Updated summary of risk management plan (version 8) for Comirnaty, Comirnaty Original/Omicron BA.1, and Comirnaty Original/Omicron BA.4-5 (COVID-19 mRNA vaccine)

This document is a summary of the updated risk management plan (RMP) for Comirnaty, Comirnaty Original/Omicron BA.1, and Comirnaty Original/Omicron BA.4-5. The RMP is created by the vaccine manufacturer and is submitted to medicine regulators as part of the vaccine approval and safety monitoring processes. The RMP details important risks of Comirnaty, Comirnaty Original/Omicron BA.1, and Comirnaty Original/Omicron BA.4-5, how these risks can be minimised, and how more information will be obtained about Comirnaty's risks and uncertainties (missing information).

Over time, the RMP is updated as more information becomes available, including any new risks or changes to current ones. This RMP (version 8) update was made in conjunction with the provisional approval of Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 vaccines and also includes the extension of the indication to children 6 months to 4 years of age.

The Comirnaty, Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 data sheets, consumer medicine information (CMIs) and the package leaflets give essential information for healthcare professionals and patients on how to use the vaccine.

Search for a data sheet or consumer medicine information

RMP definitions

Important risks

Important risks need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks are classified as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of the medicine.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Activities to minimise or further characterise identified risks

Measures to minimise the identified risks for medicinal products may include:

- specific information for healthcare professionals and patients, such as warnings, precautions and advice on correct use, in the data sheet, consumer medicine information and package leaflet
- important advice on the medicine’s packaging
- the authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- the medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously by the company and regularly analysed, so that immediate action can be taken by the company as necessary. These measures constitute *routine pharmacovigilance activities*.

Other non-routine Measures to further characterise the risks include safety and efficacy studies. The studies may be in particular risk groups or for particular safety concerns. They may also be a condition of the medicine's approval. These measures constitute *additional pharmacovigilance activities.*

Comirnaty, Comirnaty Original/Omicron BA.1 and Comirnaty Original/BA.4-5 RMP

The Vaccine and what it is used for

Comirnaty is a vaccine for active immunisation to prevent COVID-19 caused by SARSCoV-2 virus, in individuals 6 months of age and older (see the data sheets for the full indication).

There are 3 different strengths of Comirnaty:

- 30 mcg/dose for immunisation of individuals aged 12 years and older
- 10 mcg/dose for immunisation of individuals aged 5 to 11 years
- 3 mcg/dose for immunisation of individuals aged 6 months to 4 years

Comirnaty Original/Omicron BA.1 and *Comirnaty Original/Omicron BA.4-5* are bivalent vaccines indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19 (see the data sheets for the full indication).

- Comirnaty Original/Omicron BA.1 contains 15 mcg/dose of original Comirnaty and 15 mcg/dose of riltozinameran that target the Omicron BA.1 subvariant.
- Comirnaty Original/Omicron BA.4-5 contains 15 mcg/dose of original Comirnaty and 15 mcg/dose of famtozinameran that target the Omicron BA.4-5 subvariants.

All vaccines listed above contain nucleoside-modified messenger RNA encapsulated in lipid nanoparticles as the active substance and are given intramuscularly.

Important risks, missing information and additional pharmacovigilance activities

The tables below summarise the risks for Comirnaty, Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 as described in the updated RMP.

- Table 1 is a list of the important risks (identified and potential) and missing information.
- Tables 2 - 9 provide the evidence for linking the risk to the medicine, risk factors and risk groups, risk minimisation measures and a list of additional pharmacovigilance activities.
- Table 10 summarises the additional pharmacovigilance activities.

Table 1. List of Important Risks and Missing Information

Important identified risks	Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Table 2. Important Identified Risk: Myocarditis and Pericarditis

Evidence for linking the risk to the medicine	Events of myocarditis and pericarditis have been reported.
Risk factors and risk groups	Most frequently reported post-authorisation in adolescent and young adult male patients following the second dose of vaccine; however, reports have been received for males and females over a wide age range and following the first vaccination and booster doses also.
Risk minimisation measures	Routine: Data sheet sections 4.4. and 4.8. Additional: Letter to healthcare professionals (DHCP) and communication plan.
Additional pharmacovigilance activities*	C4591009 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 sub-study) C4591036 (former Paediatric Heart Network study)

* See Table 10 for a summary of the studies.

Table 3. Important Potential Risk: Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	VAED is considered a potential risk because it has not been seen in human studies with this or other COVID-19 vaccines being studied. It has not been seen in vaccine studies in animal models of the SARS-CoV-2 virus either. However, in selected vaccine studies in animal models as well as in some laboratory studies in animal cells infected with 2 other related coronaviruses (SARS-CoV-1 and MERS-CoV), abnormalities in immune responses or cellular responses indicative of VAED were observed. Because of this, VAED is considered a potential risk. In the past there have been other examples of particularly respiratory viruses where VAED has been observed. For example, some children who received an inactivated respiratory syncytial virus vaccine (a different type of virus), had worse signs of disease when they were subsequently infected with respiratory syncytial virus. VAED is thought to occur by several mechanisms where the immune response is not fully protective and actually either causes the body to have an inflammatory reaction due to the type of immune response with specific types of T-cells, or the body does not produce enough strong antibodies to prevent SARS-CoV-2 infection of cells or produces weak antibodies that actually bind to the virus and help it to enter cells more easily, leading to worse signs of disease.
Risk factors and risk groups	It is thought that the potential risk of VAED may be increased in individuals producing a weak antibody response or in individuals with decreasing immunity over time.
Risk minimisation measures	Routine: None Additional: None
Pharmacovigilance activities	Routine: Facilitate capture of clinical details of COVID-19 illness in previously vaccinated individuals to provide insight into potential cases of vaccine lack of effect or VAED.

