Allegato 1

REG 174 INFORMATION FOR UK HEALTHCARE PROFESSIONALS

This medicinal product does not have a UK marketing authorisation but has been given authorisation for temporary supply by the UK Department of Health and Social Care and the Medicines & Healthcare products Regulatory Agency for active immunization to prevent COVID-19 disease caused by SARS-CoV-2 virus in individuals aged 16 years of age and over.

As with any new medicine in the UK, this product will be closely monitored to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

COVID-19 mRNA Vaccine BNT162b2 concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and must be diluted before use. 1 vial (0.45 mL) contains 5 doses of 30 micrograms of BNT162b2 RNA (embedded in lipid nanoparticles).

COVID-19 mRNA Vaccine BNT162b2 is highly purified single-stranded, 5'-capped messenger RNA (mRNA) produced by cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

Excipients with known effect:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection.
The vaccine is a white to off-white frozen solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older.

The use of COVID-19 mRNA Vaccine BNT162b2 should be in accordance with official guidance.

4.2 Posology and method of administration

Posology
Individuals 16 years of age and older
COVID-19 mRNA Vaccine BNT162b2 is administered intramuscularly after dilution as a series of two doses (0.3 mL each) 21 days apart (see section 5.1).

There are no data available on the interchangeability of COVID-19 mRNA Vaccine BNT162b2 with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of COVID-19 mRNA Vaccine BNT162b2 should receive a second dose of COVID-19 mRNA Vaccine BNT162b2 to complete the vaccination series.

Individuals may not be protected until at least 7 days after their second dose of the vaccine.

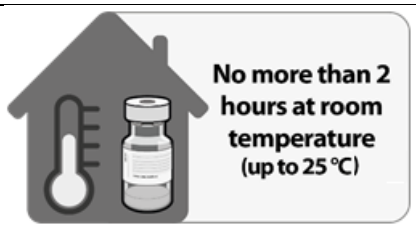
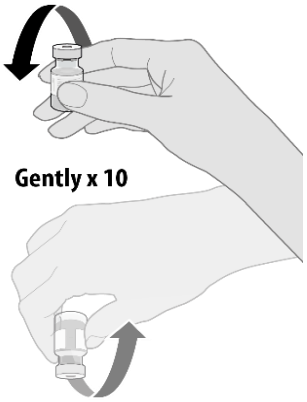
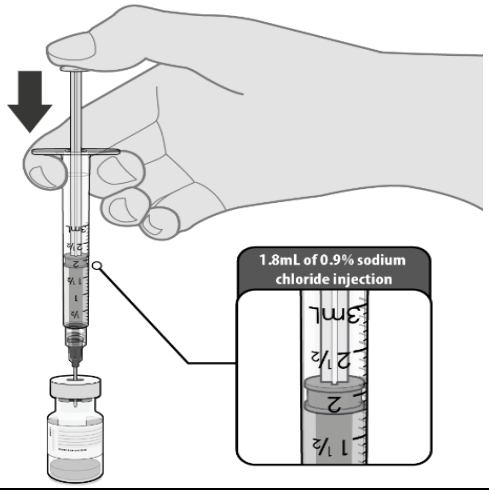
For further information on efficacy, see section 5.1.

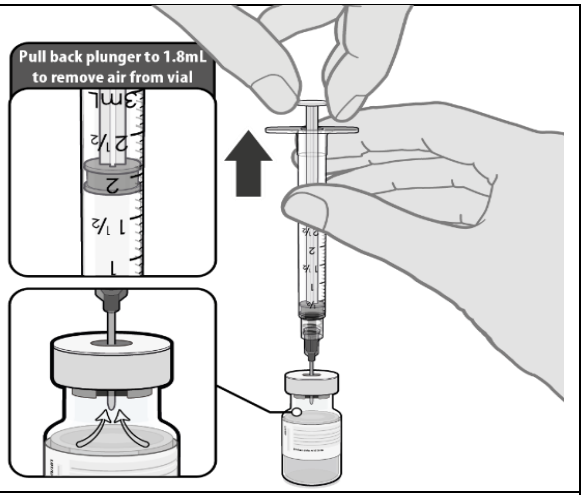
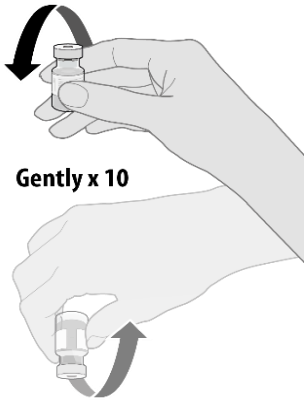
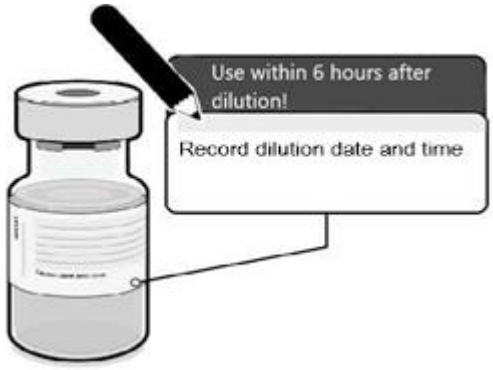
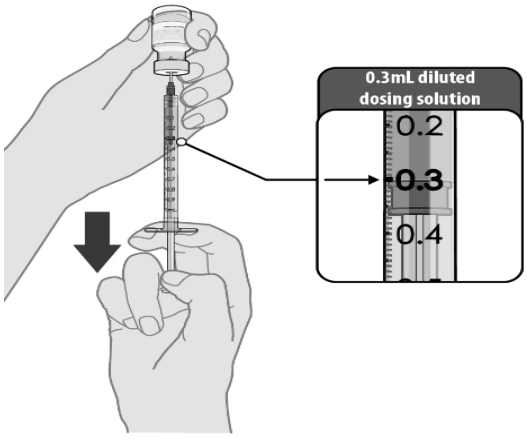
Paediatric population
The safety and efficacy of COVID-19 mRNA Vaccine BNT162b2 in children under 16 years of age have not yet been established.

Method of administration
Administer the COVID-19 mRNA Vaccine BNT162b2 vaccine intramuscularly in the deltoid muscle after dilution.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

Preparation: The multidose vial is stored frozen and must be thawed prior to dilution.

Frozen vials should be transferred to 2 °C to 8 °C to thaw; a 195 vial pack may take 3 hours to thaw (see section 6.4). Alternatively, frozen vials may also be thawed for 30 minutes at temperatures up to 25 °C for immediate use. Once thawed, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, and up to 2 hours.at temperatures up to 25 °C.	
Allow the thawed vial to come to room temperature and gently invert 10 times prior to dilution. Do not shake. Prior to dilution the vaccine should present as an off-white solution with no particulates visible. Discard the vaccine if particulates or discolouration are present.	
The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and **aseptic** techniques. **Warning:** Unpreserved sodium chloride 9 mg/mL (0.9%) solution for injection is the **only** diluent that should be used. This diluent is not provided in the vaccine carton.	

