2 S proteins, containing the two prefusion stabilizing point mutations, one from the wild-type (*Wuhan-Hu-1*) strain and a second from either Omicron BA.1 (EPI_ISL_6752026) or Omicron BA.4-5 (EPI_ISL_13017830) [34]. The Comirnaty Omicron XBB.1.5 vaccine is a monovalent vaccine comprising of mRNA encoding the full-length SARS-COV-2 protein, containing the two prefusion stabilizing point mutations, from the XBB.1.5 strain (EPI_ISL_17157779) [34].	
4.3 Factors enhancing/controlling gene expression	In addition to the codon-optimized sequence encoding SARS-CoV-2 S, the RNA displays structural elements to maximize translational efficiency, including: (i) a cap1 structure at the 5'-end of the RNA drug substance [180,181]; (ii) a 5'-untranslated region (5'-UTR) derived from the human alpha-globin RNA, together with an optimized Kozak sequence [182]; (iii) a 3'-UTR derived from the AES mRNA and the mitochondrial encoded 12S ribosomal RNA [31]; and (iv) a poly(A) tail designed to enhance RNA stability and translational efficiency in dendritic cells [32]. Of note, BNT162b2 and the variant-adapted vaccines, use N1-methylpseudouridine instead of uridine to reduce cytokine induction and thus enhance translation [30,183,184].	
4.4 Non-expressed features impacting vaccine efficacy (CpG sequences, other)	The drug product contains the two functional lipids, ALC-0315 ([4-hydroxybutyl]azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) and ALC-0159 (2-([polyethylene glycol]-2000)-N,N-ditetradecylacetamide), and the two structural lipids, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and cholesterol. The mRNA contains non-coding regions that extend the mRNA half-life and increase protein expression. mRNA triggers innate pattern recognition receptors which was reduced by implementing factors mentioned in 4.3 [30] but is not fully ablated. In combination with the immune stimulation through the LNPs, this contributes to vaccine efficacy. This is further discussed in Section 5.1.	
4.5 Other sequence features that may impact safety (e.g. sequences in DNA that might facilitate insertion or recombination)	No long terminal repeats or similar were included that could trigger reverse transcription or integration into the genome. As per regulation, the vaccine is considered DNA free, and no DNA is part of the drug product.	

4.6 Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?	The vaccine provides immunity to encoded strain(s) with varying degrees of immune escape for more antigenically distant variants and provides cross-protection to strains that are antigenically similar [185-189].	
4.7 What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	Neutralizing antibody and cellular immune responses to the spike (S) antigen elicited due to the vaccine help protect against COVID-19 [44,59]. An IM dose of BNT162b2 was shown to elicit a dose-dependent antibody response with high virus-entry inhibition titers and strong T-helper-1 CD4+ and IFNγ+CD8+ T-cell responses in mice [26]. Additionally, prime-boost vaccination of rhesus macaques with BNT162b2 elicited SARS-CoV-2-neutralizing geometric mean titers 8.2–18.2× that of a panel of SARS-CoV-2-convalescent human sera. BNT162b2 vaccination protected the macaques against infection with SARS-CoV-2; in particular, it was shown to protect the lower respiratory tract against the presence of viral RNA with no evidence of disease enhancement [26]. In the BNT162-01 trial, two doses of BNT162b2 induced strong dose-dependent SARS-CoV-2 S protein-specific immune responses in healthy participants aged 18 to 85 years [23]. In a Phase 1/2 trial, BNT162b2 prime-boost vaccination elicited strong antibody responses in healthy adults (18 –55 years old); compared with trial participants that had recovered from COVID-19, SARS-CoV-2 serum 50% neutralizing titers were up to 3.3-fold higher one week after receiving dose 2 vaccination.[23] Twenty-two pseudoviruses that included spike glycoproteins from different variants were neutralized by BNT162b2-immune sera[23]. Strong IFNγ^+ or IL-2^+ $CD8^+$ and $CD4^+$ T-helper type 1 cell responses were obtained from most participants, and were detectable across the nine-week observation period after the boost. S epitopes, presented to BNT162b2-induced T cells, were identified using peptide–major histocompatilibity complex (MHC) multimer technology via frequent presentation of MHC alleles and their conservation in mutant strains. Early-differentiated effector-memory phenotype epitope-specific $CD8^+$ T cells made up 0.02-2.92% of circulating $CD8^+$ T cells one week after boost vaccination; eight weeks later they were still detectable (0.01–0.28%) [23].	
5. Delivery and Administration	**Information**	**Comments/ Concerns**
5.1 Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.4) impact the safety profile of the vaccine?	The drug products are a preservative-free, sterile dispersion of RNA formulated in LNP in aqueous cryoprotectant buffer for IM administration [190] After injection, the RNA-LNPs are taken up by the cells, and the RNA is translated to the encoded viral antigen [34]. The RNA drug substances are the only active ingredients in the drug product [190]. The lipid nanoparticle is comprised of four lipids in addition to the RNA drug substance to form an RNA-lipid complex LNP [190]. The LNP protects the RNA from nuclease degradation and also serves as the delivery vehicle to the target cells.[191] The drug products contain the two functional	

