Date: 30 April 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

International non-proprietary name: tozinameranum (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).

Pharmaceutical form: Concentrate for dispersion for injection (sterile concentrate).

Dosage strength: 1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Route(s) of administration: Comirnaty should be administered intramuscularly

Marketing Authorisation Holder: Pfizer AG, Zurich

Marketing Authorisation No.: 68225

Decision and Decision date: approved on 19.12.2020, (temporary authorisation in accordance with Art. 9a TPA)

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BAG	Bundesamt für Gesundheit (Swiss Federal Office of Public Health)
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease caused by the SARS-CoV-2 virus
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
FIH	First in Human
GMC	Geometric mean concentration
GMT	Geometric mean titre
HCS	Human convalescent sera
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
Ig	Immunoglobulin
IMM	Immunogenicity set
IMP	Investigational medicinal product
INN	International Nonproprietary Name
LNP	Lipid nanoparticle
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Paediatric Study Plan (US-FDA)
RBD	Receptor-binding domain
RMP	Risk Management Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
WHO	World Health Organisation
µg	Microgram

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance tozinameran (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) of the medicinal product mentioned above.

Rolling authorisation procedure (FTP)
The applicant requested a rolling authorisation procedure. According to the Guidance document *"Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4",* for the exceptional case of a pandemic, and at the request of the applicant during a Presubmission Advice meeting, an authorisation application may be submitted as a "Rolling Submission". The "Rolling Submission" procedure represents a special form of a first authorisation procedure or a variation procedure.

Marketing authorisation for human medical products
The applicant requested a marketing authorisation in accordance with Art. 9a, para. 1 TPA. However, based on the submitted clinical data material and the results of the evaluation, Swissmedic granted a temporary authorisation in accordance with Art. 9a TPA and with regard to the guidance document "*Authorisation procedures for COVID-19 medicinal products during a pandemic, HMV4*".

OPEN project EMA
In the context of the EMA's OPEN project, Swissmedic has been participating in the meetings of the CHMP. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

2.2 Indication and Dosage

2.2.1 Requested Indication

Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 16 years of age and older.
The use of Comirnaty vaccine should be in accordance with official guidance.

2.2.2 Approved Indication

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older. The use of this vaccine should be in accordance with official recommendations.

2.2.3 Requested Dosage

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Individuals 16 years of age and older
Comirnaty is administered intramuscularly after dilution as a series of two doses (0.3 ml each) at greater than or equal to 21 days apart.
There are no data available on the interchangeability of Comirnaty with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Comirnaty should receive a second dose of Comirnaty to complete the vaccination series.
Individuals may not be protected until at least 7 days after their second dose of the vaccine.

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2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 October 2020
Formal control completed	16 October 2020
List of Questions (LoQ)	Rolling Lists of Questions
Answers to LoQ	Rolling Answers to List of Questions
Predecision	18 December 2020
Answers to Predecision	19 December 2020
Labelling corrections	18 December 2020
Answers to Labelling corrections:	19 December 2020
Final Decision	19 December 2020
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2. COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2. WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard) reports on the number of cases and deaths globally and per country. **As of 27 February 2021**, there have been, globally, 113,076,707 confirmed cases of COVID-19, including 2,512,272 deaths.

In Switzerland, epidemiological data on COVID-19 are collected by the Swiss Federal Office of Public Health (BAG, Bundesamt für Gesundheitswesen), Situation in Switzerland (admin.ch) and (BAG_COVID-19_Woechentliche_Lage.pdf). Cumulatively and up to February 21, 2021, there have been 550,066 confirmed cases of COVID-19 (6,391.6 per 100,000 inhabitants), 23,617 hospitalisations (274.4 per 100,000 inhabitants) and 9,204 deaths (106.9 per 100,000 inhabitants).

While hospitalisations occur in every age group, more than 80% of hospitalisations in Switzerland are in people aged 50 and over, with incidence increasing with age.

Underlying health conditions such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, chronic kidney disease, immunocompromised status, cancer and obesity are considered risk factors for the development of severe COVID-19.

Symptoms may appear 2-14 days after exposure to the virus. Symptoms may include: fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhoea. Severe COVID-19 can cause dyspnoea, pneumonia and ARDS (Acute Respiratory Distress Syndrome), thromboembolism and other conditions that may require ICU care. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular and renal sequelae and neurological complications. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

4 Quality Aspects

4.1 Drug Substance

Drug Substance

BNT162b2 (tozinameran), the active substance of Comirnaty, is a single-stranded, 5'-capped mRNA encoding S1S2, the full-length surface antigen from the SARS-CoV-2 virus. The S1S2 protein sequence includes an intrinsic signal peptide at the N-terminal end and two proline point mutations resulting in the protein in the optimised prefusion conformation. The RNA sequence contains common structural elements, such as 5'cap, 5' and 3' UTRs, poly(A) tail. Uridine in the full sequence is replaced by N-methyl pseudouridine.
The mRNA drug substance is formulated with lipid nanoparticles for the protection of mRNA after administration and to facilitate transfection into the host cells. Upon uptake, mRNA is released and translated in the cell to generate the encoded S1S2 protein antigen.

The drug substance is manufactured in a cell-free system by an *in vitro* transcription reaction using enzymatic reagents and utilising nucleotide triphosphates, a 5'-cap structure and linearised plasmid template as starting materials. The *in vitro* transcription reaction is followed by several purification and filtration steps. The purified drug substance is filled into the primary containers and frozen.
Linearised plasmid is not a structural component of the drug substance but serves as a template for the respective enzyme, thus defining the correct nucleotide sequence of the mRNA drug substance. Plasmid is produced by fermentation in established and characterised bacterial cell banks. For plasmid manufacture and control, sufficient information was provided.

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Manufacturing process changes during the process development, including new manufacturing sites, process changes and scale-up, were adequately described, and supporting data from comparability studies between commercial and clinical batches were provided. Drug substance and its impurities were sufficiently characterised using state-of-the-art analytical methods.
The process performance qualification runs were performed, and the presented control strategy, validation data and extended characterisation results demonstrated that the manufacturing process is capable of producing drug substance batches that consistently meet the requirements.

The specification tests and acceptance criteria were provided and include e.g. identity test, purity and impurity testing. Analytical methods were described, and non-compendial methods have been validated in accordance with ICH guidelines.

A shelf-life proposed for the drug substance stored at -20±5 °C in the original container was accepted.

4.2 Drug Product

Comirnaty is a white to off-white concentrate for dispersion for injection containing 225 µg/0.45 mL of mRNA embedded in lipid nanoparticles. The lipid nanoparticles consist of four lipids: cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), ALC-0315 ((4-hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) and ALC-0159 (2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide).
The drug product is supplied as a sterile, preservative-free, multidose presentation. After dilution with 1.8 mL of 0.9% sterile sodium chloride, at least 5 doses of 0.3 mL, each containing 30 µg of drug substance, can be withdrawn. The applicant demonstrated that up to 6 doses dose may be extracted when low-dead volume syringes are used.
The drug product after dilution is intended for intramuscular administration.

The drug product as concentrate is formulated in an aqueous buffer containing potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium phosphate dihydrate and sucrose. All excipients, with the exception of DSPC and the novel excipients ALC-0315 and ALC-0159, comply with the European Pharmacopoeia.

The drug product is supplied in a 2 mL glass vial (glass type I) with a bromobutyl rubber stopper and an aluminium seal with flip-off plastic cap. The primary packaging materials comply with the Ph. Eur. requirements.

The manufacturing process for the finished product consists of thawing and dilution of the drug substance, formation of lipid nanoparticles, buffer exchange, concentration and formulation, followed by sterile filtration, aseptic filling into the final containers, inspection, labelling and freezing.

A detailed description of the manufacturing process development and process characterisation studies was provided, and critical parameters were defined. The manufacturing history, including process changes and transfer to commercial facilities, was sufficiently described. Comparability of the material for emergency use and commercial supply with clinical batches has been demonstrated, based on the release testing and extended characterisation studies.
The manufacturing process validation is ongoing. The data from several GMP batches were provided prior to approval. A full process validation report, including extended characterisation and comparability studies of the drug product, will be submitted as one of the conditions of temporary authorisation.
The specification tests and acceptance criteria were provided and include a panel of analytical procedures to confirm identity, composition, purity, potency and safety. Analytical methods are described, and non-compendial methods have been validated in accordance with ICH requirements.

The drug product is stored at -90 to -60 °C in the original container. A preliminary shelf-life of 6 months has been granted based on the data available during the assessment.

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The proposed in-use shelf-life for undiluted and thawed drug product of 5 days at 2-8 °C, followed by up to 2 hours at up to 30 °C, was accepted.
Drug product after dilution with 0.9% sodium chloride can be held for up for 6 hours at 2-30 °C. From the microbiological standpoint, the diluted product should be used as soon as possible.
Exposure to light should be minimised.

The manufacturing process for the drug substance and drug product incorporates adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination.

4.3 Quality Conclusions

From the quality perspective the data presented in the application support the conclusion that the manufacture of Comirnaty is robust and sufficiently controlled to yield the product of consistent quality.

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5 Nonclinical Aspects

Pharmacodynamics / efficacy

BNT162b2 is a vaccine intended to prevent COVID-19, which is caused by SARS-CoV-2. BNT162b2 is a nucleoside modified mRNA (modRNA) expressing trimeric full-length spike (S) protein with two proline mutations (P2) to lock the transmembrane protein in an antigenically optimal prefusion conformation. The modified mRNA contains a 5'cap-structure and a poly(A) 3'-tail. The codons are humanised and uridine is replaced by N1-methyl-pseudouridine to allow efficient translation in human cells. The vaccine is formulated in lipid nanoparticles (LNPs), which are composed of 4 lipids: ALC-0315, ALC-0159, DSPC, and cholesterol. Other excipients in the formulation include sucrose, NaCl, KCL, Na_2HPO_4, and KH_2PO_4. The drug product is a preservative-free, sterile dispersion of RNA formulated in LNPs in an aqueous cryoprotectant buffer for intramuscular (IM) administration. For more details, see above (Quality Aspects).

In cell culture it was shown that, after uptake of the modRNA, the S protein is localised in the endoplasmic reticulum (ER) and on the surface of cells in the plasma membrane. Ultrastructural analyses confirmed the prefusion conformation in 20.5% of the trimeric S protein.

Animal studies were performed in mice and non-human primates (NHPs). In **mice**, the immunogenicity of BNT162b2 was evaluated after **single IM injections** of 0.2, 1 and 5 μg of lipid-formulated modRNA/animal. BNT162b2 induced a humoral immune response characterised by a balanced induction of S protein-specific IgG1 and IgG2 immunoglobulins binding to important S protein domains such as the S1 and the ACE2 receptor-binding domain. Neutralising immunoglobulins were induced in a BNT162b2-dose-dependent manner as measured by an S protein-pseudotyped VSV virus-based neutralisation assay. The balanced IgG2/IgG1 ratio pointed to a BNT162b2-mediated Th1 immune response. The Th1 immune response was further characterised by an induction of Th1-specific cytokines in splenocytes such as INFγ and IL-2, but not Th2-specific cytokines such as IL-4, IL-5 and IL-13. INFγ was secreted by CD4+ and CD8+ T-cells. In all analysed compartments of the immune system, BNT162b2 application mediated the increase and activation of Tfh cells, a T-cell type supporting B cell responses. No prime-boost regimen was applied, no old animals were tested, and no long-term immunity data were generated in mice.

An **NHP prime-boost study** with i.m. injections of 30 or 100 μg BNT162b2 on study days 0 and 21 was performed in adult animals. No old animals were studied, and no long-term study was performed to assess long-term immunity. The prime-boost regimen induced an IgG humoral response with neutralising antibody titres of similar or higher range as compared to human convalescent plasma. Three weeks after boost, there was a trend showing a reduction in the neutralising antibody titres. The available data with respect to the cell-mediated immunity point to a Th1 response as measured by a strong induction of INFγ and only a low induction of IL-4. No analysis was performed regarding the innate immune responses.

An **NHP challenge study** was performed after prime-boost vaccination with BNT162b2 and animals infected with 10^6 PFU of the SARS-CoV-2 strain USA-WA1/2020. Macaques are a model for viral infection, but not a model for virus-induced pathogenicity, as animals show no clear signs of illness after challenge SARS-CoV-2. Furthermore, the immune response of non-vaccinated animals against the challenge virus reduces the viral load by day 6. Therefore, only a short time window of 3 to 6 days can be used to show differences between vaccinated and non-vaccinated animals. After prime-boost vaccination, the viral load in bronchoalveolar lavage (BAL), nasal and oropharyngeal (OP) swabs was reduced as compared to controls. The maximum viral load in controls was determined three days after infection.

No studies with respect to **safety pharmacology** were conducted, which can be accepted based on the absence of safety signals from GLP toxicity studies.

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Pharmacokinetics

Standard pharmacokinetic studies with respect to absorption, metabolism and excretion (ADME studies) were not performed with modRNA. Detailed ADME studies are not usually required for vaccines by international agreement, and the lack of these data is acceptable due to the nature of the mRNA-LNP product.