Equalise vial pressure before removing the needle from the vial by withdrawing 1.8 mL air into the empty diluent syringe.	
Gently invert the diluted solution 10 times. Do not shake.	
The diluted vaccine should present as an off-white solution with no particulates visible. Discard the diluted vaccine if particulates or discolouration are present.	
The diluted vials should be marked with the dilution date and time and stored between 2 °C to 25 °C. Use immediately, and within 6 hours after dilution.	
After dilution, the vial contains 5 doses of 0.3 mL. Withdraw the required 0.3 mL dose of diluted vaccine using a sterile needle and syringe and discard any unused vaccine within 6 hours after dilution.	

For instructions on disposal see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

The administration of COVID-19 mRNA Vaccine BNT162b2 should be postponed in individuals suffering from acute severe febrile illness.

Individuals receiving anticoagulant therapy or those with a bleeding disorder that would contraindicate intramuscular injection, should not be given the vaccine unless the potential benefit clearly outweighs the risk of administration.

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the vaccine. No data are available about concomitant use of immunosuppressants.

As with any vaccine, vaccination with COVID-19 mRNA Vaccine BNT162b2 may not protect all vaccine recipients.

No data are available on the use of COVID-19 mRNA Vaccine BNT162b2 in persons that have previously received a full or partial vaccine series with another COVID-19 vaccine.

Excipient information
This vaccine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially ‘potassium-free’.
This vaccine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concomitant administration of COVID-19 mRNA Vaccine BNT162b2 with other vaccines has not been studied (see section 5.1).

Do not mix COVID-19 mRNA Vaccine BNT162b2 with other vaccines/products in the same syringe.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of COVID-19 mRNA Vaccine BNT162b2. Animal reproductive toxicity studies have not been completed. COVID-19 mRNA Vaccine BNT162b2 is not recommended during pregnancy.

For women of childbearing age, pregnancy should be excluded before vaccination. In addition, women of childbearing age should be advised to avoid pregnancy for at least 2 months after their second dose.

Breast-feeding
It is unknown whether COVID-19 mRNA Vaccine BNT162b2 is excreted in human milk. A risk to the newborns/infants cannot be excluded. COVID-19 mRNA Vaccine BNT162b2 should not be used during breast-feeding.

Fertility
It is unknown whether COVID-19 mRNA Vaccine BNT162b2 has an impact on fertility.

4.7 Effects on ability to drive and use machines

COVID-19 mRNA Vaccine BNT162b2 has no or negligible influence on the ability to drive and use machines. However, some of the adverse reactions mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile
The safety of COVID-19 mRNA Vaccine BNT162b2 was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America. Study BNT162-01 (Study 1) enrolled 60 participants, 18 through 55 years of age. Study C4591001 (Study 2) enrolled approximately 44,000 participants, 12 years of age or older. In Study 2, a total of 21,720 participants 16 years of age or older received at least one dose of COVID-19 mRNA Vaccine BNT162b and 21,728 participants 16 years of age or older received placebo. Out of these, at the time of the analysis, 19,067 (9531 COVID-19 mRNA Vaccine BNT162b2 and 9536 placebo) were evaluated for safety 2 months after the second dose of COVID-19 mRNA Vaccine BNT162b2.

Demographic characteristics were generally similar with regard to age, gender, race and ethnicity among participants who received COVID-19 mRNA Vaccine and those who received placebo. Overall, among the participants who received COVID-19 mRNA Vaccine BNT162b2, 51.5% were male and 48.5% were female, 82.1% were White, 9.6% were Black or African American, 26.1% were Hispanic/Latino, 4.3% were Asian and 0.7% were Native American/Alaskan native.

The most frequent adverse reactions in participants 16 years of age and older were pain at the injection site (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 30%), chills (> 30%), arthralgia (> 20%) and pyrexia (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. If required, symptomatic treatment with analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used.

Adverse reactions from clinical studies
Adverse reactions reported in clinical studies are listed in this section per MedDRA system organ class, in decreasing order of frequency and seriousness. The frequency is defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from available data).

Blood and lymphatic system disorders
Uncommon: Lymphadenopathy

Nervous system disorders
Very common: Headache

Musculoskeletal and connective tissue disorders
Very common: Arthralgia; myalgia

General disorders and administration site conditions
Very common: Injection-site pain; fatigue; chills; pyrexia

Common:	Redness at injection site; injection site swelling
Uncommon:	Malaise

Gastrointestinal disorders

Common	Nausea

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Coronavirus Yellow Card reporting site https://coronavirus-yellowcard.mhra.gov.uk/
or search for MHRA Yellow Card in the Google Play or Apple App Store
and include the vaccine brand and batch/Lot number if available.

4.9 Overdose

Participants who received 58 micrograms of COVID-19 mRNA Vaccine in clinical trials did not report an increase in reactogenicity or adverse events.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

5. PHARMACODYNAMIC PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: {group}, ATC code: not yet assigned

Mechanism of action

The nucleoside-modified messenger RNA in COVID-19 mRNA Vaccine BNT162b2 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 neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19 disease.

Efficacy in participants 16 years of age and older

The efficacy of COVID-19 mRNA Vaccine BNT162b2 was evaluated in participants 16 years of age and older in two clinical studies conducted in the United States, Europe, Turkey, South Africa and South America. Study 1 enrolled 60 participants, 18 through 55 years of age. Study 2 is a multicentre, placebo-controlled efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 through 15 years of age, 16 through 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19 disease. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). There was no requirement for prophylactic use of paracetamol or analgesics. Influenza vaccines could be administered outside a window ± 14 days of the vaccine doses.

In Study 2, approximately 44,000 participants 12 years of age and older were randomised equally and received 2 doses of COVID-19 mRNA Vaccine or placebo with a planned interval of 21 days. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. Participants are planned to be followed for up to 24 months, for assessments of safety and efficacy against COVID-19 disease.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose.

Demographic characteristics were generally similar with regard to age, gender, race and ethnicity among participants who received COVID-19 mRNA BNT162b2 vaccine and those who received placebo. Overall, among the participants who received COVID-19 mRNA vaccine, 51.1% were male and 48.9% were female, 82.8% were White, 8.9% were Black or African American, 26.8% were Hispanic/Latino, 4.5% were Asian and 0.6% were Native American/Alaskan native. 57.2% were aged 16-55 years, 42.6% were aged > 55 years and 21.8% were ≥ 65 years.

Efficacy against COVID-19 disease

At the time of the analysis of Study 2, information presented is based on participants 16 years and older. Participants had been followed for symptomatic COVID-19 disease for at least 2,214 person-years for the COVID-19 mRNA Vaccine and at least 2,222 person-years in the placebo group. There were 8 confirmed COVID-19 cases identified in the COVID-19 mRNA Vaccine group and 162 cases in the placebo group, respectively. In this analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine BNT162b2 from first COVID-19 occurrence from 7 days after Dose 2 in participants **without evidence** of prior infection with SARS-CoV-2 was 95.0% (95% credible interval of 90.3% to 97.6%). In participants 65 years of age and older and 75 years of age and older without evidence of prior infections with SARS-CoV-2, efficacy of COVID-19 mRNA Vaccine BNT162b2 was 94.7% (two-sided 95% confidence interval of 66.7% to 99.9%) and 100% (two-sided 95% confidence interval of -13.1% to 100.0%) respectively.