	lipids ALC-0315 ([4-hydroxybutyl]azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) and ALC-0159 (2-([polyethylene glycol]-2000)-N,Nditetradecyclacetamide) and the two structural lipids DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and cholesterol [190]. Other excipients: Sucrose as cryoprotectant as well as Tromethamine (Tris base) and Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl) as buffer components are not expected to impact safety [190]. The safety profile of the vaccine is based on the encoded antigen as well as the vaccine platform. For mRNA-based vaccines the platform appears to be a main driver of reactogenicity, as the RNA can stimulate pattern recognition receptors (PRRs) such as MDA5 [192] and therapy inducing production of proinflammatory cytokines. The LNP component of the vaccines, especially the ionizable lipid, is also contributing to such a proinflammatory response [86]. Published [14] and unpublished nonclinical data with untranslatable mRNA LNPs indicate that the innate immune response induced by mRNA vaccines is almost independent of the antigen encoded but largely depends on the mRNA LNP platform. It can therefore be assumed that a large extent of the reactogenicity of RNA vaccines is attributable to the mRNA LNP platform used.	
***** Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purposes. For example, among the safety considerations noted by WHO, FDA, and EMA for the use of DNA vaccines is integration into the recipient's chromosomal DNA with the resulting risk of insertional mutagenesis or spreading of antibiotics resistance genes. The probability of chromosomal integration increases if the introduced pDNA has been linearized, and this is the reason that regulatory authorities require the plasmid preparation intended for vaccination or gene therapy to contain a high percentage of supercoiled material (usually >80%). The percentage of supercoiled material is also used as a criterion of DNA vaccine stability at different storage temperatures.		
5.2 Describe how the mode of vaccine delivery may impact safety [*](e.g., electroporation (please specify name of device), intradermal needle injection)	Standard IM injection [34] Apart from localized reactions, such as injection site pain and haematoma, no side effects are expected based on the delivery mode.	
[*] Also consider the safety impact of multidose delivery methods, the use of multidose vaccine vials, and any special considerations for disposal.		
5.3 How might any co-administered components (e.g. adjuvants, cytokines, immunomodulatory molecules) impact the safety profile?	Not applicable.	The vaccine does not contain an adjuvant [34].
5.4 If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety	In a US-based, Phase 1/2 clinical trial, in 458 adults that had completed a COVID-19 vaccine regimen more than 12-weeks prior, booster vaccines (homologous and heterologous) were shown to be immunogenic with an acceptable safety profile [193]. Additionally, there were no new safety issues reported in five separate studies evaluating the receipt of a Comirnaty booster after primary vaccination with a different approved COVID-19 vaccine [34].	

	The overall safety profile for the Comirnaty Original/Omicron BA.1 and the Comirnaty Original/Omicron BA.4-5 booster (fourth dose) was similar to that seen after the Comirnaty booster (third dose). No new adverse reactions were identified for the bivalent vaccines and safety surveillance continues [34].	
6. Toxicology and Nonclinical	**Information**	**Comments/ Concerns**
6.1 What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?	No biodistribution studies were performed with BNT162b2. Instead, biodistribution of a comparable RNA-LNP formulation was assessed in mice using luciferase as a surrogate marker in place of the antigens encoded in the vaccines [59]. Injection of RNA led to an expression of luciferase *in vivo* in mice 6 hours post dose. Expression of the luciferase reporter was observed at the site of injection and, to a lesser extent, in the liver [59]. The distribution of a radiolabeled LNP with an identical lipid composition to BNT162b2, but with a luciferase reporter mRNA, was also investigated in blood, plasma, and selected tissues in rats after a single IM injection. The highest mean concentration of LNP was found at the injection site. Outside the injection site, low levels of LNP were detected in the liver, adrenal glands, spleen and ovaries, with the highest concentrations detected in the liver [59].	
6.2 How long does the RNA or DNA persist *in vivo* (may specify in tissue/serum, proximal/distal to site of administration)?	The COVID-19 mRNA vaccines consist of non-infectious, non-replicating RNA in a lipid-based formulation, which delivers the RNA to cells in the immunized person [23,59] Vaccine mRNA is transiently expressed and does not integrate into the recipient's genome; it is subsequently degraded in the cytosol, similar to endogenous mRNA, via physiological pathways [23,59]. RNA is degraded by cellular RNases and subject to nucleic acid metabolism [194,195]. Nucleotide metabolism occurs continuously within the cell, with the nucleoside being degraded to waste products and excreted or recycled for nucleotide synthesis [195]. The expressed protein antigens encoded by the RNA in the vaccines are proteolytically degraded, just like endogenous proteins [11]. The COVID-19 mRNA and lipids contain no known toxic degradation products [59].	Vacuolation of hepatocytes was observed in rat toxicity studies and believed to be associated with the uptake of the LNP and was without evidence of any effect on liver function. The liver vacuolation was reversed approximately 3-weeks after the last administration [49].
6.3 What is the risk of integration of sequences from the platform nucleic acid into the host genome?	mRNA enters the cytosol of the cell where it is translated into protein which is presented as antigen epitopes on the cell surface. The mRNA does not enter the nucleus (where genome is located) at any stage and does not integrate into the genome [11,196].	
6.4 What is the possible risk of autoimmunity or a harmful immune response?	The purpose of a vaccine is to cause an immune response, therefore, a historical concern in vaccinology is the possibility that vaccination may lead to autoimmunity or a harmful immune response in some individuals. There is no clear evidence that mRNA vaccines cause or contribute to worsening autoimmune diseases [197-200]. In a cohort study conducted in public healthcare service settings (579,998 individuals that received at least one dose of tozinameran) harmful autoimmune conditions were found with similar incidence to non-vaccinated individuals [201].	