The **metabolism** of the modRNA was not investigated. It is estimated that the mRNA is degraded within the target cells within hours to a few days. From the four lipid compounds, **ALC-0315** and **ALC-0159** were assessed. The other two lipids (distearoylphosphatidylcholine, cholesterol) are natural lipids that are metabolised in the same way as the endogenous counterparts. Following intravenous injection, plasma concentrations of ALC-0315 and ALC-0159 decreased rapidly, with an initial $T_{½}$ of 1.6 and 1.7 hours, respectively. ALC-0315 and ALC-0159 were then cleared from plasma, resulting in a terminal elimination $t_{½}$ of 139 and 72.7 hours, respectively. ALC-0315 and ALC-0159 were stable for two hours in liver microsomes, S9 fractions and after incubation for four hours with hepatocytes. When incubated for longer time points in blood, liver S9 and liver hepatocytes, ALC-0315 was hydrolysed by de-esterification. The estimated **percent of dose distributed to the liver** was ~60% for ALC-0315 and ~20% for ALC-0159. The percent of **dose excreted unchanged in faeces** was ~1% for ALC-0315 and ~50% for ALC-0159.

The **biodistribution** of lipid-mRNA particles was assessed in mice using various LNP-formulated modRNAs encoding luciferase. After IM injection, luciferase activity was monitored *in vivo* for 9 days. The highest signals were detected at the injection site and, 6 hours after injection, in the liver. The activation of the innate immune system was also determined in the same studies in mice with the mRNA-LNP encoding luciferase by measuring several chemokines/cytokines. The mRNA-LNP injection resulted in a transient induction of IL-6, MCP-1 and IP-10, indicating activation of macrophages. Following intramuscular administration of radiolabelled mRNA-LNP in rats, the highest concentration was found at the injection site. Outside the injection site, low levels of radioactivity were detected in most tissues, with the highest levels in the liver.

Toxicity

The toxicity of BNT162b2 was assessed in rats, with **three weekly IM injections** at dose levels of 30 or 100 µg and a recovery phase of three weeks. There were no vaccine-related mortalities or gross clinical signs. **Clinical findings** included slightly reduced body weights and body weight gain and elevations in body temperatures. There were no changes in food intake. There were no vaccine-related ophthalmologic or auditory alterations. None of the animals of any treatment group revealed any systemic changes in behaviour, external appearance, or consistency of faeces. **Local reactions** included thickening at injection sites, with reversible erythema and oedema development. The reactions were stronger after the second and third injections and resolved prior to the subsequent dosing. **Microscopic findings** confirmed a local inflammatory reaction associated with mixed mononuclear cell infiltration, variable fibrosis, myofibre degeneration and inflammation of the perineural tissue of the sciatic nerve, increased cellularity of germinal centres and increased plasma cells in the draining lymph nodes, increased cellularity of haematopoietic cells and germinal centres of the spleen and increased cellularity of hematopoietic cells in the bone marrow. In addition, reversible vaccine-related vacuolation of periportal hepatocytes was observed in the liver, with no evidence of liver injury. Liver enzymes (AST, ALP) were increased in vaccinated animals. **Macroscopic analyses** revealed the local injection reactions (abnormal colour, abnormal consistency) transient enlargements of draining lymph nodes associated with inflammation and enlarged spleens with increased haematopoiesis. **Haematological** observations were reversible and included a transient reduction in reticulocytes, minimal decreases in RBC, HGB, HCT, sporadic small-magnitude decreases in platelets, increases in white blood cells (neutrophils, eosinophils, basophils, monocytes and large unstained cells) and changes in acute phase markers (higher alpha-1 acid glycoprotein and alpha-2-

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macroglobulin and fibrinogen and lower albumin). In addition, a higher red cell distribution width, higher globulin levels, and a lower albumin:globulin ratio were observed.

With the exception of the microscopic injection site reaction, all findings were reversible. Administration of three once-weekly doses of BNT162b2 elicited SARS-CoV-2 neutralising antibody responses at the end of the dosing and recovery phases of the study.

No **genotoxicity** studies were performed. Based on the current scientific findings, and by international agreement, this can be accepted, as neither the mRNA nor the lipids are expected to have a genotoxic potential.

The **developmental and reproductive toxicity** (DART) was evaluated in rats by IM injection of BNT162b2 (30 μg/dose) in female rats 21 and 14 days before mating and on gestation days 9 and 20. Neutralising antibodies were measurable in female animals and in foetuses. There were no adverse effects on mating performance or fertility in F0 female rats or on embryo-foetal or postnatal survival, growth, or the development of the F1 offspring. It is not known whether the vaccine can be transferred via placental transfer or with the milk during lactation.

Nonclinical benefit risk assessment

In nonclinical studies, BNT162b2 showed humoral and cellular immune stimulation towards a Th1 response. The vaccine induces neutralising antibodies that are able to control SARS-CoV-2 amplification. Based on the pharmacokinetics, it can be assumed that most of the BNT162b2 stays locally at the injection site. Outside the injection site, low levels of radioactivity were detected in most tissues, with the highest levels in the liver. This systemic distribution might be favourable for the immune response. On the other hand, it also poses a risk with respect to the development of unpredictable adverse events. The toxicity profile is acceptable. All local effects show a reversible tendency, and systemic effects are fully reversible within three weeks after the vaccine administration. Considering the totality of data, it can be concluded that, in the light of the current pandemic, the benefit of the vaccine outweighs the risk. The BNT162b2 vaccine can be approved from the preclinical perspective.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs).

Mechanism of Action

The nucleoside-modified messenger RNA in the vaccine is formulated in lipid nanoparticles, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralising antibody and cellular immune responses to the spike (S) antigen.

Immunogenicity

Immunogenicity data are available from two studies: the phase 1 **study BNT162-01** (First in Human, FIH), conducted in Germany since April 2020, and phase 1 of the phase 1/2/3 **study C4591001**, started shortly afterwards in the USA. Both studies are still ongoing.

In both studies phase 1 was designed to choose the optimal vaccine candidate and an appropriate dose and schedule for **phase 2/3 of study C4591001**, which is the pivotal efficacy and safety study.

For both phase 1 studies, immunogenicity data are available for up to 1 month after the second dose.

STUDY BNT-162-01

Study BNT162-01 is a multi-site, dose-escalation trial, initially investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines. Healthy adults 18 to 55 years of age all received active vaccine. The protocol was later amended to allow inclusion of older adult participants up to 85 years of age. By the time Comirnaty® had received its temporary authorisation by Swissmedic, safety and immunogenicity data were available for up to 28 days after dose two in adults 18 to 55 years of age. **The study is ongoing**, and subjects will be followed for immunogenicity and safety for up to 162 days post-dose two. This will include adults aged 56 to 85 years.

The final two vaccine candidates were **BNT162b1** and **BNT162b2**, and BNT162b2 was ultimately chosen, based on the overall humoral and cellular response as well as the reactogenicity profile (see sections 6.2 and 6.4). **The results for the final vaccine candidate, BNT162b2, are presented here**.

The dose levels tested for BNT162b2 were as follows: 1 µg, 3 µg, 10 µg, 20 µg, 30 µg (at the time of interim study report preparation, data for the dose levels of 50 µg and 60 µg were not available). Dosage frequency: Two injections about 21 days apart.

12 subjects were planned for each dose level.

The humoral immune response in healthy adults after dose 1 only or after both doses 1 and 2 was tested primarily by looking at functional antibody responses, fold increase in functional antibody GMTs, and the number of participants with seroconversion, defined as a minimum of a 4-fold increase in functional antibody GMTs compared to baseline.

The cell-mediated immunity (CMI) responses (induced SARS-CoV-2 specific CD4+ and CD8+ T-cell responses, functionality and polarisation of IMP-induced SARS-CoV-2 specific T-cells as assessed by ICS) were also tested.

Key humoral and cellular immunity results are summarised below.

Humoral Immunity

Fold increase from baseline in functional 50% SARS-CoV-2 neutralising antibody titres (VN_{50}) – IMM

IMM = Immunogenicity set; VN50 = 50% SARS-CoV-2 neutralising antibody titres

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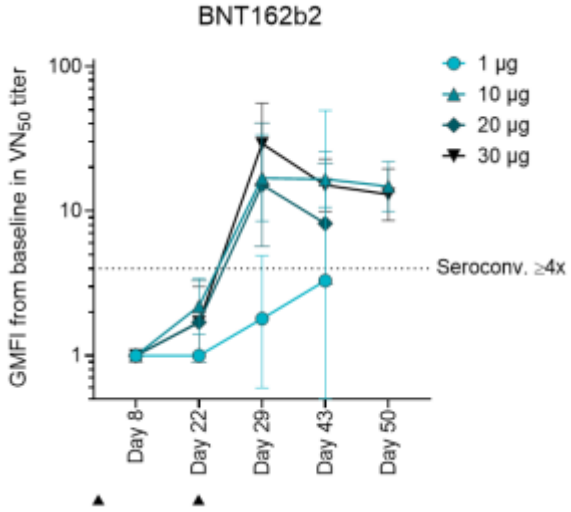
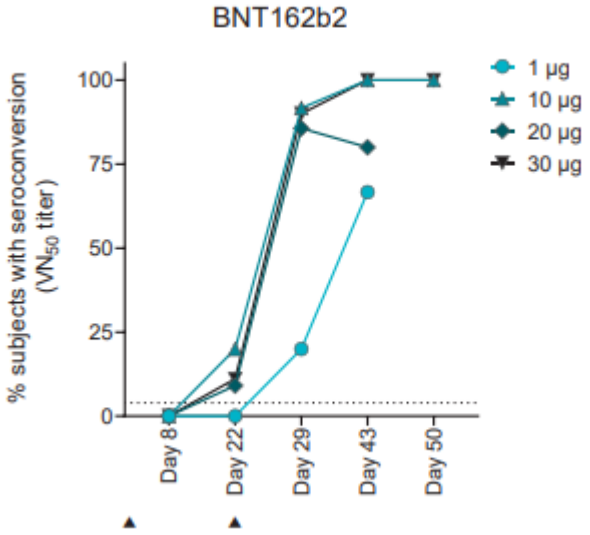


Geometric means fold increase (GMFI) from baseline in VN50 titre with 95% confidence intervals are shown for BNT162b2 dose levels. Arrowheads indicate baseline (dose 1, Day 1) and dose 2 (Day 22). The dotted horizontal line represents the threshold for seroconversion (fold increase ≥4).

One can see that on Day 29 (= 7 days after the second dose of BNT162b2), virus neutralising GMTs were highest for the 30 µg dose level, although by day 43 they had diminished somewhat and were similar to the 10 µg level.

Day 43 virus neutralising GMTs were 0.3-fold (1 µg dose) to 1.7-fold (30 µg dose) those of a COVID-19 human convalescent sera (HCS) panel comprised of 38 human COVID-19 HCS. This panel included individuals aged 18 to 83 years, at least 14 days after confirmed diagnosis (symptomatic disease for 35 of the 38 sera obtained at a time when the individuals were asymptomatic). This confirmed that the 30 µg dose of BNT162b2 induces virus neutralising GMTs which are, on average, higher than those induced by a natural infection.

Frequency of subjects with SARS-CoV-2 GMT seroconversion: BNT162b2 IMM
Seroconversion is defined as a minimum of 4-fold increase in functional antibody response compared to baseline. The frequency of younger adults aged 18 to 55 years with seroconversion is displayed below:



GMT = geometric mean titre; IMM = Immunogenicity set.
Note: At the cut-off date for this report, only limited data for the 20 µg dose level were available (7 sera evaluable for Day 29, 4 sera evaluable for Day 43).

In summary, at least for the 10 µg and 30 µg doses, participants vaccinated with two doses of BNT162b2 showed both neutralising antibody titres that were higher than human convalescent sera *and* at least a 4-fold increase in functional antibody response compared to baseline. In the absence of known correlates of protection against SARS-CoV-2, this was deemed acceptable by both the company and by Swissmedic.

Cellular Immunity

SARS-CoV-2-specific CD4+ and CD8+ T-cell responses
Evaluable CD4+ and CD8+ T-cell response data (ELISpot data) were available from 39 participants dosed with 1, 3, 10, 20, or 30 µg BNT162b2.

BNT162b2 induced strong SARS-CoV-2 S protein-specific CD4+ and CD8+ T-cell responses in all, or almost all, the dosed participants (39 of 39 [100%] and 35 of 39 [89.7%]), respectively. These T-cell responses were directed against different parts of the antigen, including epitopes in the RBD, indicating the induction of multi-epitopic responses by BNT162b2.

Dosing twice with BNT162b2 led to a substantial increase in incidence and magnitude of T-cell responses, especially for dose levels of 10 µg or higher.

Functional and pro-inflammatory CD4+/CD8+ T-cell responses, including Th1 (IFNγ and IL-2) and Th2 (IL-4) cytokine profile of T-cells specific to S or RBD of SARS-CoV-2 were assessed by ICS. De novo induction of SARS-CoV-2 S or RBD protein directed T-cells was confirmed. INFγ-producing CD4 and CD8 T-cells against SARS-CoV-2 S or RBD were not detected at baseline in participants and were induced robustly by BNT162b2. No clear dose dependency was observed.

The results confirm that the Th1 response is greater than the Th2 response. Th1 / Th2 > 1 is desired, because a Th2 response may be associated with vaccine-associated enhanced respiratory disease.

The data presented in this first-in-human study were obtained from healthy younger adults (aged between 18 and 55 years). Adults aged between 56 and 85 years of age have already been enrolled in the study, but the results will be reported at a later date, in any case before a full marketing authorisation is granted. Follow-up data up to six months will be available for both age groups.

PHASE 1/2/3 STUDY C4591001
Study C4591001 is a Phase 1/2/3, Placebo-Controlled, Randomised, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine.