In a separate analysis, compared to placebo, efficacy of COVID-19 mRNA Vaccine from first COVID-19 occurrence from 7 days after Dose 2 in participants **with or without evidence** of prior infection with SARS-CoV-2 was 94.6% (95% credible interval of 89.9% to 97.3%).

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 disease including those with one or more comorbidities that increase the risk of severe COVID-19 disease (e.g. asthma, BMI ≥ 30 kg/m^2, chronic pulmonary disease, diabetes mellitus, hypertension).

Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 disease.*

**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.*

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of repeat dose toxicity. Animal studies into potential toxicity to reproduction and development have not been completed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ALC-0315 = (4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate),
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide,

1,2-Distearoyl-sn-glycero-3-phosphocholine,
cholesterol,
potassium chloride,
potassium dihydrogen phosphate,
sodium chloride,
disodium hydrogen phosphate dihydrate,
sucrose,
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

6 months at -80 °C to -60 °C.

6.4 Special precautions for storage

Store in a freezer at -80 °C to -60 °C.
Store in the thermal container at -90 ºC to -60 ºC.

Store in the original package in order to protect from light.

After thawing, the vaccine should be diluted and used immediately. However, in-use stability data have demonstrated that once thawed, the undiluted vaccine can be stored for up to 5 days at 2 °C to 8 °C, or up to 2 hours at temperatures up to 25 °C, prior to use. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. Thawed vials can be handled in room light conditions.

After dilution, store the vaccine at 2 °C to 25 °C and use immediately and within 6 hours. The vaccine does not contain a preservative. Discard any unused vaccine.

Once diluted, the vials should be marked with the dilution date and time. Once thawed, the vaccine cannot be re-frozen.

6.5 Nature and contents of container

Concentrate for solution for injection for 5 doses in a 2 mL clear vial (type I glass) with a stopper (bromobutyl) and a flip-off plastic cap with aluminium seal.

Pack size: 195 vials

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
For instructions on dose preparation of the medicinal product before administration, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Not applicable.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

Allegato 2

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

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A Quick Take is available at NEJM.org

Coronavirus disease 2019 (COVID-19) has affected tens of millions of people globally[1] since it was declared a pandemic by the World Health Organization on March 11, 2020.[2] Older adults, persons with certain coexisting conditions, and front-line workers are at highest risk for Covid-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 in other populations, including younger adults.[3] Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which has had devastating medical, economic, and social consequences.

We previously reported phase 1 safety and immunogenicity results from clinical trials of the vaccine candidate BNT162b2,[4] a lipid nanoparticle–formulated,[5] nucleoside-modified RNA (modRNA)[6] encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation.[7] Findings from studies conducted in the United States and Germany among healthy men and women showed that two 30-μg doses of BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.[8] The 50% neutralizing geometric mean titers elicited by 30 μg of BNT162b2 in older and younger adults exceeded the geometric mean titer measured in a human convalescent serum panel, despite a lower neutralizing response in older adults than in younger adults. In addition, the reactogenicity profile of BNT162b2 represented mainly short-term local (i.e., injection site) and systemic responses. These findings supported progression of the BNT162b2 vaccine candidate into phase 3.

Here, we report safety and efficacy findings from the phase 2/3 part of a global phase 1/2/3 trial evaluating the safety, immunogenicity, and efficacy of 30 μg of BNT162b2 in preventing Covid-19 in persons 16 years of age or older. This data set and these trial results are the basis for an application for emergency use authorization.[9] Collection of phase 2/3 data on vaccine immunogenicity and the durability of the immune response to immunization is ongoing, and those data are not reported here.

METHODS

TRIAL OBJECTIVES, PARTICIPANTS AND OVERSIGHT

We assessed the safety and efficacy of two 30-μg doses of BNT162b2, administered intramuscularly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript. BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data.

TRIAL PROCEDURES

With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 μg of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.

SAFETY

The primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in this report. In this report, safety

data are reported for all participants who provided informed consent and received at least one dose of vaccine or placebo. Per protocol, safety results for participants infected with HIV (196 patients) will be analyzed separately and are not included here.

During the phase 2/3 portion of the study, a stopping rule for the theoretical concern of vaccine-enhanced disease was to be triggered if the one-sided probability of observing the same or a more unfavorable adverse severe case split (a split with a greater proportion of severe cases in vaccine recipients) was 5% or less, given the same true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: 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, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-COV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Details are provided in the protocol.

An explanation of the various denominator values for use in assessing the results of the trial is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. In brief, the safety population includes persons 16 years of age or older; a total of 43,448 participants constituted the population of enrolled persons injected with the vaccine or placebo. The main safety subset as defined by the FDA, with a median of 2 months of follow-up as of October 9, 2020, consisted of 37,706 persons, and the reactogenicity subset consisted of 8183 persons. The modified intention-to-treat (mITT) efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases). The number of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%.