6.5 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products	In GLP-compliant repeat-dose toxicity studies, BNT162b2 was administered by IM injection to Wistar Han rats once a week for three weeks and was tolerated with no evidence of systemic toxicity [49]. Expected inflammatory responses were observed including edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants and lower A:G ratios [14,49]. Injection site reactions were common in animals receiving the vaccine and were more common post-booster immunizations [14,49]. Changes as a result of inflammation included small, transient reductions in body weight and transient reduction in reticulocytes, platelets and red blood cell mass parameters [14,49]. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase for BNT162b2 with the exception of higher red cell distribution width, higher globulins, and lower A:G ratios in animals administered BNT162b2 [14,49]. Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and weight of spleen. Vaccine related microscopic findings at the end of the dosing phase consisted of edema and inflammation in injection sites and surrounding tissues, increased cellularity in the draining iliac lymph nodes, bone marrow, and spleen and hepatocyte vacuolation in the liver [14,49]. Mostly minimal periportal vacuolation of hepatocytes was not associated with any microscopic evidence of hepatic injury or alterations in liver function tests and is interpreted to reflect hepatocyte uptake of the LNP lipids [14,49,202]. Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the recovery phase for BNT162b2 [14,49]. Administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day) was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups) [36].	
6.6 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products	*In vitro*, the expression of the vaccine antigen was evaluated to confirm functionality of the RNA. *In vivo* studies were performed to provide proof of concept, i.e., to demonstrate that BNT162b2 can induce an anti-SARS-CoV-2 immune response, supporting clinical investigation in humans. A SARS-CoV-2 challenge study in BNT162b2-immunized NHPs was conducted to demonstrate lack of disease enhancement [59]. Nonclinical immunogenicity studies were performed in mice. Here, the S-specific IgG antibody response was detected at a very early time point (7 d) post-immunization. The observed induction of an antibody response in mice by a very low immunization dose (0.2 µg) with BNT162b2 indicates a high vaccine potency [26]. Additionally, pseudovirus neutralizing antibody responses were detectable 14 d post-immunization in mice immunized with intermediate doses [203].	

	In repeat-dose toxicity studies in rats, administration of BNT162b2 doses of up to 100 µg once weekly for three weeks demonstrated a safety profile in line with the anticipated immune and transient inflammatory responses [14]. Additionally, in a development and reproduction toxicity study in rats, after immunization with BNT162b2, an immune response was detected in the majority of maternal females as well as in most of their offspring (fetuses and pups) [36,49]. The variant-modified bivalent vaccines – Original/Omicron BA.1 and Original/Omicron BA.4-5 – elicited robust neutralizing antibody responses in mice, with the highest responses generally observed with variant-matched vaccines [49]. In mice that had received two prior doses of BNT162b2, given as a third dose booster, the Original/Omicron BA.4-5 variant vaccine resulted in a more balanced response against Omicron sub-lineages versus booster with the Original/Omicron BA.1 variant vaccine [49]. Data collected in mice showed that the Comirnaty Omicron XBB.1.5 vaccine has higher pan-XBB neutralizing antibody responses when administered as a booster, or as a primary series, compared with the bivalent Original/BA.4-5 vaccine in a booster setting [84,85]. One month post-booster vaccination, neutralizing antibody titers against XBB.1.5, XBB.1.16, XBB.2.3 and EG.5.1 were 4-7-fold higher with the Comirnaty Omicron XBB.1.5 compared with a bivalent BA.4-5 vaccine [84,85]. When administered as a primary series, neutralizing antibody titers against XBB.1.5, XBB.1.16, XBB.2.3 and EG.5.1 were 20-64-fold higher with the Comirnaty Omicron XBB.1.5 compared with a bivalent BA.4-5 vaccine [84,85].	
6.7 What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine-associated enhanced respiratory disease (VAERD).) or absence thereof *in vitro* or in animal models?[14]	There is no evidence for a potential association between BNT162b2; as of June 2023, vaccine-associated enhanced disease (VAED)/VAERD has been removed from the EU-RMP [49].	Based on betacoronavirus data, there is a theoretical risk of VAED occurring prior to complete administration of the vaccine regimen or in vaccinated individuals with waning immunity overtime. However, this has not been observed or identified in clinical studies or in post-authorization experience with COVID-19 vaccines [59]. In some vaccine studies conducted in animal models, and in some laboratory studies in animal cells, that were infected with SARS-CoV-1 and MERS-CoV (corona viruses related to COVID-19) immune- and cellular-response abnormalities