This study is also ongoing.
Subject First Visit: 29 April 2020
Data Cut-off dates:
• 24 August 2020 (Phase 1 safety and immunogenicity data through 1 month after Dose 2)
• 02 September 2020 (Phase 2 safety data 7 days after Dose 2 only)
• 06 October 2020 (Phase 2/3 safety data 1 month after Dose 2 for the first 6610 participants, and available safety data for all 36,855 participants)
• 04 November 2020 (Phase 2/3 first interim analysis for efficacy at 94 cases)
• 14 November 2020 (Phase 2/3 final analysis for efficacy at 178 cases, safety data 1 month after Dose 2 for 37,586 participants with a median of at least 2 months of follow-up, and available safety data for all 43,252 participants).

Study C4591001 was started as a Phase 1/2 study in adults in the US, and was subsequently expanded into a global Phase 2/3 study. 44,822 subjects were enrolled, and 43,386 subjects were

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randomised at 153 centres in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).

The study was also later amended to include older adolescents 16 to 17 years of age, then later amended to include younger adolescents 12 to 15 years of age. For the current, temporary authorisation, only participants 16 and over were considered in the interim and final (primary efficacy endpoint) interim analyses.

A last protocol amendment, dated 01 December 2020, was submitted by the company around the time that Swissmedic granted a temporary authorisation for Comirnaty®. The reason for the amendment was that, after emergency and/or temporary authorisations were granted in countries with study centres, it would no longer be feasible to keep all participants in the study. The amendment added the possibility of administering BNT162b2 to participants who originally received placebo, following completion of an active blinded safety surveillance period of maximum 6 months after dose two.

A final study report from study C4591001 is planned for 2023.

Phase 1 Immunogenicity Endpoints
In Phase 1, two age groups were studied separately, younger participants (18 to 55 years of age) and older participants (65 to 85 years of age). The study population included healthy male and female participants. The immunogenicity objectives were to describe the immune response in healthy adults after dose 1 only or after both doses 1 and 2 (two injections about 21 days apart). The doses tested were 10, 20 and 30 micrograms for both age groups.

For each dose group of 12 participants receiving one of the two vaccine candidates, three additional participants received a placebo vaccine (randomisation ratio of 4:1). The placebo consisted of normal saline.

Humoral immunogenicity was assessed at Day 1 (before Dose 1) and 7 days after Dose 1, at Day 21 (before Dose 2) and 7 days, 14 days, and 1 month after Dose 2. Data were summarised for each dose level and age group.

BNT162b2 SARS-CoV-2 Neutralising Titres
In the younger age group, SARS-CoV-2 50% neutralising GMTs increased by Day 21 after Dose 1 and were substantially increased 7 days after Dose 2 (Day 28) of BNT162b2.
Similar trends were generally observed in the older age group, with higher GMTs observed in the 30 µg dose groups compared to the 20 µg and 10 µg dose groups. In the older age group, SARS-CoV-2 50% neutralising GMTs were generally lower than the GMTs in the younger age group.

Phase 2 Immunogenicity Endpoints

The phase 2 part of the study was comprised of the first 360 participants enrolled (1:1 randomisation between BNT162b2 and placebo, stratified by age groups [18 to 55 years and >55 to 85 years] with approximately 50% in each age stratum), and was designed to assess safety data through 7 days after dose 2 and immunogenicity data through 1 month after dose 2. In Phase 2, immunogenicity was assessed at Day 1 (before dose 1) and 1 month after dose 2.

Immunogenicity results from the 360 participants in Phase 2 of the study demonstrated that BNT162b2 at 30 µg elicited SARS-CoV-2 neutralisation and S1-binding IgG antibody responses at 1 month after dose 2 similar to those previously observed in phase 1 of the study. Notably, SARS-CoV-2 neutralising titres were higher in the younger age cohort compared with the older age cohort.

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S1-binding GMCs were generally also higher in the younger age cohort compared to the older age cohort, again concordant with observations in the Phase 1 portion of the study.

Phase 3 Immunogenicity Endpoints

In the **phase 3** part of the study, **immunogenicity is a secondary** (12 to 15-year-olds compared with 16 to 25-year-olds) and **exploratory** endpoint. These data will be reported by the company at a later date and were not included in the interim study report.
Further evaluation of immunogenicity is scheduled for months 6, 12 and 24 following dose 2.
The exploratory immunogenicity assessments are therefore planned at time points up to 24 months.

One of the planned exploratory endpoints includes the description of the serological responses to the BNT vaccine candidate in cases of:
 Confirmed COVID-19
 Confirmed severe COVID-19
 SARS-CoV-2 infection without confirmed COVID-19
This might help in the determination of correlates of protection.

Immune responses induced by the vaccine against emerging circulating strains of SARS-CoV-2 will also be investigated. Effectiveness studies included in the RMP will be important to understand the performance of the vaccine in case of e.g. mutating variants.

Efficient neutralisation of spike protein mutants including RBD sequence variants was observed with sera from vaccine-immunised study BNT162-01 participants, demonstrating the neutralisation breadth of vaccine-elicited polyclonal antibodies. It may be important to consider this aspect when facing emerging variants with mutations in the spike proteins, e.g. the UK variant, as the vaccine might still be able to confer sufficient cross-neutralisation.

6.2 Dose Finding and Dose Recommendation

The choice and dose of vaccine candidate were based on the results of the two clinical phase 1 trials presented above (study BNT-162-01 and phase 1 of study C4591001) and took into account safety, tolerability, and immunogenicity. For safety data see section 6.4 below.

Choice of Vaccine Candidate
The neutralising antibody responses between the two vaccine candidates were considered similar. For both BNT162b1 and BNT162b2, the S1- and RBD-binding IgG kinetics were comparable with the kinetics of neutralising antibodies, with lower IgG concentrations in the older age group than in the younger age group.

For the 30 µg dose cohort vaccinated with BNT162b2, however, CD4 and CD8 cytokine responses showed the same intensity in adults and older adults, whereas for the 30 µg dose cohort vaccinated with BNT162b1, RBD-specific IL-2-producing CD4+ and CD8+ T cells were reduced in older adults.

Also in older adults, the vaccine candidate **BNT162b2** had a reactogenicity profile in clinical trials that seemed more favourable than that observed with BNT162b1 (see section 6.4).

Thus, **BNT162b2** was eventually chosen over BNT162b1 to proceed to the phase 2 and 3 parts of study C4591001 as it provided the optimum combination of a favourable reactogenicity profile and a robust immune response likely to afford protection against COVID-19 in younger and older adults.

Benefits of Second Dose
The immune responses in terms of neutralising antibody responses clearly demonstrated that two doses resulted in increased geometric mean titres (GMTs) compared to responses after only the first

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dose. Thus, in the absence of a serological correlate of protection, these data supported the need for two doses in adults. The responses to the vaccines were higher compared to a pool of human convalescent sera in study BNT162-001.

Choice of the 30 µg Dose Level
The S1- and RBD-binding IgG kinetics were comparable with the kinetics of neutralising antibodies, with lower IgG concentrations in the older age group than in the younger age group.
The responses were numerically higher in higher dose groups compared to lower doses but did not substantially differ between 10 ug and 30 ug. However, S1-IgG antibody-binding concentrations after BNT162b2 favoured the selection of the 30 µg dose level. When selecting the dose level for Phase 2/3, the major driver was the need to maximise SARS-CoV-2 neutralising antibody responses in the older age group, who are at the highest risk of severe disease.

6.3 Efficacy

Pivotal Study C4591001: Phase 2/3 of the 1/2/3 Study
The phase 2/3 evaluation part of pivotal **Study C4591001 phases 1/2/3** started on 27 July 2020, using BNT162b2 at the 30 µg dose level. The 360 phase 2 participants are included in the efficacy evaluation of the phase 2/3 study.

Phases 2 and 3 of study C4591001 constituted the pivotal efficacy and safety study. It was a placebo-controlled, randomised, observer-blind[1], event-based study. Two interim efficacy analyses were carried out once a certain number of symptomatic and PCR positive COVID-19 cases had occurred in the study (event-based study).

First Interim Analysis for Efficacy
The first interim analysis was based on 94 total cases of COVID-19 occurring at least seven days after the second dose. The cut-off date was 04 November 2020.

This first interim analysis met the minimal statistical analysis plan requirements for vaccine efficacy, and, with the final interim analysis (see below), the minimal median safety follow-up of two months following the second dose was also met.

Among participants included in the evaluable efficacy population, 32,279 participants (16,061 in the BNT162b2 group and 16,218 in the placebo group) did not have evidence of infection with SARS-CoV-2 through 7 days after the second dose. From that point in time onward, 4 COVID-19 cases were reported in the BNT162b2 group compared to 90 COVID-19 cases reported in the placebo group. These data give an estimated vaccine efficacy of 95.5% for BNT162b2.

Final Interim Analysis for Efficacy
On 09 December 2020, the company submitted a final interim efficacy report dated 03 December 2020, with a data cut-off date of 14 November 2020. This “Final Analysis Interim Report” was based on 178 cases of COVID-19 (169 in the placebo group and 9 in the vaccine group) occurring at least 7 days after the second dose.

44,822 subjects had been enrolled and 43,386 subjects had been randomised at 153 centres, in 6 countries worldwide, including: United States (131 centres, 33,068 subjects), Argentina (1 site, 5,776 subjects), Brazil (2 sites, 2,900 subjects), Turkey (9 sites, 342 subjects), South Africa (4 sites, 800 subjects) and Germany (6 sites, 500 subjects).The **evaluable efficacy population** included all eligible randomised participants who received all vaccinations as randomised, with Dose 2 received

[1] The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff are blinded. At the study site, only the dispensers/administrators are unblinded

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within the predefined window of 19-42 days after dose 1, and who had no other important protocol deviations as determined by the clinician on or before 7 days after dose 2. This was **the primary analysis population for all efficacy analyses.** Additional analyses based on the **all-available efficacy populations**, including all randomised participants who completed one and two vaccination doses respectively, were also performed.

There were two parts to the primary efficacy endpoint:

- **First primary efficacy endpoint**: To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination.
- **Second primary efficacy endpoint:** To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of SARS-CoV-2 infection before vaccination.

First primary efficacy endpoint:

The first primary efficacy endpoint included 18,198 vaccine group and 18,325 placebo group subjects. In the **first primary analysis**, the efficacy of COVID-19 mRNA vaccine from 7 days after Dose 2 was measured in participants without evidence of prior infection with SARS-CoV-2. The results showed a 95.0% (95% confidence interval of 90.0% to 97.9%) vaccine efficacy in participants 16 years of age and older.

Demographics table (population for the first primary efficacy endpoint)[a]

a. All eligible randomised participants who receive all vaccinations as randomised within the predefined window, have no other important protocol deviations as determined by the clinician, and have no evidence of SARS-CoV-2 infection prior to 7 days after Dose 2.
b. Includes multiracial and not reported.
c. Number of participants who have 1 or more comorbidities that increase the risk of severe COVID-19 disease
– Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
– Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
– Obesity (body mass index ≥ 30 kg/m2)
– Diabetes (Type 1, Type 2 or gestational)
– Liver disease
– Human Immunodeficiency Virus (HIV) infection (not included in the efficacy evaluation)

As can be seen from this demographics table, extremely few persons over 85 years of age were included in the study (five individuals only were vaccinated and five received placebo), and only 4.4% of the study population was between 75 and 85 years of age. This explains the very large confidence intervals around the efficacy results and therefore the uncertainty of the results in persons over 75 years of age (see table below).

Vaccine efficacy table – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population:

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First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection*			
Subgroup	**COVID-19 mRNA Vaccine N[a] = 18,198 Cases** n1[b] Surveillance time[c] (n2[d])	**Placebo N[a] = 18,325 Cases** n1[b] Surveillance time[c] (n2[d])	**Vaccine efficacy** % (95% CI)[f]
All subjects[e]	8 2.214 (17,411)	162 2.222 (17,511)	95.0 (90.0, 97.9)
16 to 64 years	7 1.706 (13,549)	143 1.710 (13,618)	95.1 (89.6, 98.1)
65 years and older	1 0.508 (3848)	19 0.511 (3880)	94.7 (66.7, 99.9)
65 to 74 years	1 0.406 (3074)	14 0.406 (3095)	92.9 (53.1, 99.8)
75 years and older	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea or vomiting.]
* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. No confirmed cases were identified in participants 12 to 15 years of age.
f. Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Second primary efficacy endpoint:

In the **second primary analysis**, efficacy of COVID-19 mRNA Vaccine from 7 days after Dose 2 was measured in participants with or without evidence of prior infection with SARS-CoV-2. The results showed a 94.6% (95% confidence interval of 89.9% to 97.3%) vaccine efficacy in participants 16 years of age and older.