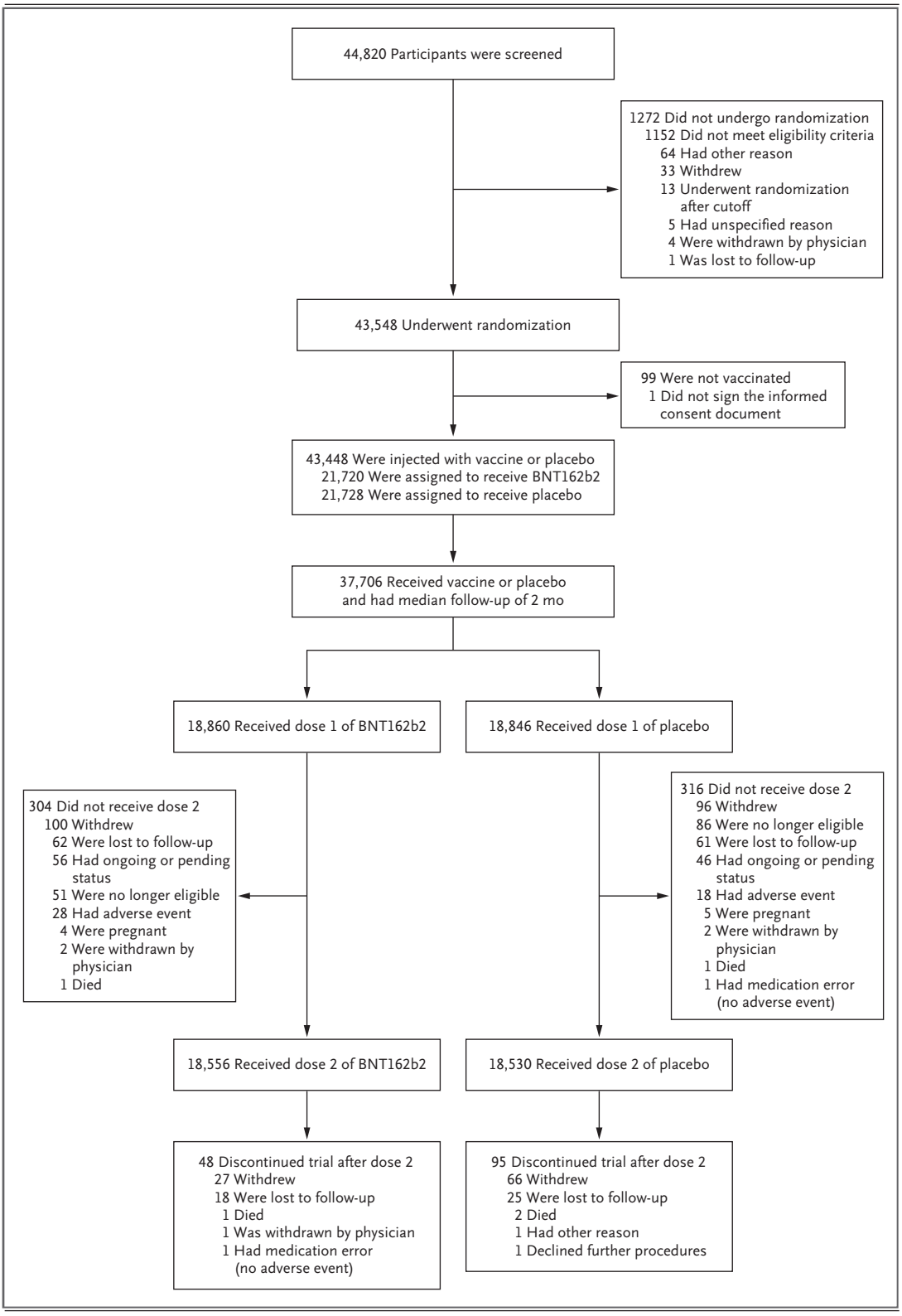


Figure 1 (facing page). Enrollment and Randomization.
The diagram represents all enrolled participants through November 14, 2020. The safety subset (those with a median of 2 months of follow-up, in accordance with application requirements for Emergency Use Authorization) is based on an October 9, 2020, data cutoff date. The further procedures that one participant in the placebo group declined after dose 2 (lower right corner of the diagram) were those involving collection of blood and nasal swab samples.

Moreover, primary and secondary efficacy end points are evaluated sequentially to control the familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

RESULTS

PARTICIPANTS

Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of

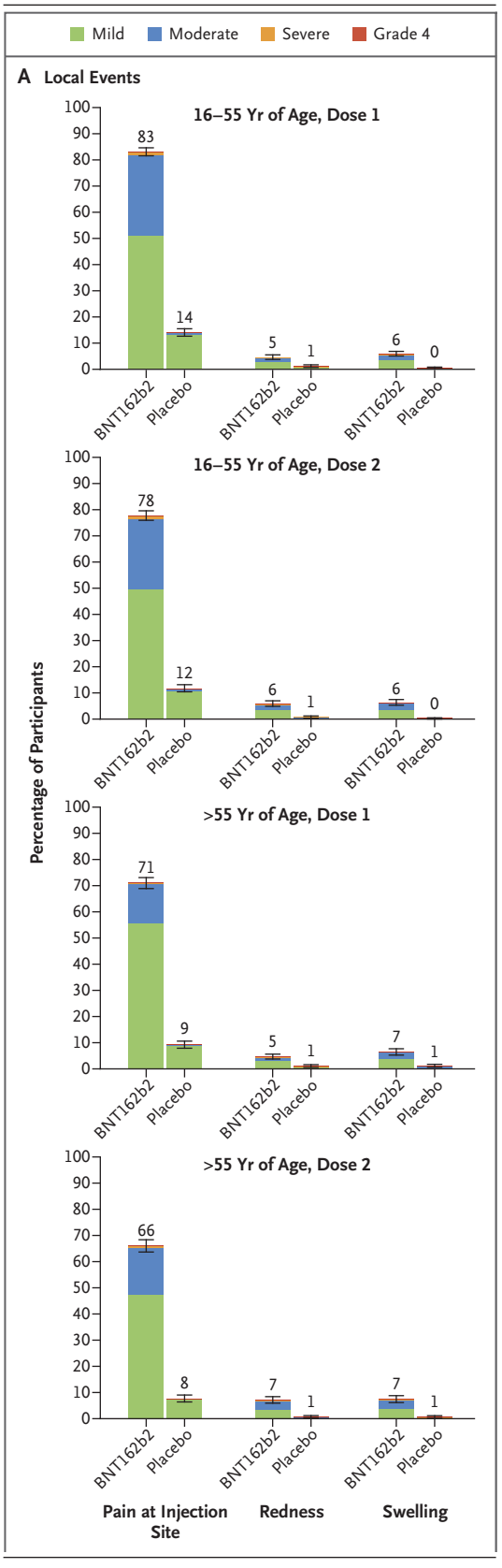
Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Figure 2. Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.

Data on local and systemic reactions and use of medication were collected with electronic diaries from participants in the reactogenicity subset (8,183 participants) for 7 days after each vaccination. Solicited injection-site (local) reactions are shown in Panel A. Pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and grade 4, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Systemic events and medication use are shown in Panel B. Fever categories are designated in the key; medication use was not graded. Additional scales were as follows: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); grade 4 for all events indicated an emergency department visit or hospitalization. I bars represent 95% confidence intervals, and numbers above the I bars are the percentage of participants who reported the specified reaction.