		have been observed, suggestive of VAED and resulting in VAED being considered a potential risk [59,204,205]. An effective vaccine against COVID-19 that produces high neutralizing titers, a Th1 predominant response with a balanced CD4/CD8 T-cell response, is expected to mitigate the risk of VAED/VAERD [205]. This immune profile is elicited by BNT162b in clinical and preclinical studies [26,206]. The clinical and post-authorization studies and pharmacovigilance activities monitored the potential risk of VAED/VAERD within the EU_RMP for BNT162b2 until mid-2023, at which point cumulative safety data review indicated no evidence for a potential association between BNT162b2 and VAED/VAERD. Therefore, with agreement of the EMA, the potential risk was removed from the EU-RMP [49].
6.8 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit- risk?	After vaccination with exogenous mRNA, innate immune cells are activated via toll-like receptors (TLRs), including TLR3, TLR7 and TLR8; an innate inflammatory response, including IFN1, is triggered when PRRs, such as MDA5 become aware of PAMPs and this subsequently leads to activation of the adaptive immune response [192,207]. Proinflammatory cytokines, including TNF-α, IFN-α, IL-6, IP-10, are produced and costimulatory molecules are induced on antigen-presenting cells, for example dendritic cells; this results in adaptive B and T-cell responses [207]. B cells express TLR7 and are activated via the MYD88/TLR7-dependent signaling pathway; this stimulates regulation of adaptive immune responses induced by mRNA vaccines and memory B-cell survival is improved [207]. TLR7 signaling also increases production of proinflammatory cytokines and antigen presentation [207]. The benefit-risk is weighted toward benefit [59].	
7. Human Efficacy and Other Important Information	**Information**	**Comments/ Concerns**

7.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	**Results from the Phase 1/2/3 Clinical Trial NCT04368728** *Healthy adults* In the Phase 1/2/3 multicenter, multinational, randomized, placebo-controlled, observer-blind, trial evaluating the vaccine candidates against COVID-19 in healthy adults (NCT04368728), the safety and efficacy data has been reported for BNT162b2 through 6 months of follow-up among participants. Participants aged 16 and over, were randomized in a 1:1 ratio to receive two doses of placebo or BNT162b2 21 days apart. The trial included 44,047 participants (BNT162b2 N=22,026; placebo N=22,021), of which 50.9% were male, 82% were White and median age at vaccination was 51 years (range 16 to 91 years) [39]. The vaccine efficacy against COVID-19 was 91.1% (95% CI 88.8–93.0) from seven days after the second dose in participants with or without previous SARS-CoV-2 infection. Against severe disease vaccine efficacy was 96.7% (95% CI 80.3–99.9). There was a gradual decline in vaccine efficacy in the 6 months of follow-up. Any AE was reported by 30.2% of BNT162b2 recipients and 13.9% placebo recipients. Any serious AE was reported by 0.6% of BNT162b2 recipients and 0.5% of placebo recipients [39]. *Adolescents* Adolescents aged 12 to 15 years (N = 2,260) and 16 to 25 years (N = 1,098) were randomized 1:1 to receive 2 doses of BNT162b2 (30 µg per dose) or placebo. The vaccine efficacy against COVID-19 was 100% (95% CI 78.1–100) from seven days after the second dose in participants aged 12 to 15 years with or without previous SARS-CoV-2 infection [43]. For participants aged 12 – 15 years any AE was reported by 0.4% of BNT162b2 recipients and 0.1% placebo recipients. Any serious AE was reported by 0.6% of BNT162b2 recipients and 0.5% of placebo recipients. For those aged 16 to 25 years, any AE was reported by 10.8% of BNT162b2 recipients and 8.0% placebo recipients. Any serious AE was reported by 0.4% of BNT162b2 recipients and 0.4% of placebo recipients. Local and systemic AEs were mild to moderate and resolved within 1-2 days [43]. The geometric mean ratio (GMR) of SARS-CoV-2 50% neutralizing titers after the second dose in participants aged 12 to 15 compared to participants aged 16 to 25 years was 1.76 (95% CI 1.47–2.10). This GMR met the noninferiority criteria of the 95% CI lower boundary > 0.67. **Results from the Phase 1/2/3 Clinical Trial NCT04816643** The Phase 1/2/3 trial evaluated the safety, tolerability, and immunogenicity of the different dose regimens of BNT162b2 in children. A two-dose schedule (21 days apart) was administered in three age groups; ages 5 to 11 years; ages 2 to 4 years; and ages 6 to 23 months[44]. *Children Aged 5 to 11 Years* In the Phase 1 trial, 48 participants received BNT162b2 10 µg, 20 µg, or 30 µg (16 children at each dose level). Participants were 50% male, 79.2% White, and mean age was 7.9±1.90. Any AE was reported by 43.8% of BNT162b2 10 µg recipients (dose 1 and 2), 31.3% of 20 µg recipients (dose 1 and 2), 50% of 30 µg recipients (dose 1 and 2), and 25.0% of 30 µg dose 1 and 10 µg dose 2	