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Efficacy Endpoint Subgroup	Vaccine Group (as Randomized) BNT162b2 (30 µg) (N[a]=19965) n1[b]	Surveillance Time[c] (n2[d])	Placebo (N[a]=20172) n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence from 7 days after Dose 2						
Overall	9	2.332 (18559)	169	2.345 (18708)	94.6	(89.6, 97.6)
Age group (years)						
16 to 55	6	1.309 (10653)	120	1.317 (10738)	95.0	(88.7, 98.2)
>55	3	1.022 (7892)	49	1.028 (7956)	93.8	(80.9, 98.8)
≥65	1	0.530 (4044)	19	0.532 (4067)	94.7	(66.8, 99.9)
Sex						
Male	4	1.183 (9457)	85	1.170 (9342)	95.3	(87.6, 98.8)
Female	5	1.149 (9102)	84	1.176 (9366)	93.9	(85.2, 98.1)
Race						
White	7	1.975 (15294)	153	1.990 (15473)	95.4	(90.3, 98.2)
Black or African American	0	0.187 (1758)	7	0.188 (1758)	100.0	(30.4, 100.0)
All others[f]	2	0.170 (1507)	9	0.167 (1477)	78.2	(-5.4, 97.7)
Ethnicity						
Hispanic/Latino	3	0.637 (5074)	55	0.638 (5090)	94.5	(83.2, 98.9)
Non-Hispanic/non-Latino	6	1.681 (13380)	114	1.693 (13509)	94.7	(88.1, 98.1)
Country						
Argentina	1	0.366 (2664)	36	0.367 (2684)	97.2	(83.5, 99.9)
Brazil	2	0.134 (1274)	8	0.132 (1257)	75.4	(-23.5, 97.5)
USA	6	1.816 (14141)	124	1.830 (14287)	95.1	(89.1, 98.2)
South Africa	0	0.015 (362)	1	0.015 (363)	100.0	(-3818.9, 100.0)
Prior SARS-CoV-2 Status						
Positive at baseline[g]	1	0.056 (526)	1	0.060 (567)	-7.1	(-8309.9, 98.6)
Negative at baseline but positive prior to 7 days after Dose 2[h]	0	0.003 (27)	1	0.004 (34)	100.0	(-6004.9, 100.0)
Negative prior to 7 days after Dose 2[i]	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.0, 97.9)
Unknown	0	0.059 (595)	5	0.060 (596)	100.0	(-9.6, 100.0)

Secondary endpoints

One of the most important secondary endpoints was the **prevention of severe COVID-19 cases**.

Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

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Efficacy Endpoint	Vaccine Group (as Randomized) BNT162b2 (30 µg) (N[a]=18198) n1[b]	Surveillance Time[c] (n2[d])	Placebo (N[a]=18325) n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.

As the number of cases was very low, only numerical trends can be seen. As defined in the protocol (**cases occurring after day 7 following dose two**), a secondary endpoint, there were 3 cases in the placebo group and 1 case in the vaccine group. This corresponds to a 66.4% vaccine efficacy (95% confidence interval of -124.8; 96.3). The power of the study did not allow for a statistically significant result.

Counting **all** severe COVID-19 cases occurring after dose 1 (thus including the 4 cases mentioned in the previous paragraph), there was a total of one case in the vaccine group and 9 cases in the placebo group.

All confirmed cases of COVID-19 after dose 1

An analysis of the cases occurring from dose 1 and until dose 2 or 1 week after dose 2 provides information on the onset of protection.

The table below lists all reports of COVID-19 with onset at any time after Dose 1 (all participants in the all-available efficacy population, regardless of evidence of infection before or during the vaccination regimen).

Among these participants, 50 cases of COVID-19 occurred after Dose 1 in the BNT162b2 group compared to 275 cases in the placebo group. Notably, in the BNT162b2 group, most cases occurred before Dose 2.

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Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All- Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
≥10 days after Dose 1 to before Dose 2	6		45		86.7	(68.6, 95.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).

The table above shows that the first dose offers partial protection, especially starting 14 days after dose one. However, maximum protection only occurs after 7 days have elapsed following dose 2. Since maximum immunogenicity is seen after dose two, the duration of the immunogenicity observed after dose one may be shorter than that observed after dose two. It is also important to note that, even though the efficacy analyses included participants who received their second vaccination within 19 to 42 days after their first vaccination, the majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after the first dose.

Duration of follow-up
The primary analysis of efficacy was conducted when the pre-defined number of 164 COVID-19 cases had occurred. This corresponds to about 1.5 months of median follow-up time after completion of the full vaccination regimen. Therefore, available efficacy data are limited in terms of follow-up duration, and the efficacy of the vaccine over longer periods remains unknown. Data are expected to become available post-authorisation.

6.4 Safety

Overall Safety Database

For safety, the median follow-up time was two months after dose two (phase 2/3 of study C4591001).

At the cut-off date of 14 November 2020, the longest follow-up time available was 12-13 weeks after Dose 2 (N=780: N=382 BNT162b2 and N=398 placebo).

Overall, study C4591001 enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of the duration of follow-up.

The safety database consisted of:

- Study BNT162-01 (N=60 any dose of BNT162b2; N=12 BNT162b2 30 µg; placebo N=0).

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- Phase 1 of study C4591001 (N=72 any dose of BNT162b2; N=12 BNT162b2 30 µg; placebo N=18).
- Phase 2/3 participants with a follow-up ≥ 2 months after Dose 2 (N=19,037) of either BNT162b2 (N=9531) or placebo (N=9536).
- All enrolled Phase 2/3 participants (N=43,448) that received at least one dose of BNT162b2 (N=21,720) or placebo (N=21,728), regardless of the duration of follow-up.
- Phase 2/3 participants (N=37,706) randomised before 9 October 2020 who received BNT162b2 (N=18,860) or placebo (N=18,846). These subjects had a median follow-up time of 2 months after Dose 2 (at least 1 month after dose 2). Of these, 1,148 subjects had a positive SARS-CoV-2 baseline status (vaccinated N=558; placebo N=590).

Reactogenicity was evaluated based on a subset of subjects in the Phase 2/3 study, i.e. 8,183 (N=4,093 BNT162b2; N=4,090 placebo), who reported on local reactions, systemic events, and antipyretic/pain medication usage for 7 days after each dose in an e-diary.

Adverse Events

The adverse event (AE) profile did not suggest any serious safety concerns. The incidence of serious adverse events (SAEs) and deaths occurring during the study were low and similar between the two groups. There were two deaths in the BNT162b2 group and four in the placebo group, none due to COVID-19 or to the study intervention. The incidence of discontinuations due to AEs was similar between the BNT162b2 and the placebo groups.

At the time of the analysis of Study C4591001, a total of 19,067 (9,531 Comirnaty and 9,536 placebo) participants 16 years of age or older were evaluated for safety for at least 2 months after the second dose of Comirnaty. This included a total of 10,727 (5,350 Comirnaty and 5,377 placebo) participants 16 to 55 years of age and a total of 8,340 (4,181 Comirnaty and 4,159 placebo) participants 56 years and older.

The most frequent adverse reactions were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%). Other reactogenicity events included pain in extremity, injection site redness, malaise, injection site pruritus, lymphadenopathy, insomnia, and nausea. All reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. The frequencies of headache, fatigue and fever were higher after Dose 2 in both age groups.

Four participants in the vaccine group (frequency category “Rare” (≥ 1/10,000 to < 1/1,000) reported an event of acute peripheral facial paralysis (or palsy). Onset was Day 37 after Dose 1 and Days 3, 9, and 48 after Dose 2. No cases of acute peripheral facial paralysis (or palsy) were reported in the placebo group.

Cases of hypersensitivity and anaphylaxis have been identified post-marketing. A waiting time post-vaccination of at least 15 minutes has been established in each vaccination centre.

There were no clinically meaningful differences by age group, baseline SARS-CoV-2 status, ethnicity, race, or sex.

Laboratory Results

Laboratory results are available for the two Phase 1 studies. Except for a minor transient decrease in the lymphocyte count observed for some of the subjects, no abnormal lab results were reported from the Phase 1 studies.

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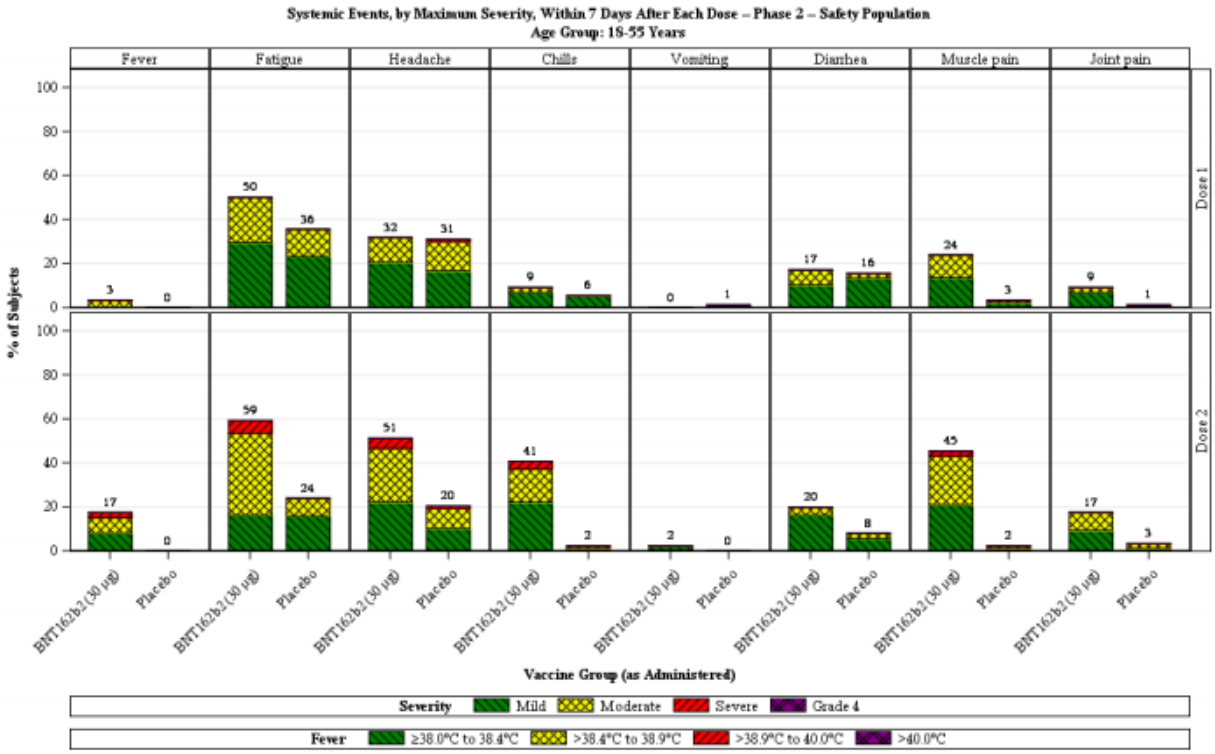
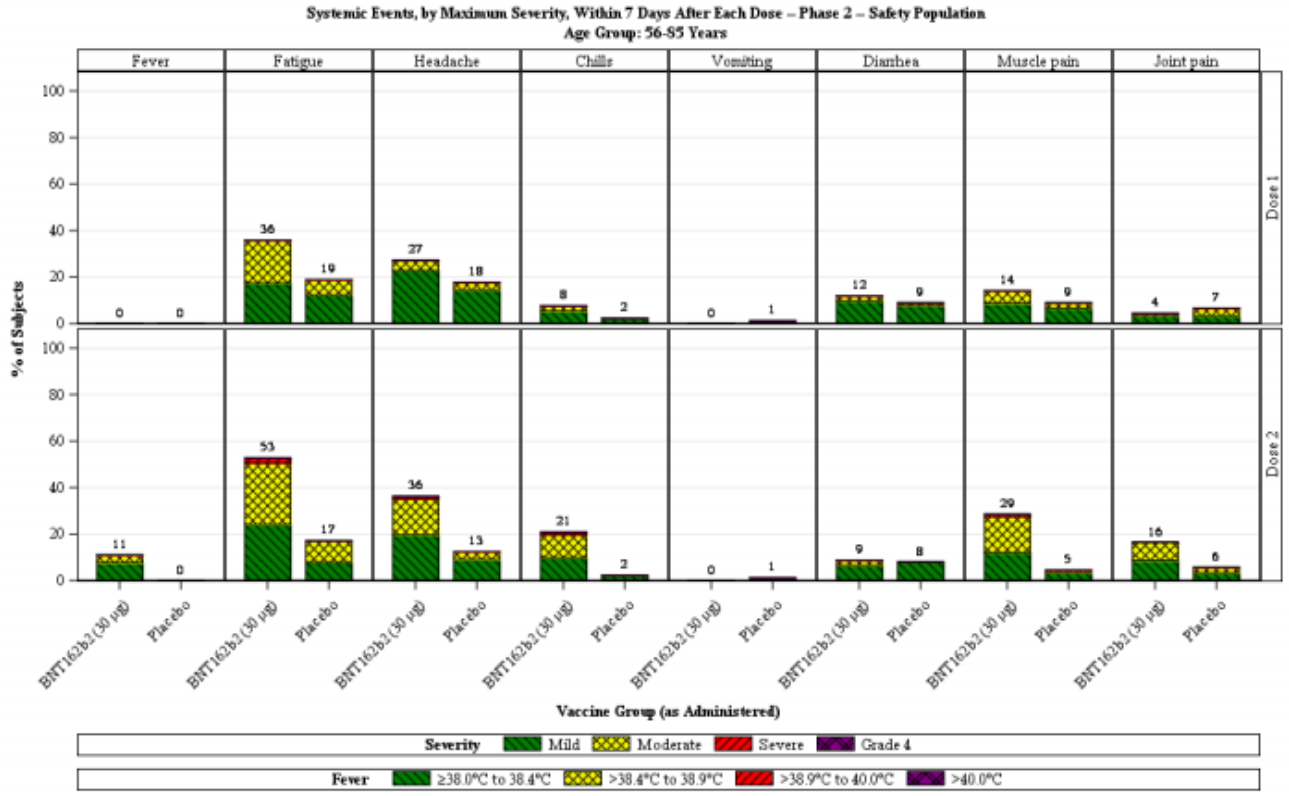
Reactogenicity

Available reactogenicity data were based on the 360 participants of the phase 2 of trial C4591001:

Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 18-55 Years – Phase 2 – Safety Population



Subjects Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, Age Group 56-85 Years – Phase 2 – Safety Population



Overall, it is worth noting that reactogenicity events may be more severe after the second dose and that the degree of severity may, in a small percentage of cases, reach grade 3 or 4.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Benefit

A vaccine efficacy of 95.0% (with 95% CI of 90% to 97.9%) was demonstrated for Comirnaty in a pre-defined primary analysis (symptomatic cases of COVID-19 from seven days onward after second dose in participants without evidence of prior infection). The lower limit of 90.0% for the 95% CI for the primary endpoint exceeded the pre-specified 30% lower margin established by the WHO and FDA.