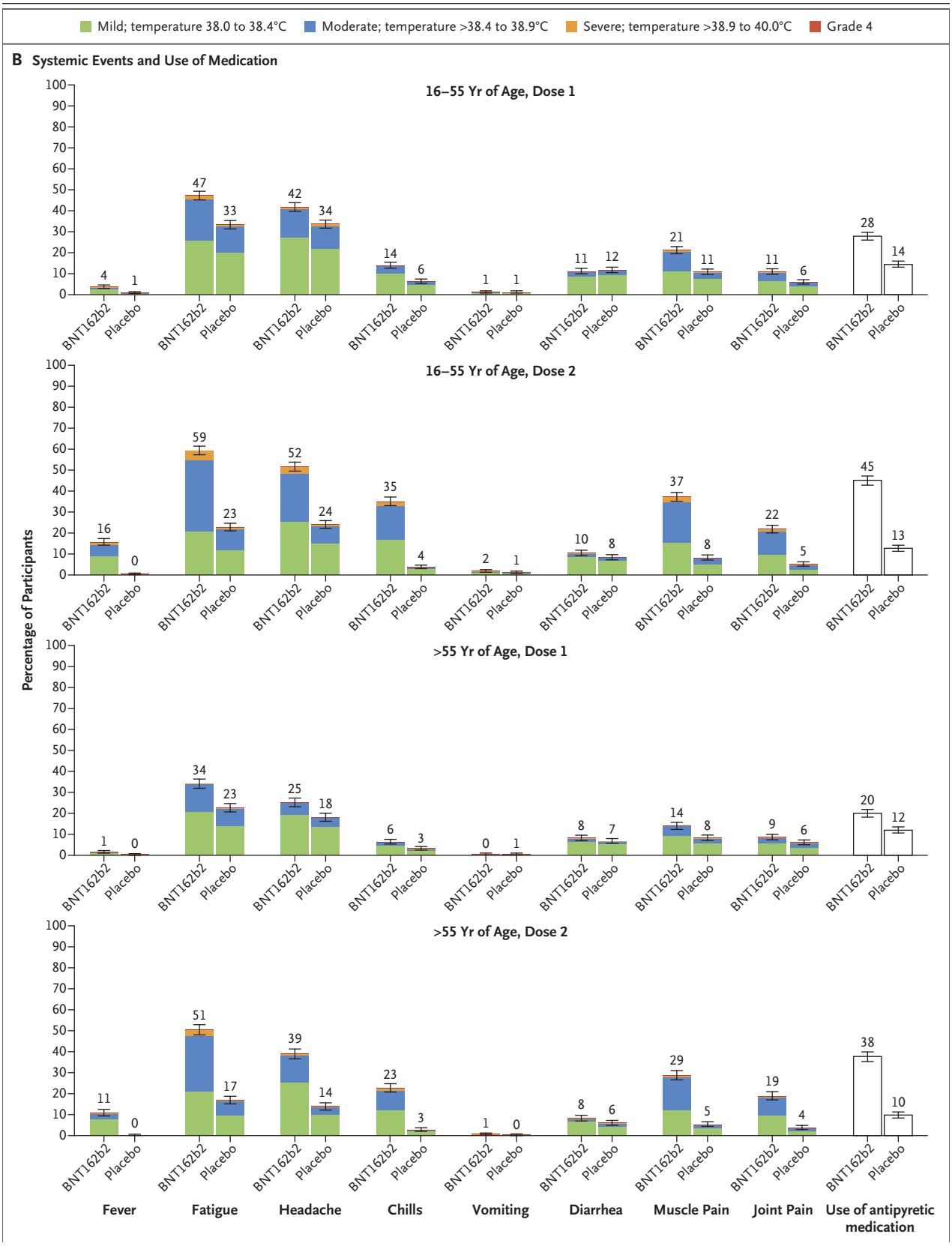


43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo (Fig. 1). At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

SAFETY

Local Reactogenicity

The reactogenicity subset included 8183 participants. Overall, BNT162b2 recipients reported more local reactions than placebo recipients. Among BNT162b2 recipients, mild-to-moderate pain at



the injection site within 7 days after an injection was the most commonly reported local reaction, with less than 1% of participants across all age groups reporting severe pain (Fig. 2). Pain was reported less frequently among participants older than 55 years of age (71% reported pain after the first dose; 66% after the second dose) than among younger participants (83% after the first dose; 78% after the second dose). A noticeably lower percentage of participants reported injection-site redness or swelling. The proportion of participants reporting local reactions did not increase after the second dose (Fig. 2A), and no participant reported a grade 4 local reaction. In general, local reactions were mostly mild-to-moderate in severity and resolved within 1 to 2 days.

Systemic Reactogenicity

Systemic events were reported more often by younger vaccine recipients (16 to 55 years of age) than by older vaccine recipients (more than 55 years of age) in the reactogenicity subset and more often after dose 2 than dose 1 (Fig. 2B). The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older recipients). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose.

Fever (temperature, ≥38°C) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients reported fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Two participants each in the vaccine and placebo groups reported temperatures above 40.0°C. Younger vaccine recipients were more likely to use antipyretic or pain medication (28% after dose 1; 45% after dose 2) than older vaccine recipients (20% after dose 1; 38% after dose 2), and placebo recipients were less likely (10 to 14%) than vaccine recipients to use the medications, regardless of age or dose. Systemic events including fever and chills were observed with the first 1 to 2 days after vaccination and resolved shortly thereafter.

Daily use of the electronic diary ranged from 90 to 93% for each day after the first dose and from 75 to 83% for each day after the second dose. No difference was noted between the BNT162b2 group and the placebo group.

ADVERSE EVENTS

Adverse event analyses are provided for all enrolled 43,252 participants, with variable follow-up time after dose 1 (Table S3). More BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). This distribution largely reflects the inclusion of transient reactogenicity events, which were reported as adverse events more commonly by vaccine recipients than by placebo recipients. Sixty-four vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) reported lymphadenopathy. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Two BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered by the investigators to be related to the vaccine or placebo. No Covid-19–associated deaths were observed. No stopping rules were met during the reporting period. Safety monitoring will continue for 2 years after administration of the second dose of vaccine.

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Ta-

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

ble 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

DISCUSSION

A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19. The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%. These results met our prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum FDA criteria for authorization.[9] Although the study was not powered to definitively assess efficacy by subgroup, the point estimates of efficacy for subgroups based on age, sex, race, ethnicity, body-mass index, or the presence of an underlying condition associated with a high risk of Covid-19 complications are also high. For all analyzed subgroups in which more than 10 cases of Covid-19 occurred, the lower limit of the 95% confidence interval for efficacy was more than 30%.

The cumulative incidence of Covid-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incuba-

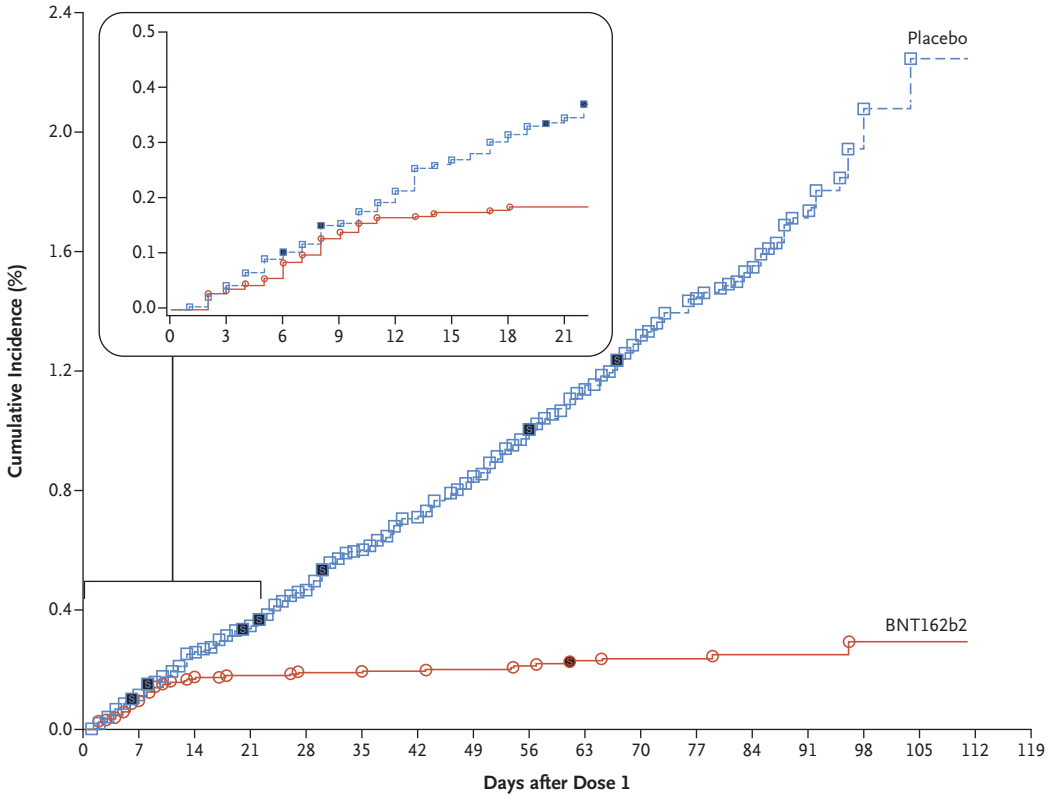
Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI)†
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group‡					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
† The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.
‡ Race or ethnic group was reported by the participants. "All others" included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.