	Additional pharmacovigilance activities* C4591001 C4591007 C4591009 C4591011[a] C4591012[a] C4591021 (former ACCESS/VAC4EU)

a The study addresses safety events of interest including vaccine associated enhanced disease.
* See Table 10 for a summary of the studies.

Table 4. Missing Information: Use in pregnancy and while breast feeding

Risk minimisation measures	Data sheet section 4.6
Additional pharmacovigilance activities*	C4591009 C4591010[b] C4591011[b] C4591015 C4591021 (former ACCESS/VAC4EU)[b] C4591022[b]

b Studies C4591009, C4591010, C4591011 and C4591021 and C4591022 address only 'Use in pregnancy' and not 'Breast feeding'.
* See Table 10 for a summary of the studies.

Table 5. Missing Information: Use in immunocompromised patients

Risk minimisation measures	Data sheet sections 4.4 and 5.1.
Additional pharmacovigilance activities*	BNT162-01 cohort 13 C4591010[c] C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and Immunogenicity in high-risk adults)

c The study addresses safety events of interest.
*See Table 1 for a summary of the studies.

Table 6. Missing Information: Use in frail patients with co-morbidities (e.g.chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	Data sheet section 5.1.
Additional pharmacovigilance activities*	C4591001 subset C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 10 for a summary of the studies.

Table 7. Missing Information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591011 C4501012 C4591021 (former ACCESS/VAC4EU) C4591024 (former Safety and immunogenicity in high-risk adults)

* See Table 10 for a summary of the studies.

Table 8. Missing Information: Interaction with other vaccines

Risk minimisation measures	Data sheet section 4.5
Additional pharmacovigilance activities*	C4591030 (Co-administration study with seasonal influenza vaccine)

*See Table 10 for a summary of the studies.

Table 9. Missing Information: Long term safety data

Risk minimisation measures	None
Additional pharmacovigilance activities*	C4591001 C4591007 C4591010 C4591011 C4591012 C4591021 (former ACCESS/VAC4EU) C4591038 (former C4591021 substudy) C4591036 (former PHN)

*See Table 10 for a summary of the studies.

Studies

Table 10. Summaries of the studies listed in tables 2-9

Study	Purpose of the study
C4591001	The objective of the study is to evaluate the safety, tolerability, immunogenicity and efficacy of COVID-19 mRNA vaccine. An imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of vaccine associated enhanced disease. Surveillance is planned for 2 years following Dose 2.
C4591007	To assess the safety, tolerability, immunogenicity and efficacy of of the BNT162b2 RNA-based COVID-19 vaccine candidate against COVID-19 in healthy paediatric subjects.
C4591009	To assess the occurrence of safety events of interest, including myocarditis and pericarditis, in the general US population, pregnant women, the immunocompromised and persons with a prior history of COVID-19 within selected data sources participating in the US Sentinel System (FDA's national electronic system).
C4591011	To assess whether individuals (all ages) in the US Department of Defense Military Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the COVID-19 mRNA vaccine.
C4591012	To assess whether individuals in the US Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the COVID-19 mRNA vaccine including the bivalent Omicron modified vaccine, if feasible.
C4591010	Assessment of occurrence of safety events in real-world use of COVID-19 mRNA vaccine and whether these rates elevated relative to estimated expected rates.
C4591015	To assess safety and immunogenicity in pregnant women. In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding women vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding women who received COVID-19 mRNA vaccine during pregnancy.
BNT162-01 cohort 13	To assess potentially protective immune responses in immunocompromised adults.
C4591024 (former Safety and immunogenicity in high-risk adults)	Safety, tolerability and immunogenicity based on representative medical conditions (≥18 years: NSCLC, CLL, in hemodialysis for end-stage renal disease).

C4591021 (former ACCESS/VAC4EU)	Assessment of occurrence of safety events of interest, including myocarditis or pericarditis in real-world use of COVID-19 mRNA vaccine (including the bivalent Omicron modified vaccine, if feasible). Estimating the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.
C4591038 (former C4591021 substudy)	To assess the natural history of post-vaccination myocarditis/pericarditis, including recovery status, risk factors, and/or identification of serious cardiovascular outcomes within 1 year of myocarditis/pericarditis diagnosis among individuals vaccinated with Comirnaty as well as individuals not vaccinated with a COVID-19 vaccine.
C4591022	To assess whether pregnant women receiving Comirnaty experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.
C4591036 (former Paediatric Heart Network study)	To characterise the clinical course, risk factors, long-term effects, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis after vaccination with bivalent Omicron modified vaccine, if feasible.
C4591030 (Co-administration study with seasonal influenza vaccine)	Safety and immunogenicity of BNT162b2 and quadrivalent seasonal influenza vaccine when administered separately or concomitantly.

Table 11 Other studies

C4591014	Estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.
W1235284	To estimate the effectiveness of 2 doses of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection.
W1255886	To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalisation for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of bivalent Omicron-modified vaccines following their introduction.
C4591031 substudy E	To describe the safety and tolerability profile of BNT162b2 (30 mcg or 60 mcg), BNT162b2 OMI (30 mcg or 60 mcg), and bivalent BNT162b2 and BNT162b2 OMI (30 mcg or 60 mcg) given as a fourth dose to BNT162b2 experienced participants >55 years of age. To obtain data on bivalent vaccine in participants 18 to 55 years of age.
C4591044	Study boosting strategies against variants of concern. To describe safety and tolerability and immune response to BNT162b5 bivalent and BNT162b2 bivalents given as a second booster dose to COVID-19-vaccine-experienced participants ≥12 years of age.