A vaccine efficacy (VE) of 95.0% shows a very high degree of protection against COVID-19 and thus a highly significant benefit of vaccination. It is likely that the vaccine also protects against severe COVID-19 although, because of a very low number of severe cases, the power of the study did not allow any statistical conclusions to be drawn.

A vaccine efficacy of 95% means that if 100 unvaccinated persons are ill with COVID-19, had they been vaccinated only 5 instead of 100 would have fallen ill. Vaccine efficacy is the relative reduction in the risk: whatever a person's risk was before, it is reduced by 95% by the vaccine. It does NOT mean there is a 5% chance of getting COVID-19 if vaccinated. The risk of infection will depend on vaccination status, prevalence of the disease in the population, precautionary measures put in place and individual behaviour.

Uncertainties and Risks

Uncertainties at the time Swissmedic granted a temporary authorisation included:

- The median follow-up after completion of the full vaccination regimen was 1.5 months. Available efficacy data are therefore limited in terms of follow-up duration, and the efficacy of the vaccine over a longer time (duration of protection) remains unknown. More data are expected to become available post-authorisation.

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- As COVID-19 vaccines are becoming available in the form of EUAs or conditional / temporary approvals in different countries, several phase 3 study participants are likely to quit the study and/or to want to break the blind in order to get the vaccine. Moreover, according to study amendment 10, all study participants will be unblinded 6 months after the second dose and those in the placebo group will receive vaccine. This will make an efficacy and safety follow-up with full study integrity impossible.
- The percentage of study subjects from certain subgroups is low in view of the targeted population at risk for severe COVID: only about 25% of participants are over 65 years of age, and only about 20% have comorbidities.
- In the 75-85 years and >85 years age groups, 837 and 5 participants respectively had been vaccinated with BNT162b2 (Dose 2 all-available efficacy). There are therefore not enough participants over 85 years of age to provide interpretable data for this age group. Nevertheless, the vaccine efficacy for persons over 65 overall is 94.7% (66.7%, 99.9%).
- The design of the study did not test for asymptomatic infections in vaccine recipients or the potential spread to contacts.
- Persistence of immunogenicity is unknown.
- The correlates of protection (specific immunogenic responses that are particularly protective or not protective of infection) have not been elucidated to date.
- There are no long-term data on rare, unexpected risks that may appear with time or as more people get vaccinated.
- As seasonal influenza vaccines and other vaccines were not given concurrently with the COVID-19 vaccine, there are no data on the possibility of simultaneous vaccinations with other types of vaccines.
- Potential interactions between vaccine and medicines have not been studied.
- Protection after only one dose, as well as the need for a second dose in previously infected persons, have not been tested.
- No data, or very limited data, are available on pregnant and lactating women, immunocompromised persons, and paediatric subjects.

Benefit / Risk Assessment

Comirnaty was the first COVID-19 vaccine to receive a temporary marketing authorisation in Switzerland.

The pandemic situation as described above under “Medical Context” and the vaccine’s high efficacy for protection against the development of COVID-19 symptoms, together with an acceptable safety profile, justified an early, **temporary authorisation.** The risk reduction benefit clearly exceeds the potential safety risks. Additional and longer-term data are being collected with a view to definitive authorisation. Post-marketing data are also being gathered under the overview of regulatory authorities (such as FDA, EMA, Health Canada, MHRA, Swissmedic) using established database networks, thus guaranteeing adequate surveillance of efficacy and safety over the long term. Risk minimisation activities and safety studies are ongoing (see the RMP summary on the Swissmedic website).

In view of the rolling submission procedure and temporary authorisation in accordance with Art. 9a TPA, the Swiss prescribing information will be updated as needed.

See www.swissmedicinfo.ch for the latest version.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix. For latest version, see www.swissmedicinfo.ch.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Comirnaty concentrate for dispersion for injection was the version approved at the time of the SwissPAR publication. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Dies ermöglicht eine schnelle Identifizierung neuer Erkenntnisse über die Sicherheit. Angehörige von Gesundheitsberufen sind aufgefordert, den Verdacht einer neuen oder schwerwiegenden Nebenwirkung zu melden. Hinweise zur Meldung von Nebenwirkungen, siehe Rubrik «Unerwünschte Wirkungen».

Die vorliegende Produktinformation wird regelmässig aktualisiert, sobald weitere Daten und Sicherheitsberichte verfügbar sind.

Comirnaty ist befristet zugelassen – siehe Rubrik «Eigenschaften/Wirkungen».

Comirnaty®

Zusammensetzung

Wirkstoffe

Tozinameranum (Einzelsträngige Boten-RNA [messenger RNA, mRNA] mit 5'-Cap-Struktur, durch zellfreie *In-vitro*-Transkription mit entsprechenden DNA-Vorlagen hergestellt und für das Spike [S]-Protein des SARS-CoV-2-Virus kodierend).

Das Produkt enthält nicht replizierende nukleosidmodifizierte mRNA.

Hilfsstoffe

ALC-0315 (= [(4-Hydroxybutyl)azandiyl]bis(hexan-6,1-diyl)bis(2-hexyldecanoat)), ALC-0159 (=2-[(Polyethylenglycol)-2000]-N,N-ditetradecylacetamid), DSPC (= 1,2-Distearoyl-sn-glycero-3 phosphocholin), cholesterolum, kalii chloridum (entspr. 0.005 mg Kalium pro Dosis), kalii dihydrogenophosphas (entspr. 0.003 mg Kalium pro Dosis), natrii chloridum (entspr. 0.141 mg Natrium pro Dosis), dinatrii phosphas dihydricus (entspr. 0.017 mg Natrium pro Dosis), saccharum, aqua ad iniectabilia.

Natriumgehalt pro Dosis: 0.16 mg.

Kaliumgehalt pro Dosis: 0.01 mg.

Darreichungsform und Wirkstoffmenge pro Einheit

Konzentrat zur Herstellung einer Injektionsdispersion (steriles Konzentrat) zur intramuskulären Anwendung.

Der Impfstoff ist eine weisse bis gebrochen weisse gefrorene Dispersion (pH: 6.9–7.9).

Es handelt sich um eine Mehrfachdosis-Durchstechflasche.

Das Konzentrat muss vor Anwendung verdünnt werden. Eine Durchstechflasche (0.45 ml) enthält nach dem Verdünnen bis zu 6 Dosen zu je 0.3 ml.

1 Dosis (0.3 ml) enthält 30 µg COVID-19-mRNA-Impfstoff (in Lipid-Nanopartikel eingebettet).

Indikationen/Anwendungsmöglichkeiten

Comirnaty ist indiziert für die aktive Immunisierung zur Vorbeugung der durch das SARS-CoV-2-Virus hervorgerufenen COVID-19-Erkrankung bei Personen ab 16 Jahren.

Der Comirnaty-Impfstoff sollte gemäss offiziellen Empfehlungen angewendet werden.

Dosierung/Anwendung

Rückverfolgbarkeit

Dem Impfempfänger oder seiner Betreuungsperson ist eine Rückverfolgbarkeits- und Impferinnerungskarte auszuhändigen, auf welcher der Name des Impfstoffs, die Chargennummer, die möglichen Meldestellen und das Datum vermerkt sind, an dem die betreffende Person zur Verabreichung der zweiten Dosis Comirnaty erscheinen muss.

Um die Rückverfolgbarkeit biologischer Arzneimittel zu verbessern, sollten der Name und die Chargennummer des verabreichten Produkts eindeutig dokumentiert werden.

Personen ab 16 Jahren

Comirnaty wird nach Verdünnung in einer Impfserie mit 2 Dosen (je 0.3 ml) intramuskulär verabreicht. Es wird empfohlen, die zweite Dosis 3 Wochen nach der ersten Dosis zu verabreichen (siehe Rubrik «Warnhinweise und Vorsichtsmassnahmen» und «Eigenschaften/Wirkungen»).

Es liegen keine Daten zu einer möglichen Austauschbarkeit von Comirnaty mit anderen COVID-19-Impfstoffen zur Vervollständigung der Impfserie vor. Personen, die 1 Dosis Comirnaty erhalten haben, sollten zur Vervollständigung der Impfserie eine zweite Dosis Comirnaty erhalten.

Für weitere Angaben zur Wirksamkeit, siehe Rubrik «Eigenschaften/Wirkungen».

Kinder und Jugendliche

Die Sicherheit und Wirksamkeit bei Kindern und Jugendlichen unter 16 Jahren sind noch nicht belegt. Es stehen Daten in begrenztem Umfang zur Verfügung.

Ältere Personen

Bei älteren Personen ≥65 Jahren ist keine Dosierungsanpassung erforderlich.

Art der Verabreichung

Comirnaty ist nach dem Verdünnen intramuskulär zu verabreichen (siehe Rubrik «Sonstige Hinweise – Hinweise für die Handhabung»).

Nach dem Verdünnen enthalten die Durchstechflaschen von Comirnaty sechs Dosen von je 0.3 ml des Impfstoffs. Um 6 Dosen aus einer einzelnen Durchstechflasche zu entnehmen, sollten Spritzen und/oder Nadeln mit geringem Totvolumen verwendet werden. Die Kombination aus Spritze und Nadel mit geringem Totvolumen sollte ein Totvolumen von nicht mehr als 35 Mikrolitern haben. Wenn Standardspritzen und -nadeln verwendet werden, reicht das Volumen möglicherweise nicht aus, um eine sechste Dosis aus einer einzelnen Durchstechflasche zu entnehmen.

Unabhängig vom Typ der Spritze und Nadel:

- Jede Dosis MUSS 0.3 ml des Impfstoffes enthalten.
- Wenn die in der Durchstechflasche verbleibende Impfstoffmenge nicht für eine volle Dosis von 0.3 ml ausreicht, entsorgen Sie die Durchstechflasche mit dem überschüssigen Volumen.
- Überschüssiger Impfstoff von mehreren Durchstechflaschen darf nicht zusammengeführt werden.

Die bevorzugte Injektionsstelle ist der Deltamuskel (Musculus deltoideus) am Oberarm.

Der Impfstoff darf nicht intravaskulär, subkutan oder intradermal injiziert werden.

Der Impfstoff darf nicht in derselben Spritze mit anderen Impfstoffen oder Arzneimitteln gemischt werden.

Vorsichtsmassnahmen, die vor der Verabreichung des Impfstoffs zu beachten sind, sind in der Rubrik «Warnhinweise und Vorsichtsmassnahmen» aufgeführt.

Für weitere Hinweise zum Auftauen, zur Handhabung und zur Entsorgung des Impfstoffs siehe Rubrik «Sonstige Hinweise – Hinweise für die Handhabung».

Kontraindikationen

Überempfindlichkeit gegenüber dem Wirkstoff oder einem der Hilfsstoffe.

Warnhinweise und Vorsichtsmassnahmen

Allgemeine Empfehlungen

Überempfindlichkeit und Anaphylaxie

Es wurden Fälle von Anaphylaxie berichtet. Für den Fall einer anaphylaktischen Reaktion nach der Verabreichung des Impfstoffs sollte immer eine angemessene medizinische Behandlung und Überwachung gewährleistet sein.

Nach der Impfung wird eine engmaschige Beobachtung von mindestens 15 Minuten empfohlen. Eine zweite Dosis des Impfstoffs sollte nicht an Personen verabreicht werden, bei denen eine Anaphylaxie nach der ersten Dosis von Comirnaty aufgetreten ist.

Angstbedingte Reaktionen

Angstbedingte Reaktionen, einschliesslich vasovagaler Reaktionen (Synkope), Hyperventilation oder stressbedingte Reaktionen können in Zusammenhang mit der Impfung als psychogene Reaktion auf die Injektion mit einer Nadel auftreten. Es ist wichtig, Vorsichtsmassnahmen zur Vermeidung von Verletzungen infolge einer Ohnmacht zu treffen.

Gleichzeitige Erkrankung

Bei Personen, die an einer akuten schweren fieberhaften Erkrankung oder einer akuten Infektion leiden, sollte die Impfung verschoben werden.

Thrombozytopenie und Gerinnungsstörungen

Wie bei anderen intramuskulären Injektionen sollte der Impfstoff bei Personen, die eine Therapie mit Antikoagulantien erhalten, oder bei Personen mit Thrombozytopenie oder einer Gerinnungsstörung (z.B. Hämophilie) mit Vorsicht verabreicht werden, da bei diesem Personenkreis nach einer intramuskulären Verabreichung Blutungen oder Blutergüsse auftreten können.