tion period of 5 days,[10] indicating the early onset of a partially protective effect of immunization. The study was not designed to assess the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficacy against Covid-19 was 52%, and in the first 7 days after dose 2, it was 91%, reaching full efficacy against disease with onset at least 7 days after dose 2. Of the 10 cases of severe Covid-19 that were observed after the first dose, only 1 occurred in the vaccine group. This finding is consistent with overall high efficacy against all Covid-19 cases. The severe case split provides preliminary evidence of vaccine-mediated protection against severe disease, alleviating many of the theoretical concerns over vaccine-mediated disease enhancement.[11]

The favorable safety profile observed during phase 1 testing of BNT162b2[4,8] was confirmed in the phase 2/3 portion of the trial. As in phase 1, reactogenicity was generally mild or moderate, and reactions were less common and milder in older adults than in younger adults. Systemic reactogenicity was more common and severe after the second dose than after the first dose, although local reactogenicity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of some vaccines recommended for older adults.[12] This rate of severe fatigue is also lower than that observed in recipients of another approved viral vaccine for older adults.[13] Overall, reactogenicity events were transient and resolved within a couple



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
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)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Shown is the cumulative incidence of Covid-19 after the first dose (modified intention-to-treat population). Each symbol represents Covid-19 cases starting on a given day; filled symbols represent severe Covid-19 cases. Some symbols represent more than one case, owing to overlapping dates. The inset shows the same data on an enlarged y axis, through 21 days. Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from the first dose to the end of the surveillance period. The confidence interval (CI) for vaccine efficacy (VE) is derived according to the Clopper–Pearson method.

of days after onset. Lymphadenopathy, which generally resolved within 10 days, is likely to have resulted from a robust vaccine-elicited immune response. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively).

This trial and its preliminary report have several limitations. With approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both

the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later. Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establishment of a correlate of protection has not been feasible at the time of this report.

This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women. Safety and immune response data from this trial after immunization of adolescents 12 to 15 years of age will be reported subsequently, and additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups, such as immunocompromised persons. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage. The current cold storage requirement may be alleviated by ongoing stability studies and formulation optimization, which may also be described in subsequent reports.

The data presented in this report have significance beyond the performance of this vaccine candidate. The results demonstrate that Covid-19 can be prevented by immunization, provide proof of concept that RNA-based vaccines are a promising new approach for protecting humans against infectious diseases, and demonstrate the speed with which an RNA-based vaccine can be developed with a sufficient investment of resources. The development of BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative. This rigorous demonstration of safety and efficacy less than 11 months later provides a practical demonstration that RNA-based vaccines, which require only viral genetic sequence information to initiate development, are a major new tool to combat pandemics and other infectious disease outbreaks. The continuous phase 1/2/3 trial design may provide a model to reduce the protracted development timelines that have delayed the availability of vaccines against other infectious diseases of medical importance. In the context of the current, still expanding pandemic, the BNT162b2 vaccine, if approved, can contribute, together with other public health measures, to reducing the devastating loss of health, life, and economic and social well-being that has resulted from the global spread of Covid-19.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Allegato 3

REG 174 INFORMAZIONI PER I PROFESSIONISTI SANITARI DEL REGNO UNITO

Questo medicinale non ha un'autorizzazione all'immissione in commercio nel Regno Unito, ma ha ricevuto l'autorizzazione per la fornitura temporanea dal Dipartimento della salute e dell'assistenza sociale del Regno Unito e dall'Agenzia di regolamentazione dei medicinali e dei prodotti sanitari per l'immunizzazione attiva per prevenire la malattia COVID-19 causata da SARS-CoV-2 in individui di età pari o superiore a 16 anni.

Come con qualsiasi nuovo medicinale nel Regno Unito, questo prodotto sarà attentamente monitorato per consentire una rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 per come segnalare le reazioni avverse.

1. NOME DEL PRODOTTO MEDICINALE

COVID-19 mRNA Vaccine BNT162b2 concentrato per soluzione iniettabile.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Questa è una fiala multidose e deve essere diluita prima dell'uso. 1 flaconcino (0,45 mL) contiene 5 dosi da 30 microgrammi di BNT162b2 RNA (incorporato in nanoparticelle lipidiche).

Il vaccino COVID-19 mRNA BNT162b2 è un RNA messaggero con cappuccio 5' (mRNA) a filamento singolo altamente purificato, prodotto tramite tecnica *cell-free in vitro transcription* dai corrispondenti modelli di DNA, che codifica per la proteina virale spike (S) di SARS-CoV-2.

Eccipienti con effetti noti:

Per l'elenco completo degli eccipienti, vedere la sezione 6.1.

3. FORMA FARMACEUTICA

Concentrato per soluzione iniettabile.

Il vaccino è una soluzione congelata di colore da bianco a biancastro.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Immunizzazione attiva per prevenire COVID-19 causato dal virus SARS-CoV-2, in individui di età pari o superiore a 16 anni. L'uso del vaccino COVID-19 mRNA BNT162b2 deve essere conforme alle linee guida ufficiali.

4.2 Posologia e modo di somministrazione

Posologia

Individui di età pari o superiore a 16 anni

Il vaccino COVID-19 mRNA BNT162b2 viene somministrato per via intramuscolare dopo la diluizione come un ciclo di due dosi (0,3 mL ciascuna) a 21 giorni di distanza (vedere paragrafo 5.1).

Non ci sono dati disponibili sull'intercambiabilità del vaccino COVID-19 mRNA BNT162b2 con altri vaccini COVID-19 per completare il ciclo di vaccinazioni.
Gli individui che hanno ricevuto una dose di vaccino COVID-19 mRNA BNT162b2 dovrebbero ricevere una seconda dose di vaccino COVID-19 mRNA BNT162b2 per completare il ciclo di vaccinazione.