	recipients. No serious AEs were reported during the Phase 1 trial. Most local AEs were mild to moderate and transient [44]. The 50% serum neutralizing titer seven days after dose 2 was 4,163 for 10 µg BNT162b2 recipients and 4,583 for 20 µg BNT162b2 recipients. Based on the reactogenicity profile and immunogenicity results, BNT162b2 10 µg was selected as an optimal dose of vaccine for individuals aged 5 to 11 years [44]. In the Phase 2/3 trial, participants were randomly assigned in a 2:1 ratio to receive 2 doses of BNT162b2 10 µg (N=1517) or placebo (N=751). Participants were 52.1% male, 78.9% White, and mean age at vaccination was 8.2±1.94 years. Any AE was reported by 10.9% of BNT162b2 recipients and 9.2% placebo recipients. Any serious AE was reported by 0.1% of BNT162b2 recipients and 0.1% of placebo recipients. Local and systemic AEs were generally mild to moderate and lasted for 1-2 days. GMR of SARS-CoV-2 50% neutralizing titers 1 month after second dose in participants aged 5 to 11 compared with participants aged 16 to 25 years was 1.04 (95% CI 0.93-1.18). This GMR met the noninferiority criteria of the 95% CI lower boundary > 0.67 [44]. The immunogenicity and safety of a third dose of BNT162b2 (10 µg) in individuals aged 5 to 11 years (n=401) has also been published. Participants were 52.4% male, 70.1% White and mean age at dose 1 was 7.9± 1.75. Any AE was reported by 9.0% of the participants. Any serious AE was reported by 0.5% of the participants. Most AEs were mild to moderate in severity and transient. Ancestral SARS-CoV-2 neutralizing responses 1 month after dose 3 were substantially increased compared with those 1 month after dose 2, with a GMR of 2.17. The percentage of participants achieving seroresponse was 100% at 1 month after dose 2, decreasing to 77.6% before dose 3, and increasing to 98.5% 1 month after dose 3. [48]. *Infants and Children Aged 6 Month to 4 Years* BNT162b2 3 µg was selected as an optimal dose for individuals aged 6 months to 4 years based on the reactogenicity profile and immunogenicity from the Phase 1 trial [45]. The Phase 2/3 study investigated two doses of BNT162b2 3 µg, 21 days apart, in children aged 6 months to 4 years (6 months to 23 months N=1778; 2 to 4 years N=1835). Following preliminary immunogenicity results, a third 3 µg dose at least 8 weeks after dose 2, was added to the schedule. [45]. In infants aged 6 months to 23 months: ● Any AE was reported by 30.1% who received BNT162b2 and by 27.1% of placebo recipients. ● Any serious AE was reported by 1.4% of BNT162b2 recipients and by 2.3% of placebo recipients. In infants aged 2-4 years:	

	• Any AE was reported 1 month after dose 3 by 18.7% who received BNT162b2 and 18.7% of placebo recipients. • Any serious AE was reported by 0.7% of BNT162b2 recipients and by 0.9% of placebo recipients, 1 month after dose 3. Most AEs were mild to moderate and resolved within 1-2 days. The overall vaccine efficacy against SARS-CoV-2 infection was 73.2% (95% CI 43.8–87.6) for participants aged 6 months to 4 years. The vaccine efficacy against Omicron variants infection was 71.8% (95% CI 40.5–87.1). Geometric mean ratios of neutralizing GMTs for 3 µg of BNT162b2 among children 6 months to 23 months and children 2 to 4 years of age, 1 month after dose 3, to GMTs for 30 µg of BNT162b2 among persons 16 to 25 years of age 1 month after dose 2 were 1.19 (95% CI 1.00 to 1.42) and 1.30 (95% CI, 1.13 to 1.50), respectively. These findings met the immunobridging criterion. The geometric mean fold rises from before vaccination to 1 month after dose 3 among different age groups were: for 6 months to 23 months of age, 68.4, and for 2 to 4 years of age, 73.3. These can be compared with a fold rise of 55.3 from before vaccination to 1 month after dose 2 among persons16 to 25 years of age [45]. **Results from Phase 3 clinical trial NCT04955626** In the Phase 3 trial that assessed the administration of a third dose of BNT162b2 30 µg, 10,125 healthy participants (aged 16 years or older) who had received the primary two-dose series at least 6 months earlier in the pivotal trial (NCT04368728) received either a third dose of BNT162b2 (N=5,081) or placebo (N=5,044) [46]. Any AE was reported by 25.0% of BNT162b2 recipients and by 6.5% of placebo recipients within 1 month after dose 3. Any severe AE was reported by 0.3% of BNT162b2 recipients and by 0.5% of placebo recipients within 1 month after dose 3. Local and systemic AEs were generally of low grade after the third dose of BNT162b2. The overall vaccine efficacy against COVID-19 infection from 7 days after dose 3 was 94.6 (95% CI 88.5–97.9) [46]. Phase 3 results showing the immunogenicity and safety of BNT162b2 (n=305) and BNT162b2 Original/Omicron BA.1 (n=305) in adults aged >55 years who previously received 3 doses of BNT162b2 have been published. Any AE was reported by 5.9% of BNT162b2 recipients and 6.2% of BNT162b2 Original/ Omicron BA.1 recipients within 1 month after vaccination. Any serious AE was reported by 0.7% of BNT162b2 recipients and 0.3% of BNT162b2 Original/ Omicron BA.1 recipients through data cutoff. Most AEs were mild to moderate, lasting for 1-2 days. The geometric mean fold rise (GMFR) against Omicron BA.1 strain 1 month after vaccination was 5.8 (95% CI 4.6–7.2) for BNT162b2 recipients and 9.1 (95% CI 7.3–11.2) for BNT162b2 Original/ Omicron BA.1 recipients. The GMFR against ancestral USA-WA1/2020 strain 1 month after vaccination was 4.3 (95% CI 3.7–5.0) for BNT162b2 recipients and 4.3 (95% CI 3.6–5.1) for BNT162b2 Original/ Omicron BA.1 recipients [47].	