Immungeschwächte Personen

Die Wirksamkeit, Sicherheit und Immunogenität des Impfstoffs wurden bei immungeschwächten Personen, einschliesslich Personen unter immunsuppressiver Behandlung, nicht untersucht. Die Wirksamkeit von Comirnaty kann bei immunsupprimierten Personen verringert sein.

Dauer des Schutzes

Die Dauer des durch den Impfstoff induzierten Schutzes ist nicht bekannt, da sie noch in laufenden klinischen Studien ermittelt wird.

Einschränkungen der Effektivität des Impfstoffs

Wie bei jedem Impfstoff schützt die Impfung mit Comirnaty möglicherweise nicht jeden Geimpften. Personen sind möglicherweise erst 7 Tage nach ihrer zweiten Impfdosis vollständig geschützt.

Hilfsstoffe von besonderem Interesse

Dieses Arzneimittel enthält Kalium, jedoch weniger als 1 mmol (39 mg) Kalium pro Dosis, d.h., es ist nahezu «kaliumfrei».

Dieses Arzneimittel enthält weniger als 1 mmol Natrium (23 mg) pro Dosis, d.h., es ist nahezu «natriumfrei».

Interaktionen

Es wurden keine Interaktionsstudien durchgeführt.

Die gleichzeitige Verabreichung von Comirnaty mit anderen Impfstoffen wurde nicht untersucht.

Schwangerschaft, Stillzeit

Schwangerschaft

Es liegen nur begrenzte Erfahrungen zur Anwendung von Comirnaty bei Schwangeren vor. Tierexperimentelle Studien weisen nicht auf direkte oder indirekte schädliche Wirkungen in Bezug auf Schwangerschaft, embryonale/fötale Entwicklung, Geburt oder postnatale Entwicklung hin (siehe Rubrik «Präklinische Daten»). Die Verabreichung von Comirnaty in der Schwangerschaft sollte nur in Betracht gezogen werden, wenn der potenzielle Nutzen die möglichen Risiken für Mutter und Fötus überwiegt.

Stillzeit

Es ist nicht bekannt ob Comirnaty in die Muttermilch übergeht.

Fertilität

Tierexperimentelle Studien ergaben keine Hinweise auf direkte oder indirekte gesundheitsschädliche Wirkungen in Bezug auf eine Reproduktionstoxizität (siehe Rubrik «Präklinische Daten»).

Wirkung auf die Fahrtüchtigkeit und auf das Bedienen von Maschinen

Comirnaty hat keinen oder einen vernachlässigbaren Einfluss auf die Fahrtüchtigkeit und die Fähigkeit zum Bedienen von Maschinen. Jedoch können einige der in der Rubrik «Unerwünschte Wirkungen» aufgeführten Wirkungen die Fahrtüchtigkeit oder die Fähigkeit, Maschinen zu bedienen, vorübergehend beeinträchtigen.

Unerwünschte Wirkungen

Zusammenfassung des Sicherheitsprofils

Die Sicherheit von Comirnaty wurde bei Teilnehmenden ab einem Alter von 16 Jahren in 2 klinischen Studien beurteilt, in die 21’744 Teilnehmende eingeschlossen waren, die mindestens eine Dosis Comirnaty erhielten.

In Studie 2 erhielten insgesamt 21'720 Teilnehmende ab 16 Jahren mindestens 1 Dosis Comirnaty und insgesamt 21'728 Teilnehmende ab 16 Jahren Placebo (darunter 138 Jugendliche im Alter von 16 und 17 Jahren in der Impfstoffgruppe und 145 Jugendliche im Alter von 16 und 17 Jahren in der Placebo-Gruppe). Insgesamt 20'519 Teilnehmende ab 16 Jahren erhielten 2 Dosen Comirnaty.

Zum Zeitpunkt der Auswertung von Studie 2 wurden insgesamt 19'067 Teilnehmende (9’531 in der Comirnaty- und 9'536 in der Placebo-Gruppe) ab einem Alter von 16 Jahren über mindestens 2 Monate nach der zweiten Dosis Comirnaty auf die Sicherheit untersucht. Darunter waren insgesamt 10'727 (5'350 Comirnaty und 5'377 Placebo) Teilnehmende im Alter von 16 bis 55 Jahren und insgesamt 8'340 (4'181 Comirnaty und 4'159 Placebo) Teilnehmende ab 56 Jahren.

Die häufigsten unerwünschten Wirkungen bei Teilnehmenden ab 16 Jahren waren Schmerzen an der Injektionsstelle (>80%), Ermüdung (>60%), Kopfschmerzen (>50%), Myalgie und Schüttelfrost (>30%), Arthralgie (>20%), Fieber und Schwellung an der Injektionsstelle (>10%), die in der Regel von leichter bis mittelstarker Intensität waren und sich innerhalb weniger Tage nach der Impfung zurückbildeten. Eine etwas geringere Häufigkeit von Reaktogenitätsereignissen war mit höherem Alter assoziiert.

Liste der unerwünschten Wirkungen aus klinischen Studien und aus der Postmarketingphase

Die unerwünschten Wirkungen sind nach MedDRA-Systemorganklassen und Häufigkeit gemäss folgender Konvention geordnet: «sehr häufig» (≥1/10), «häufig» (≥1/100 bis <1/10), «gelegentlich» (≥1/1'000 bis <1/100), «selten» (≥1/10'000 bis <1/1'000), « sehr selten» (<1/10'000), «nicht bekannt» (kann auf Grundlage der verfügbaren Daten nicht geschätzt werden).

Erkrankungen des Blutes und des Lymphsystems

Gelegentlich: Lymphadenopathie.

Erkrankungen des Immunsystems

Gelegentlich: Überempfindlichkeitsreaktionen (z.B. Ausschlag, Pruritus, Urtikaria[a], Angioödem[a])[1].

Nicht bekannt: Anaphylaxie.

[a] Urtikaria und Angioödem wurden mit der Häufigkeit «selten» gemeldet.

Psychiatrische Erkrankungen

Gelegentlich: Schlaflosigkeit.

Erkrankungen des Nervensystems

Sehr häufig: Kopfschmerzen (55.1%).

Selten: akute periphere Fazialisparese[b].

[b] Während des Sicherheitsnachbeobachtungszeitraums bis 14. November 2020 wurde von vier Teilnehmenden in der COVID-19-mRNA-Impfstoffgruppe eine akute periphere Fazialisparese (oder Gesichtslähmung) berichtet. Der Beginn war am Tag 37 nach Dosis 1 (der Teilnehmende erhielt keine zweite Dosis) und an den Tagen 3, 9 und 48 nach Dosis 2. In der Placebogruppe wurden keine Fälle von akuter peripherer Fazialisparese (oder Gesichtslähmung) berichtet.

Erkrankungen des Gastrointestinaltrakts

Sehr häufig: Diarrhoe[c] (15.7%).

[1] Module 2.5 Clinical Overview Clinical Overview - anaphylaxis & hypersensitivity

Häufig: Übelkeit, Erbrechen[c].

[c] In der Postmarketingphase gemeldet.

Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen

Sehr häufig: Arthralgie (23.6%), Myalgie (38.3%).

Gelegentlich: Schmerzen in den Extremitäten[d].

[d] Bezieht sich auf den geimpften Arm.[2][3]

Allgemeine Erkrankungen und Beschwerden am Verabreichungsort

Sehr häufig: Schmerzen an der Injektionsstelle (84.1%), Ermüdung (62.9%), Schüttelfrost (31.9%), Fieber[e] (14.2%), Schwellung an der Injektionsstelle (10.5%).

Häufig: Rötung an der Injektionsstelle.

Gelegentlich: Unwohlsein, Juckreiz an der Injektionsstelle.

[e] Nach der 2. Dosis wurde eine höhere Häufigkeit von Fieber beobachtet.

Das Sicherheitsprofil bei 545 Teilnehmenden, die Comirnaty erhielten und bei Studienbeginn seropositiv für SARS-CoV-2 waren, ähnelte dem der Allgemeinpopulation.

Die Meldung des Verdachts auf Nebenwirkungen nach der Zulassung ist von grosser Wichtigkeit. Sie ermöglicht eine kontinuierliche Überwachung des Nutzen-Risiko-Verhältnisses des Arzneimittels. Angehörige von Gesundheitsberufen sind aufgefordert, jeden Verdacht einer neuen oder schwerwiegenden Nebenwirkung über das Online-Portal EIViS (Electronic Vigilance System) anzuzeigen. Informationen dazu finden Sie unter www.swissmedic.ch.

[2] Module 2.5 Clinical Overview to Support Inclusion of Pain in Extremity, Diarrhea, and Vomiting as Adverse Drug Reactions

[3] Module 2.5 Clinical Overview Addendum- Global Label update-Pain in Extremity (arm)

Überdosierung

Daten zur Überdosierung liegen von 52 Studienteilnehmenden vor, die aufgrund eines Verdünnungsfehlers in der klinischen Studie 58 µg Comirnaty erhalten haben. Die Geimpften berichteten weder über eine Zunahme der Reaktogenität noch über unerwünschte Reaktionen.

Im Falle einer Überdosierung wird eine Überwachung der Vitalfunktionen und gegebenenfalls eine symptomatische Behandlung empfohlen.

Eigenschaften/Wirkungen

ATC-Code

J07BX

Wirkungsmechanismus

Die nukleosidmodifizierte messenger RNA in Comirnaty ist in Lipid-Nanopartikel verpackt, welche die Aufnahme der nicht replizierenden RNA in Wirtszellen gestatten, und regelt so die transiente Expression des SARS-CoV-2-S-Antigens. Die mRNA kodiert für membranverankertes Spike-(S)-Antigen in voller Länge mit zwei Punktmutationen innerhalb der zentralen Helix. Die Mutation dieser beiden Aminosäuren zu Prolinen fixiert das S-Antigen in einer antigenisch bevorzugten Prä-Fusions-Konformation. Der Impfstoff löst sowohl die Produktion neutralisierender Antikörper als auch eine zelluläre Immunantwort gegen das Spike-(S)-Antigen aus und könnte auf diese Weise zu einem Schutz vor COVID-19 beitragen.

Pharmakodynamik

Keine weiteren Angaben.

Klinische Wirksamkeit

Wirksamkeit

Bei Studie 2 handelt es sich um eine multizentrische, multinationale, randomisierte, placebokontrollierte, beobachterverblindete Phase-I/II/III-Studie zur Dosisfindung, zur Auswahl des Impfstoffkandidaten und zur Untersuchung der Wirksamkeit bei Teilnehmenden ab einem Alter von 12 Jahren. Die Randomisierung erfolgte stratifiziert nach Alter: 12 bis 15 Jahre, 16 bis 55 Jahre bzw. 56 Jahre und älter. Mindestens 40% der Teilnehmenden befanden sich im Stratum ≥56 Jahre. Aus der Studie ausgeschlossen waren immungeschwächte Personen und Personen mit früherer klinischer

oder mikrobiologischer COVID-19-Diagnose. Personen mit vorbestehender stabiler Erkrankung, definiert als Erkrankung, für die in den 6 Wochen vor der Aufnahme in die Studie keine erhebliche Therapieumstellung oder Hospitalisierung aufgrund einer Krankheitsverschlechterung erforderlich war, wurden ebenso eingeschlossen wie Personen mit bekannter stabiler Infektion mit Humanem Immundefizienz-Virus (HIV), Hepatitis-C-Virus (HCV) oder Hepatitis-B-Virus (HBV). Zum Zeitpunkt der Auswertung von Studie 2 basieren die vorgestellten Angaben auf Daten von Teilnehmenden ab 16 Jahren.

Wirksamkeit bei Teilnehmenden ab 16 Jahren

Für den Phase-II/III-Studienabschnitt wurden etwa 44’000 Teilnehmende zu gleichen Teilen randomisiert und sollten im Abstand von 21 Tagen 2 Dosen des COVID-19-mRNA-Impfstoffs oder Placebo erhalten. Die Wirksamkeitsanalysen umfassten Teilnehmende, die ihre zweite Impfung innerhalb von 19 bis 42 Tagen nach ihrer ersten Impfung erhielten. Die Mehrheit (93.1%) der Geimpften erhielt die zweite Dosis 19 bis 23 Tage nach Dosis 1. Eine Nachbeobachtung der Teilnehmenden über einen Zeitraum von bis zu 24 Monaten nach Dosis 2 ist geplant, um die Sicherheit und Wirksamkeit des Impfstoffs gegen COVID-19 zu beurteilen. In der klinischen Studie mussten die Teilnehmenden, um entweder Placebo- oder den COVID-19-mRNA-Impfstoff zu erhalten, ein Mindestintervall von 14 Tagen vor und nach der Verabreichung eines Influenza-Impfstoffs einhalten. In der klinische Studie war es Teilnehmern innerhalb 60 Tagen vor Anmeldung und bis zum Abschluss der Studie nicht gestattet Blut-/Plasmaprodukte oder Immunglobuline zu erhalten.

Die Studienpopulation für die Auswertung des primären Wirksamkeitsendpunkts umfasste 36’621 Teilnehmende ab einem Alter von 12 Jahren (18’242 in der COVID-19-mRNA-Impfstoffgruppe und 18’379 in der Placebogruppe), bei denen bis 7 Tage nach Erhalt der zweiten Dosis keine vorbestehende Infektion mit SARS-CoV-2 nachgewiesen wurde. Ausserdem waren 134 Teilnehmende im Alter von 16 bis 17 Jahren (66 in der COVID-19-mRNA-Impfstoffgruppe und 68 in der Placebogruppe) und 1’616 Teilnehmende 75 Jahre und älter (804 in der COVID-19-mRNA-Impfstoffgruppe und 812 in der Placebogruppe).