Gli individui possono non essere protetti fino ad almeno 7 giorni dopo la loro seconda dose di vaccino.

Per ulteriori informazioni sull'efficacia, vedere paragrafo 5.1.

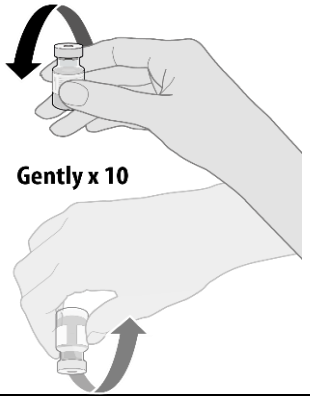
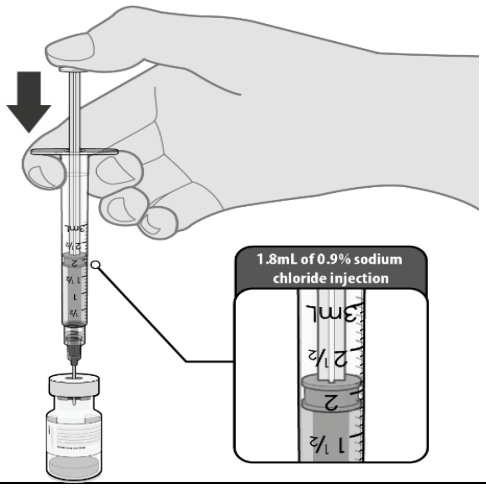
Popolazione pediatrica

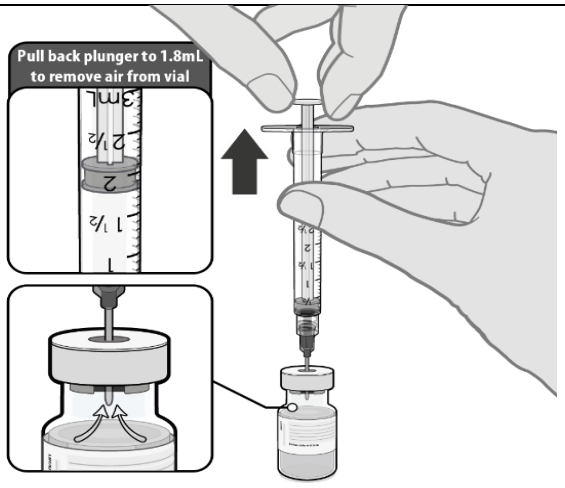
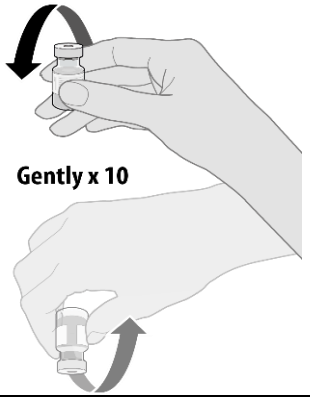
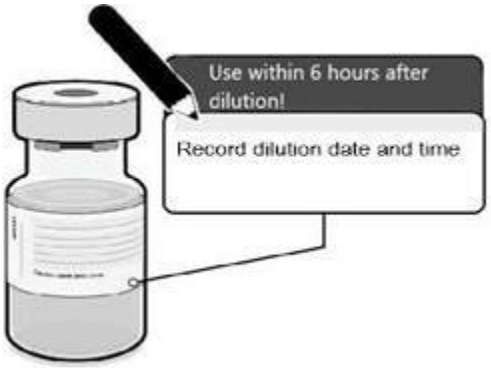
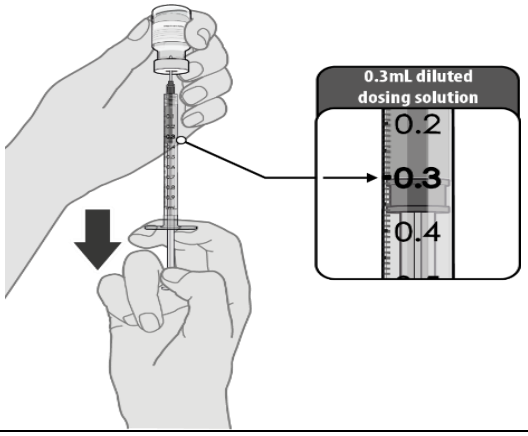
La sicurezza e l'efficacia del vaccino COVID-19 mRNA BNT162b2 nei bambini di età inferiore a 16 anni non sono state ancora stabilite.

Metodo di somministrazione

Somministrare il vaccino COVID-19 mRNA Vaccine BNT162b2 per via intramuscolare nel muscolo deltoide dopo la diluizione. Non iniettare il vaccino per via intravascolare, sottocutanea o intradermica.

Preparazione: la fiala multidose viene conservata congelata e deve essere scongelata prima della diluizione.

Le fiale congelate devono essere trasferite a 2 ° C a 8 ° C per scongelare ; una confezione da 195 flaconcini può impiegare 3 ore per scongelarsi (vedere paragrafo 6.4). In alternativa, le fiale congelate possono anche essere scongelate per 30 minuti a temperature fino a 25 ° C per un uso immediato. Una volta scongelato, il vaccino non diluito può essere conservato per un massimo di 5 giorni a una temperatura compresa tra 2 ° C e 8 ° C e fino a 2 ore a temperature fino a 25 ° C.	
Attendere che la fiala scongelata raggiunga la temperatura ambiente e capovolgerla delicatamente 10 volte prima della diluizione. Non agitare. Prima della diluizione, il vaccino deve presentarsi come una soluzione biancastra senza particelle visibili. Scartare il vaccino se sono presenti particolato o alterazione del colore.	
Il vaccino scongelato deve essere diluito nella sua fiala originale con 1,8 mL di soluzione iniettabile di cloruro di sodio 9 mg / mL (0,9%), utilizzando un ago di calibro 21 o più stretto e con **tecniche asettiche**. **Avvertimento:** l'unico diluente da utilizzare è la soluzione iniettabile di cloruro di sodio senza conservanti 9 mg / mL (0,9 %). Questo diluente non è fornito nella confezione del vaccino.	

Uniformare la pressione del flaconcino prima di rimuovere l'ago dal flaconcino prelevando 1,8 mL di aria nella siringa di diluente vuota.	
Capovolgere delicatamente la soluzione diluita 10 volte. Non agitare	
Il vaccino diluito deve presentarsi come una soluzione biancastra senza particelle visibili. Eliminare il vaccino diluito se sono presenti particolato o alterazione del colore.	
Le fiale diluite devono essere contrassegnate con la data e l'ora di diluizione e conservate tra 2°C e 25°C. Utilizzare immediatamente ed entro 6 ore dalla diluizione.	
Dopo la diluizione, la fiala contiene 5 dosi da 0,3 mL. Prelevare la dose necessaria di 0,3 mL di vaccino diluito utilizzando un ago e una siringa sterili ed eliminare l'eventuale vaccino non utilizzato entro 6 ore dalla diluizione.	