	Phase 2/3 Clinical Trial NCT05472038 Results demonstrating neutralization activities against USA-WA1/2020 strain and Omicron sub-lineages (BA.4-5, BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1) between individuals who received a fourth dose of BNT162b2 or BNT162b2 Original/Omicron BA.4-5 are available. Participants received 3 previous doses of BNT162b2, with the mean time of 10.9±1.41 months from the last dose to the trial vaccination. Participants (n=38) had a median age of 66.5±6.82 years, 81.6% were White and 63.2% were men [71].For all subjects regardless of infection status, 1 month post dose 4 GMFR against: [71] ● Ancestral USA-WA1/2020 strain was 3.0 for BNT162b2 recipients and 5.8 for BNT162b2 Original/Omicron BA.4-5 recipients. ● BA.4-5 was 2.9 for BNT162b2 recipients and 13.0 for BNT162b2 Original/Omicron BA.4-5 recipients ● XBB.1 was 1.5 for BNT162b2 recipients and 4.8 for BNT162b2 Original/Omicron BA.4-5 recipients. [71].	
7.2 Describe other key information that may impact benefit-risk	Safety data for long-term safety of COVID-19 mRNA vaccine is being collected in ongoing Study C4591001 (active safety surveillance is 6 months after the final dose) and non-interventional studies are also ongoing [59].	
8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	**Information**	**Comments/ Concerns**
8.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately _____	More than 68,997 trial participants have been exposed to BNT162b2 in the mRNA clinical development program. *United States:* 676,728,782 doses administered; 230,637,348 completed primary series, 56,478,510 received a bivalent booster (CDC US COVID data tracker, as of May 10 2023; available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total). *EU/EEA* doses administered: 697,662,433 Comirnaty, 81,036,732 Comirnaty Omicron Bivalent and 174,720 Comirnaty Omicron XBB.1.5 as of October 5 2023.; available at: (https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab) *Canada:* 57,406,055 doses of Comirnaty administered in individuals ages 12 years and older; 3,378,882, doses of Comirnaty administered in individuals ages 5-11, 39,441 doses of Comirnaty administered in infants aged 6 months to 4 years and 5,581,404 doses of bivalent BA.4-5 as of September 10 2023: (https://health-infobase.canada.ca/covid-19/vaccine-administration/).	

8.2 Method(s) used for safety monitoring:		
● Spontaneous reports/passive surveillance	Yes	*If yes, describe method:* Post licensure the CDC and FDA conduct vaccine safety monitoring, collecting data via the Vaccine AE Reporting System (VAERS). [208] These data are publicly available online. VAERS is a passive reporting system and therefore cannot be used to determine causality between a vaccine and an AE. Safety surveillance, using other passive reporting systems and methods, is conducted in all countries where the product is licensed. Additionally, the Marketing Authorization holder collects AE reports it receives directly [209].
● Diary	Yes (e-diary)	If yes, number of days: The reactogenicity data were collected by participants' e-diary for reporting prompted local reactions and systemic events for 7 days after each dose [59].
● Other active surveillance	Yes	In clinical trials, AEs were collected up to 1 month after last vaccination and serious AEs up to six months after last vaccination [59].
8.3 What criteria were used for grading the AEs?		
● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Yes	
● If no criteria were used for grading, or if other metrics	Not applicable.	