Tabelle 1: Demografische Daten (Population für den primären Wirksamkeitsendpunkt)[a]

	Comirnaty (N=18’242) n (%)	*Placebo (N=18’379) n (%)*
Geschlecht		
Männlich	9’318 (51.1)	9’225 (50.2)
Weiblich	8’924 (48.9)	9’154 (49.8)
Alter (Jahre)		

	Comirnaty (N=18'242) n (%)	*Placebo (N=18'379) n (%)*
Mittelwert (SD)	50.6 (15.70)	50.4 (15.81)
Median	52.0	52.0
Min.; Max.	(12; 89)	(12; 91)
Altersgruppe		
≥12 bis 15 Jahre	46 (0.3)	42 (0.2)
≥16 bis 17 Jahre	66 (0.4)	68 (0.4)
≥16 bis 64 Jahre	14'216 (77.9)	14'299 (77.8)
≥65 bis 74 Jahre	3'176 (17.4)	3'226 (17.6)
≥75 Jahre	804 (4.4)	812 (4.4)
75 bis 85 Jahre	799 (4.4)	807 (4.4)
>85 Jahre	5 (0.0)	5 (0.0)
Hautfarbe		
Weiss	15'110 (82.8)	15'301 (83.3)
Schwarz oder Afro-Amerikanisch	1'617 (8.9)	1'617 (8.8)
Indigene Amerikaner oder Alaskaner	118 (0.6)	106 (0.6)
Asiatisch	815 (4.5)	810 (4.4)
Indigene Hawaiianer oder andere pazifische Inselbewohner	48 (0.3)	29 (0.2)
Sonstige[b]	534 (2.9)	516 (2.8)
Ethnizität		
Hispanisch oder Latino	4'886 (26.8)	4'857 (26.4)
Nicht hispanisch oder Latino	13'253 (72.7)	13'412 (73.0)
Keine Angabe	103 (0.6)	110 (0.6)
Komorbiditäten[c]		
Ja	8'432 (46.2)	8'450 (46.0)
Nein	9'810 (53.8)	9'929 (54.0)

a. Alle geeigneten randomisierten Teilnehmenden, die alle Impfungen wie randomisiert innerhalb des vordefinierten Zeitfensters erhalten, nach Ermessen des Klinikers ansonsten keine wichtigen Protokollabweichungen aufweisen und bei denen bis Ablauf von 7 Tagen nach Dosis 2 kein Nachweis einer SARS-CoV-2-Infektion vorliegt.
b. Einschliesslich gemischte Abstammung und keine Angabe.
c. Anzahl der Teilnehmenden mit 1 oder mehr der folgenden Komorbiditäten, die das Risiko eines schweren COVID-19-Verlaufs erhöhen
   - Chronische Lungenerkrankung (z.B. Emphysem und chronische Bronchitis, idiopathische Lungenfibrose und zystische Fibrose) oder mittelschweres bis schweres Asthma
   - Signifikante Herzerkrankung (z.B. Herzinsuffizienz, koronare Herzkrankheit, angeborener Herzfehler, Kardiomyopathien und pulmonale Hypertonie)
   - Adipositas (Körpermasseindex [Body Mass Index] ≥30 kg/m^2)
   - Diabetes (Typ 1, Typ 2 oder Gestationsdiabetes)
   - Lebererkrankung
   - Infektion mit dem Humanen Immundefizienz-Virus (HIV) (nicht in der Wirksamkeitsauswertung berücksichtigt)

Wirksamkeit gegen COVID-19

Zum Zeitpunkt der primären Wirksamkeitsanalyse wurden die Teilnehmenden für insgesamt 2'214 Personenjahre in der COVID-19-mRNA-Impfstoffgruppe und für insgesamt 2'222 Personenjahre in der Placebogruppe auf symptomatisches COVID-19 untersucht.

Es wurden keine bedeutsamen klinischen Unterschiede in Bezug auf die Gesamtwirksamkeit des Impfstoffs bei Teilnehmenden mit Risiko eines schweren Verlaufs von COVID-19 festgestellt, einschliesslich Teilnehmenden mit mindestens 1 Begleiterkrankung, die das Risiko für einen schweren Verlauf von COVID-19 erhöht (z.B. Asthma, Körpermasseindex [Body Mass Index, BMI] ≥30 kg/m^2, chronische Lungenerkrankung, Diabetes mellitus, Hypertonie).

Die Informationen zur Wirksamkeit des Impfstoffs sind in Tabelle 2 aufgeführt.

Tabelle 2: Wirksamkeit des Impfstoffs – Erstes Auftreten von COVID-19 ab 7 Tage nach Dosis 2, nach Altersuntergruppen – Teilnehmende ohne Nachweis einer Infektion vor Ablauf von 7 Tagen nach Dosis 2 – auswertbare Wirksamkeitspopulation (7 Tage)

*Erstes Auftreten von COVID-19 ab 7 Tage nach Dosis 2 bei Teilnehmenden ohne Nachweis einer früheren SARS-CoV-2-Infektion**			
Untergruppe	*COVID-19-mRNA-Impfstoff N[a] = 18'198 Fälle n1[b] Beobachtungszeit[c] (n2[d])*	*Placebo N[a] = 18'325 Fälle n1[b] Beobachtungszeit[c] (n2[d])*	*Wirksamkeit des Impfstoffs % (95%-KI)[f]*
Alle Probanden[e]	8 2.214 (17'411)	162 2.222 (17'511)	95.0 (90.0; 97.9)
16 bis 64 Jahre	7 1.706 (13'549)	143 1.710 (13'618)	95.1 (89.6; 98.1)
65 Jahre und älter	1 0.508 (3'848)	19 0.511 (3'880)	94.7 (66.7; 99.9)
65 bis 74 Jahre	1 0.406 (3'074)	14 0.406 (3'095)	92.9 (53.1; 99.8)
75 Jahre und älter	0 0.102 (774)	5 0.106 (785)	100.0 (-13.1, 100.0)

Hinweis: Bestätigte Fälle wurden bestimmt durch Reverse-Transkriptase-Polymerase-Kettenreaktion (RT-PCR) und mindestens 1 auf COVID-19 hindeutendes Symptom (*Falldefinition: [mindestens 1 Symptom der Folgenden:] Fieber, neu aufgetretener oder verstärkter Husten, neu aufgetretene oder verstärkte Atemnot, Schüttelfrost, neu aufgetretene oder verstärkte Muskelschmerzen, neu aufgetretener Verlust des Geschmacks- oder Geruchssinns, Halsschmerzen, Durchfall oder Erbrechen.)

* In die Analyse gingen Teilnehmende ein, bei denen (vor Ablauf von 7 Tagen nach Erhalt der letzten Dosis) kein serologischer oder virologischer Nachweis einer früheren SARS-CoV-2-Infektion vorlag (d.h. N-bindender Antikörper [Serum] negativ bei Termin 1 und SARS-CoV-2 nicht durch NAAT [Nucleic Acid Amplification Technology; Nasenabstrich] nachweisbar bei Termin 1 und 2), und bei denen im Rahmen eines allfälligen ausserplanmässigen Besuchs vor Ablauf von 7 Tagen nach Dosis 2 ein NAAT (Nasenabstrich) negativ ausfiel.

a. N = Anzahl der Teilnehmenden in der angegebenen Gruppe.
b. n1 = Anzahl der Teilnehmenden, welche die Endpunktdefinition erfüllen.
c. Gesamtbeobachtungszeit in 1'000 Personenjahren für den jeweiligen Endpunkt über alle Teilnehmenden innerhalb jeder Endpunkt-Risikogruppe. Der Zeitraum für die Erfassung von COVID-19-Fällen erstreckt sich von 7 Tagen nach Dosis 2 bis zum Ende des Beobachtungszeitraums.
d. n2 = Anzahl der bezüglich des Endpunkts gefährdeten Personen.
e. Es wurden keine bestätigten Fälle bei Teilnehmenden im Alter von 12 bis 15 Jahren identifiziert.
f. Das Konfidenzintervall (KI) für die Wirksamkeit des Impfstoffs wurde auf der Grundlage der beobachtungszeitadjustierten Clopper-Pearson-Methode abgeleitet. KI nicht für Multiplizität adjustiert.

In der zweiten Primäranalyse betrug die Wirksamkeit des COVID-19-mRNA-Impfstoffs gegenüber Placebo in Bezug auf das erste Auftreten von COVID-19 nach Ablauf von 7 Tagen nach Dosis 2 bei Teilnehmenden mit oder ohne Nachweis einer Infektion ab 16 Jahren 94.6% (95%-Glaubwürdigkeitsintervall von 89.9 % bis 97.3 %).

Darüber hinaus zeigten Untergruppenanalysen des primären Wirksamkeitsendpunkts ähnliche Wirksamkeitspunktschätzungen für alle Geschlechter, Hautfarben und ethnischen Gruppen sowie für Teilnehmende mit medizinischen Komorbiditäten, die mit einem hohen Risiko für einen schweren COVID-19-Verlauf assoziiert sind.

Wirksamkeit gegen COVID-19 mit schwerem Verlauf

Sekundäre Wirksamkeitsanalysen deuteten auf einen Nutzen des COVID-19-mRNA-Impfstoffs hinsichtlich der Prävention von COVID-19 mit schwerem Verlauf hin, jedoch war die Anzahl der Fälle sehr gering.

Die Wirksamkeit gegen COVID-19 mit schwerem Verlauf (wie im Studienprotokoll definiert), das frühestens 7 Tage nach Dosis 2 auftrat, betrug 66.4% (95%-Glaubwürdigkeitsintervall -124.8; 96.3) (1 Fall in der COVID-19-mRNA-Impfstoffgruppe und 3 Fälle in der Placebogruppe).

Befristete Zulassung

Aufgrund einer zum Zeitpunkt der Begutachtung des Zulassungsgesuches unvollständigen klinischen Datenlage, wird das Arzneimittel Comirnaty befristet zugelassen (Art. 9a Heilmittelgesetz). Die befristete Zulassung ist zwingend an die zeitgerechte Erfüllung von Auflagen gebunden. Nach deren Erfüllung kann die befristete Zulassung in eine ordentliche Zulassung überführt werden.

Pharmakokinetik

Absorption

Nicht zutreffend.

Distribution

Nicht zutreffend.

Metabolismus

Nicht zutreffend.

Elimination

Nicht zutreffend.

Präklinische Daten

Basierend auf konventionellen Studien zur Toxizität bei wiederholter Gabe sowie zur Reproduktions- und Entwicklungstoxizität lassen die präklinischen Daten keine besonderen Gefahren für den Menschen erkennen.

Allgemeine Toxizität

Ratten, denen intramuskulär Comirnaty verabreicht wurde (einmal wöchentlich 3 volle Humandosen, die bei Ratten aufgrund von Körpergewichtsunterschieden relativ höhere Werte erzeugen), zeigten an der Injektionsstelle leichte Ödeme und Erytheme, Vergrösserungen der lokalen Lymphknoten und der Milz und einen Anstieg der Leukozyten (einschliesslich Basophile und Eosinophile), was auf eine Entzündungsreaktion hindeutet, sowie eine Vakuolisierung der portalen Hepatozyten ohne Nachweis einer Leberschädigung. Alle Erscheinungen waren reversibel.

Genotoxizität/Karzinogenität

Es wurden weder Genotoxizitäts- noch Karzinogenitätsstudien durchgeführt. Es ist nicht damit zu rechnen, dass die Bestandteile des Impfstoffs (Lipide und mRNA) ein genotoxisches Potential besitzen.

Reproduktions- und Entwicklungstoxizität

Die Reproduktions- und Entwicklungstoxizität wurde an Ratten in einer kombinierten Fertilitäts- und Entwicklungstoxizitätsstudie untersucht, bei der weiblichen Ratten Comirnaty vor der Paarung und während der Trächtigkeit intramuskulär verabreicht wurde (Gabe von 4 vollen Humandosen, die bei Ratten aufgrund von Körpergewichtsunterschieden relativ höhere Dosen erzeugen, und sich zwischen dem Tag 21 vor der Paarung und dem Tag 20 der Gravidität erstreckten). SARS-CoV-2 neutralisierende Antikörperreaktionen waren bei den mütterlichen Tieren von vor der Paarung bis zum Ende der Studie am postnatalen Tag 21 sowie bei den Föten und Nachkommen vorhanden. Es wurden keine impfstoffbedingten Wirkungen auf die weibliche Fertilität, die Trächtigkeit oder die embryofötale Entwicklung oder auf die Entwicklung der Nachkommen festgestellt. Es liegen keine Daten zu Comirnaty zum Plazentatransfer des Impfstoffs oder zur Ausscheidung in der Milch vor.

Sonstige Hinweise

Inkompatibilitäten

Das Arzneimittel darf, ausser mit den unten unter «Hinweise für die Handhabung» aufgeführten, nicht mit anderen Arzneimitteln gemischt werden.

Haltbarkeit

Das Arzneimittel darf nur bis zu dem auf der Packung mit «EXP» bezeichneten Datum verwendet werden.

Haltbarkeit der ungeöffneten Durchstechflasche: 6 Monate bei -90 °C bis -60 °C.

Alternativ können ungeöffnete Durchstechflaschen bei -25 °C bis -15 °C für insgesamt 2 Wochen gelagert und transportiert werden und können einmal auf die empfohlene Lagerungstemperatur von -90 °C bis -60 °C zurückgebracht werden. Die gesamte Lagerungszeit bei -25 °C bis -15 °C sollte 2 Wochen nicht überschreiten.

Nach dem Herausnehmen aus dem Gefrierschrank kann die ungeöffnete Durchstechflasche vor der Verwendung bis zu 5 Tage bei 2 °C bis 8 °C gelagert werden. Innerhalb der 5 Tage Haltbarkeitsdauer bei 2 °C bis 8 °C können bis zu 12 Stunden für den Transport genutzt werden. Vor der Verwendung kann die ungeöffnete Durchstechflasche bis zu 2 Stunden bei Temperaturen bis 30 °C gelagert werden.

Nach dem Auftauen darf der Impfstoff nicht erneut eingefroren werden.

Handhabung von Temperaturabweichungen nach Entnahme aus dem Gefrierschrank

Die Stabilitätsdaten zeigen, dass die ungeöffnete Durchstechflasche haltbar ist bis zu:

- 24 Stunden bei Aufbewahrung bei Temperaturen von -3 °C bis 2 °C.
- insgesamt 4 Stunden bei Aufbewahrung bei Temperaturen von 8 °C bis 30 °C; dies schliesst die oben beschriebenen 2 Stunden bei bis zu 30 °C ein.

Diese Angaben dienen nur als Orientierungshilfe für das medizinische Fachpersonal im Falle einer versehentlichen Temperaturabweichung.

Transfer von gefrorenen Durchstechflaschen, die bei Ultratiefkühlung (<-60 °C) gelagert wurden

- Flaschenträger mit geschlossenem Deckel und 195 Durchstechflaschen, die gefroren aus der Ultratiefkühlung (<-60 °C) entnommen wurden, können bis zu 5 Minuten bei Temperaturen bis zu 25 °C bleiben.
- Flaschenträger mit geöffnetem Deckel, oder Flaschenträger mit weniger als 195 Durchstechflaschen, die gefroren aus der Ultratiefkühlung (<-60 °C) entnommen wurden, können bis zu 3 Minuten bei Temperaturen bis zu 25 °C bleiben.
- Nachdem die Flaschenträger nach der Exposition bei Temperaturen bis zu 25 °C wieder in die Tiefkühlung gebracht wurden, müssen sie mindestens 2 Stunden in der Tiefkühlung verbleiben, bevor sie wieder entnommen werden können.

Transfer von gefrorenen Durchstechflaschen, die bei -25 °C bis -15 °C gelagert wurden

- Flaschenträger mit geschlossenem Deckel und 195 Durchstechflaschen, die aus gefrorener Lagerung (-25 °C bis -15 °C) entnommen wurden, können bis zu 3 Minuten bei Temperaturen bis zu 25 °C bleiben.
- Flaschenträger mit geöffnetem Deckel, oder Flaschenträger mit weniger als 195 Durchstechflaschen, die aus gefrorener Lagerung (-25 °C bis -15 °C) entnommen wurden, können bis zu 1 Minute bei Temperaturen bis zu 25 °C bleiben.

Sobald eine Durchstechflasche aus dem Flaschenträger entnommen wurde, sollte sie zur Verwendung aufgetaut werden.

Haltbarkeit nach Anbruch

Verdünntes Arzneimittel: Die chemische und physikalische Gebrauchsstabilität, einschliesslich des Transports, ist für einen Zeitraum von 6 Stunden bei 2 °C bis 30 °C nach Verdünnung in Natriumchlorid-Injektionslösung 9 mg/ml (0.9%) belegt. Aus mikrobiologischen Gründen sollte das Produkt sofort verwendet werden. Erfolgt die Anwendung nicht sofort, liegen die Aufbewahrungszeiten und -bedingungen für die Verwendung in der Verantwortung des Anwenders.

Besondere Lagerungshinweise

Tiefgekühlt bei -90 °C bis -60 °C lagern.

In der Originalverpackung aufbewahren, um den Inhalt vor Licht zu schützen.

Während der Lagerung ist die Exposition gegenüber Raumlicht so gering wie möglich zu halten, die Exposition gegenüber direktem Sonnenlicht und ultraviolettem Licht ist zu vermeiden.

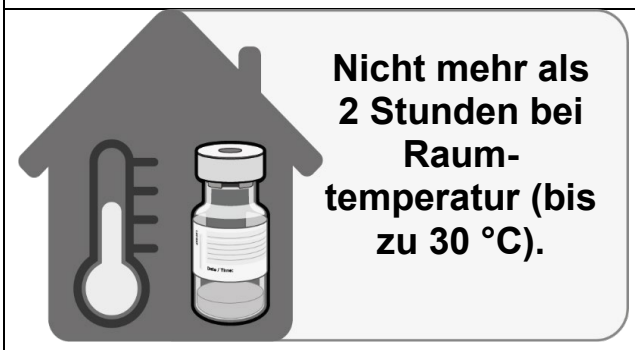
Aufgetaute Durchstechflaschen können bei Raumlicht gehandhabt werden.

Zu den Aufbewahrungsbedingungen nach Auftauen und Verdünnung des Arzneimittels, siehe oben unter «Haltbarkeit» und «Haltbarkeit nach Anbruch».

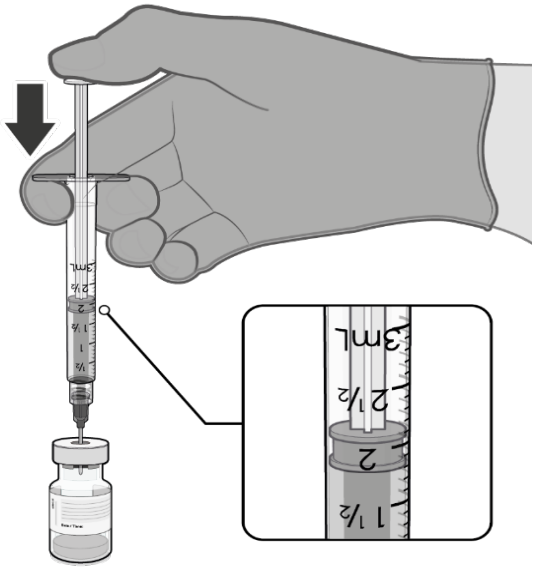
Ausser Reichweite von Kindern aufbewahren.

Hinweise für die Handhabung

Comirnaty ist von einer medizinischen Fachperson unter Verwendung aseptischer Techniken zuzubereiten, um die Sterilität der zubereiteten Dispersion sicherzustellen.

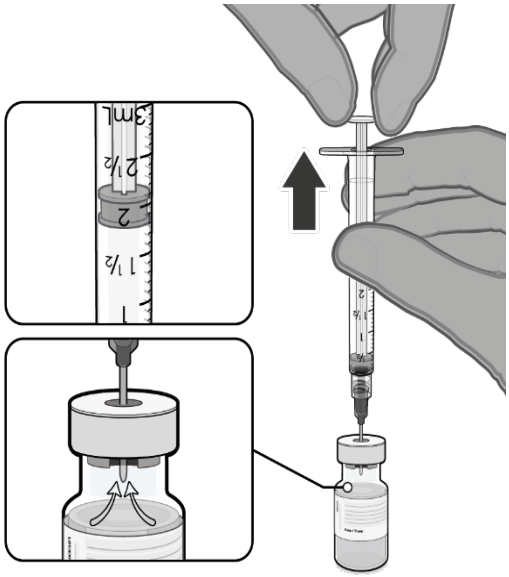
<table>
<tr><td colspan="2">AUFTAUEN VOR DEM VERDÜNNEN</td></tr>
<tr><td> 
</td><td>- Die Mehrfachdosis-Durchstechflasche wird gefroren gelagert und muss vor der Verdünnung aufgetaut werden. Die gefrorenen Durchstechflaschen sollten zum Auftauen in eine Umgebung von 2 °C bis 8 °C gebracht werden. Das Auftauen eines Flaschenträgers mit 195 Durchstechflaschen kann 3 Stunden dauern. Alternativ können gefrorene Durchstechflaschen zur sofortigen Verwendung auch 30 Minuten lang bei Temperaturen bis zu 30 °C aufgetaut werden.
- Die ungeöffnete Durchstechflasche kann bis zu 5 Tage bei 2 °C bis 8 °C gelagert werden. Innerhalb der 5 Tage Haltbarkeitsdauer bei 2 °C bis 8 °C können bis zu 12 Stunden für den Transport genutzt werden.
- Lassen Sie die aufgetaute Durchstechflasche auf Raumtemperatur kommen und drehen Sie diese vor der Verdünnung 10-mal vorsichtig um. Nicht schütteln.
- Vor dem Verdünnen kann die aufgetaute Dispersion weisse bis gebrochen weisse undurchsichtige amorphe Partikel enthalten.</td></tr>
</table>

VERDÜNNUNG



1.8 ml von 0.9% Natriumchlorid-Injektionslösung

- Der aufgetaute Impfstoff muss in seiner ursprünglichen Durchstechflasche mit 1.8 ml Natriumchlorid-Injektionslösung 9 mg/ml (0.9%) unter Verwendung einer 21-Gauge- oder dünneren Nadel unter aseptischen Techniken verdünnt werden.

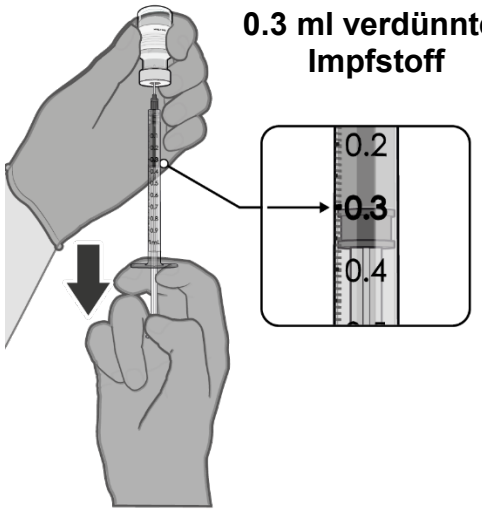


Ziehen Sie den Kolben bis zur 1.8 ml Markierung zurück, um Luft von der Durchstechflasche zu entfernen.

- Gleichen Sie den Druck in der Durchstechflasche aus, bevor Sie die Nadel aus der Durchstechflasche entfernen, indem Sie 1.8 ml Luft in die leere Verdünnungsmittelspritze ziehen.

 **Vorsichtig × 10**	- Drehen Sie die verdünnte Dispersion 10-mal vorsichtig um. Nicht schütteln. - Der verdünnte Impfstoff sollte als gebrochen weisse Dispersion ohne sichtbare Partikel vorliegen. Verwenden Sie den verdünnten Impfstoff nicht, wenn Partikel oder Verfärbungen vorhanden sind.
 **Notieren Sie das entsprechende Datum und die Uhrzeit. Innerhalb von 6 Stunden nach Verdünnung verwenden**	- Die Durchstechflaschen mit der verdünnten Dispersion sind mit dem entsprechenden Datum und Uhrzeit der Verdünnung zu kennzeichnen. - Nach Verdünnung bei 2 ºC bis 30 ºC lagern und innerhalb von 6 Stunden, einschliesslich jeglicher Transportzeit, verwenden. - Die verdünnte Dispersion nicht einfrieren oder schütteln. Lassen Sie eine gekühlte, verdünnte Dispersion vor der Verwendung auf Raumtemperatur kommen.

ZUBEREITUNG VON INDIVIDUELLEN 0.3 ml DOSEN VON COMIRNATY



- Nach der Verdünnung enthält die Durchstechflasche 2.25 ml, aus der 6 Dosen zu 0.3 ml entnommen werden können.
- Reinigen Sie den Stopfen der Durchstechflasche unter aseptischen Bedingungen mit einem antiseptischen Einmaltupfer.
- Entnehmen Sie 0.3 ml Comirnaty.

  Es sollten Spritzen und/oder Nadeln mit geringem Totvolumen verwendet werden, um 6 Dosen aus einer Durchstechflasche zu entnehmen. Die Kombination aus Spritze und Nadel mit geringem Totvolumen sollte ein Totvolumen von nicht mehr als 35 Mikrolitern haben.

  Wenn Standardspritzen und -nadeln verwendet werden, reicht das Volumen möglicherweise nicht aus, um eine sechste Dosis aus einer einzelnen Durchstechflasche zu entnehmen.

- Jede Dosis muss 0.3 ml des Impfstoffs enthalten.
- Wenn die in der Durchstechflasche verbleibende Impfstoffmenge nicht für eine volle Dosis von 0.3 ml ausreicht, entsorgen Sie die Durchstechflasche mit dem überschüssigen Volumen.

- Entsorgen Sie nicht verwendeten Impfstoff innerhalb von 6 Stunden nach der Verdünnung.

Entsorgung

Nicht verwendetes Arzneimittel oder Abfallmaterial ist entsprechend den nationalen Anforderungen zu beseitigen.

Zulassungsnummer

68225 (Swissmedic).

Packungen

1 Packung mit 195 2 ml Mehrfachdosis-Durchstechflaschen (Typ I-Glas) mit einem Stopfen (synthetischer Brombutylkautschuk) und einer Flip-off-Kunststoffkappe mit einem Verschluss aus Aluminium (mit je 6 Dosen) [B].

Zulassungsinhaberin

Pfizer AG, Zürich.

Stand der Information

April 2021