were employed, please describe:		
8.4 List and provide frequency of any related or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):	*Clinical trial experience:* No serious AEs were reported in the dose-finding Phase 1 trials [23,37]. BNT162b2 (30 µg) was shown to be safe and well tolerated across age groups based on the C4591001 trial which included Phase 2/3 data from approximately 44,000 participants aged 16 years or older with at least six months of follow-up after dose 2 [39]. No serious safety concerns were identified based on the AE profile [210]. Severe AEs were reported by 1.2% and 0.7% in the BNT162b2 and placebo groups, respectively; 0.3% of participants in each treatment group had serious AEs that were severe [39]. Three serious AEs reported in the BNT162b2 group were assessed by the investigator as related to treatment (lymphadenopathy; shoulder injury related to vaccine administration; and ventricular arrhythmia) [39]. There were three deaths in the BNT162b2 group and five deaths in the placebo group, none of which were assessed as related to treatment [39]. *Post-authorization data:* Post-marketing safety surveillance identified an elevated risk of myocarditis and pericarditis following vaccination [34]. Usually developing within 14 days of vaccination, the incidence of myocarditis and pericarditis has been observed more frequently after the second dose of BNT162b2 and in young males [34]. An estimated 3.2 excess cases per million first doses, and 22.4 excess cases per million second doses, of BNT162b2 were detected among 18–39-year-old males during the 0–7-day risk interval post-vaccination versus 22–42 days post-vaccination [57]. Safety monitoring later identified an increased risk in male adolescents aged 12 to 17 years, with no myocarditis or pericarditis signals detected in younger children (aged 5−11 years) [58]. Based on available data, most cases recover, however intensive care support has been required for some cases, and fatal cases have been reported [34]. Frequency, as reported in the label based on clinical trials and post-authorization experience, among BNT162b2 and Comirnaty Original/Omicron BA.4-5 recipients aged 5 years and older is very rare (<1/10 000) [34]. Anaphylaxis was one of the first safety signals to be detected during post-marketing surveillance for BNT162b2. However, despite the increasing exposure, the cumulative number of cases has remained small: [34]after administration of approximately 1.9 million first doses of BNT162b2, the rate of anaphylaxis was estimated to be 11.1 cases per million doses; subsequently, after administration of approximately 9.9 million doses, it was estimated to be 4.7 cases per million doses [55,56].	
8.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:	Few participants receiving BNT162b2, or placebo, had serious AEs. Four serious AEs were related to treatment with BNT162b2; these were shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia) [20].	

• Describe the control group:	The control group received a placebo (saline) injection [20].	
8.6 List and provide frequency of AEs of Special Interest	**Myocarditis/Pericarditis:** ***Comirnaty, Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Comirnaty Omicron XBB.1.5*** There is a rare risk of myocarditis and pericarditis following BNT162b2 vaccination. These conditions can develop within a few days after vaccination and have primarily occurred within 14 days. They are most observed after the second vaccination, and in younger males. Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed [34]. Two large European pharmacoepidemiology studies have estimated the excess risk for myocarditis in young males after their second dose of BNT162b2: one study showed that, during the 7 days post second dose, there were approximately 0.265 (95% CI 0.255–0.275) extra cases of myocarditis in 12–29-year-old males per 10,000 compared with unexposed persons. In another study, during the 28 days post second dose, there were 0.56 (95% CI 0.37–0.74) extra cases of myocarditis in 16–24 year old males per 10,000 compared with unexposed persons [34]. Limited data indicate that the risk of myocarditis and pericarditis after vaccination with BNT162b2 in children aged 5 to 11 years seems lower than in ages 12 to 17 years [34,58]. Events of anaphylaxis have been reported [34].	*Myocarditis/pericarditis:* A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Nonclinical studies, protein sequence analyses and animal studies in rats and NHPs have not identified a mechanism of action (MOA) [59]. Hypotheses for MOA include an immune stimulated response (including the possibility of molecular mimicry), a general systemic inflammatory response from vaccination or a hypersensitivity response [59].
8.7 What is the evidence of disease enhancement, including ADE, VAERD (if any), in humans?		VAED for vaccines against related coronaviruses (SARS-CoV-1 and MERS) has been reported only in animal models [204,205]. To date, no enhanced disease has been observed in SARS-CoV-2 animal models with any SARS-CoV-2 vaccine platform, including RNA-based vaccines. Current data cannot fully exclude tozinameran may cause enhanced disease in vaccinated participants [59]. An effective vaccine against COVID-19 that produces high neutralizing titers and a Th1 predominant with a balanced CD4/CD8 T-cell response [205]; that immune profile is elicited by BNT162b2 in clinical and

		preclinical studies of BNT162b2 [26,206]. The clinical and post-authorization studies and pharmacovigilance activities monitored the potential risk of VAED/VAERD within the EU_RMP for BNT162b until mid-2023, at which point cumulative safety data review indicated no evidence for a potential association between BNT162 and VAED/VAERD. Therefore, with agreement of the EMA, the potential risk was removed from the EU-RMP [49].
8.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes	
• Did it identify any safety issue of concern?	No	
• If so describe	Not applicable.	
9. Overall Risk Assessment	**Information**	**Comments/ Concerns**
9.1 Please summarize key safety issues of concern identified to date, if any:	Myocarditis/pericarditis, was identified as an adverse reaction after authorization. Though very rare, there is a risk of myocarditis and pericarditis following vaccination with BNT162b2 [34]. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males [34]. Excess risk of myocarditis in young males after the second dose of BNT162b2 compared with unexposed persons has been estimated to be 0.265 (95% CI 0.255–0.275) extra cases in 12–29-year-olds per 10,000 in the 7 days after the second dose, and 0.56 (95% CI 0.37–0.74) extra cases in 16-24 year olds per 10,000 in the 28 days after the second dose [34]. Risk of myocarditis/pericarditis seems lower in children ages 5 to 11 years compared with ages 12 to 17 years. Available data suggest that most cases of myocarditis and pericarditis recover; however, some cases have required intensive care support and fatal cases have been observed [34].	

	Anaphylaxis was one of the first safety signals to be detected with BNT162b2 during post-marketing surveillance and was consequently included in the product information. However, despite increasing exposure, the cumulative number of cases has remained small [34].	
● how should they be addressed going forward	*Myocarditis/pericarditis:* Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition [34].	
9.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as: none, minimal, low, moderate, high, or unknown**
● healthy humans?	Myocarditis, pericarditis (see Section 8.6). Anaphylaxis.	Minimal.
● immunocompromised humans?	The efficacy of the vaccine may be lower in immunocompromised individuals, thus decreasing their protection from COVID-19.	Insufficient data. A trial (C4591024) to evaluate the safety, tolerability, and immunogenicity of vaccine candidate BNT162b2 in immunocompromised participants 2 years or older is ongoing [49].
● human neonates, infants, children?	The safety profile in children <6 months of age is unknown. A Phase 2/3 trial included infants and children who received a 3-dose primary course [34]: ● In infants 6 to 23 months of age (386 BNT162b2, 3 µg, 184 placebo; any primary course dose; median follow-up 1.3 months post dose 3), the most frequent adverse reactions were: irritability (> 60%), drowsiness (> 40%), decreased appetite (> 30%), tenderness at the injection site (> 20%), injection site redness and fever (> 10%). ● In children aged 2 to 4 years (606 BNT162b2, 3 µg, 280 placebo; any primary course dose; median follow-up 1.4 months post dose 3), the most frequent adverse reactions were: pain at injection site and fatigue (> 40%), injection site redness and fever (> 10%). ● In children aged 5 to 11 years (481 BNT162b2, 10 µg; 725 placebo; followed for ≥4 months post dose 2), the safety evaluation is ongoing. However, the overall safety profile is similar to that seen in participants aged 16 years or older; the most frequent adverse reactions were: injection site pain (> 80%), fatigue (> 50%), headache (> 30%), injection site redness and swelling (≥ 20%), myalgia, chills, and diarrhea (> 10%). Additionally, the safety profile with the booster was similar to that seen with the primary course.	Children: minimal (myocarditis/pericarditis, anaphylaxis). No data for human neonates available.

	Evaluation of the long-term safety follow-up of adolescents aged 12 to 15 years (786 BNT162b2, 773 placebo; followed for ≥4 months post dose 2) is ongoing. However, the safety profile is similar to that seen in participants aged 16 years and older; the most frequent adverse reactions were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%) [34].	
● pregnancy and in the fetus in humans?	Based on observational data from pregnant women vaccinated with BNT162b2 during the second and third trimester, no increase in adverse pregnancy outcomes has been observed.[34] Data on pregnancy outcomes after vaccination during the first trimester are limited, however, no increased risk for miscarriage has been seen.[34] Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development; [36] BNT162b2 can be used during pregnancy [34]. Two clinical studies of the safety and immunogenicity of the COVID-19 vaccine in pregnant women are ongoing (C4591009, and C459101511); three non-interventional studies (C4591011, C4591051 and C4591052) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the COVID-19 vaccines (including modified vaccines) are planned and another two non-interventional studies, C4591021 and C459102212 are ongoing. It is important to obtain long-term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy [49]. No data are available yet regarding the use of Comirnaty Original/Omicron BA.1 (15/15 µg), Comirnaty Original/Omicron BA.4-5 (15/15 µg) or Comirnaty Omicron XBB.1.5 (30 µg) during pregnancy and breast feeding [49].	
● elderly?	The safety profile in the elderly population is comparable with the safety profile of adults under 65 [34].	Anaphylaxis: minimal. Myocarditis/pericarditis: none.
● in any other special populations (e.g., institutionalized people, individuals with associated chronic comorbidity)?	The vaccine has not been studied in frail individuals with severe comorbidities that may have compromised immune function due to their condition or treatment of their condition. A Phase 2b, open-label trial to evaluate the safety, tolerability, and immunogenicity of BNT162b2 in immunocompromised participants aged 2 years or older is currently ongoing (C4591024) [59]. External studies have shown primary series and booster vaccination with Comirnaty and the bivalent BA.4-5 vaccine to be safe in frail populations and those with comorbidities e.g. diabetes, cancer, rheumatological disease, cardiovascular disease and autoimmunity [211-216].	Insufficient data.

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