Per le istruzioni sullo smaltimento vedere il paragrafo 6.6.

4.3 Controindicazioni

Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

4.4 Avvertenze speciali e precauzioni per l'uso

Tracciabilità

Al fine di migliorare la tracciabilità dei medicinali biologici, il nome e il numero di lotto del prodotto somministrato devono essere chiaramente registrati.

Raccomandazioni generali

Come con tutti i vaccini iniettabili, devono essere sempre prontamente disponibili cure mediche e supervisione appropriate in caso di un raro evento anafilattico a seguito della somministrazione del vaccino.

La somministrazione del vaccino COVID-19 mRNA BNT162b2 deve essere posticipata nei soggetti affetti da malattie febbrili acute gravi.

Gli individui che ricevono una terapia anticoagulante o quelli con una malattia emorragica che controindicherebbe l'iniezione intramuscolare, non devono ricevere il vaccino a meno che il potenziale beneficio non superi chiaramente il rischio della somministrazione.

Le persone immunocompromesse, comprese le persone che ricevono una terapia immunosoppressiva, possono avere una risposta immunitaria ridotta al vaccino. Non sono disponibili dati sull'uso concomitante di immunosoppressori.

Come con qualsiasi vaccino, la vaccinazione con il vaccino COVID-19 mRNA BNT162b2 potrebbe non proteggere tutti i destinatari del vaccino.

Non sono disponibili dati sull'uso del vaccino COVID-19 mRNA BNT162b2 in persone che hanno precedentemente ricevuto un ciclo di vaccini completa o parziale con un altro vaccino COVID-19.

Informazioni sull'eccipiente

Questo vaccino contiene potassio, meno di 1 mmol (39 mg) per dose, cioè essenzialmente è "senza potassio". Questo vaccino contiene meno di 1 mmol di sodio (23 mg) per dose, cioè è essenzialmente "privo di sodio".

4.5 Interazione con altri medicinali e altre forme di interazione

Non sono stati effettuati studi di interazione.

La somministrazione concomitante del vaccino COVID-19 mRNA BNT162b2 con altri vaccini non è stata studiata (vedere paragrafo 5.1).

Non mescolare COVID-19 mRNA Vaccine BNT162b2 con altri vaccini / prodotti nella stessa siringa.

4.6 Fertilità, gravidanza e allattamento

Gravidanza

I dati sull'uso del vaccino mRNA COVID-19 BNT162b2 non esistono o sono limitati. Gli studi di tossicità riproduttiva sugli animali non sono stati completati. Il vaccino COVID-19 mRNA BNT162b2 non è raccomandato durante la gravidanza.

Per le donne in età fertile, la gravidanza deve essere esclusa prima della vaccinazione. Inoltre, alle donne in età fertile deve essere consigliato di evitare la gravidanza per almeno 2 mesi dopo la seconda dose.

Allattamento al seno

Non è noto se il vaccino COVID-19 mRNA BNT162b2 sia escreto nel latte umano. Non si può escludere un rischio per i neonati / bambini. Il vaccino COVID-19 mRNA BNT162b2 non deve essere utilizzato durante l'allattamento.

Fertilità

Non è noto se il vaccino COVID-19 mRNA BNT162b2 abbia un impatto sulla fertilità.

4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Il vaccino COVID-19 mRNA BNT162b2 non altera o altera in modo trascurabile la capacità di guidare veicoli e di usare macchinari. Tuttavia, alcune delle reazioni avverse menzionate al paragrafo 4.8 possono influenzare temporaneamente la capacità di guidare o usare macchinari.

4.8 Effetti indesiderati

Riassunto del profilo di sicurezza

La sicurezza del vaccino COVID-19 mRNA BNT162b2 è stata valutata in partecipanti di età pari o superiore a 16 anni in due studi clinici condotti negli Stati Uniti, Europa, Turchia, Sud Africa e Sud America. Lo studio BNT162-01 (Studio 1) ha arruolato 60 partecipanti, di età compresa tra 18 e 55 anni. Lo studio C4591001 (Studio 2) ha arruolato circa 44.000 partecipanti, di età pari o superiore a 12 anni.

Nello studio 2, un totale di 21.720 partecipanti di età pari o superiore a 16 anni hanno ricevuto almeno una dose di vaccino mRNA COVID19 BNT162b e 21.728 partecipanti di età pari o superiore a 16 anni hanno ricevuto placebo. Di questi, al momento dell'analisi, 19.067 (9531 COVID-19 mRNA Vaccine BNT162b2 e 9536 placebo) sono stati valutati per la sicurezza 2 mesi dopo la seconda dose di COVID-19 mRNA Vaccine BNT162b2.

Le caratteristiche demografiche erano generalmente simili per quanto riguarda età, sesso, razza ed etnia tra i partecipanti che hanno ricevuto il vaccino mRNA COVID-19 e quelli che hanno ricevuto il placebo. Complessivamente, tra i partecipanti che hanno ricevuto il vaccino COVID-19 mRNA BNT162b2, il 51,5% erano maschi e il 48,5% erano femmine, l'82,1% erano bianchi, il 9,6% erano neri o afroamericani, il 26,1% erano ispanici / latini, il 4,3% erano asiatici e 0,7 % erano nativi americani / nativi dell'Alaska.

Le reazioni avverse più frequenti nei partecipanti di età pari o superiore a 16 anni sono state dolore al sito di iniezione (> 80%), affaticamento (> 60%), mal di testa (> 50%), mialgia (> 30%), brividi (> 30 %), artralgia (> 20%) e piressia (> 10%) e sono stati generalmente di intensità lieve o moderata e si sono risolti entro pochi giorni dalla vaccinazione. Se necessario, può essere utilizzato un trattamento sintomatico con medicinali analgesici e / o antipiretici (ad es. prodotti contenenti paracetamolo).

Reazioni avverse da studi clinici

Le reazioni avverse riportate negli studi clinici sono elencate in questa sezione per classificazione per sistemi e organi MedDRA, in ordine decrescente di frequenza e gravità. La frequenza è definita come segue: molto comune (≥ 1/10), comune (da ≥ 1/100 a <1/10), non comune (da ≥ 1 / 1.000 a <1/100), raro (da ≥ 1 / 10.000 a < 1 / 1.000), molto raro (<1 / 10.000), non nota (non può essere definita sulla base dei dati disponibili).

Patologie del sistema sanguigno e linfatico
Raro: Linfoadenopatia

Disturbi del sistema nervoso
Molto comune: Mal di testa

Disturbi muscoloscheletrici e del tessuto connettivo
Molto comune: Artralgia; mialgia

Patologie sistemiche e condizioni relative alla sede di somministrazione
Molto comune: Dolore al sito di iniezione; fatica; brividi; piressia
Comune: Rossore al sito di iniezione; gonfiore al sito di iniezione
Raro: Malessere

Disordini gastrointestinali
Comune: Nausea

Segnalazione di sospette reazioni avverse

La segnalazione di sospette reazioni avverse dopo l'autorizzazione del medicinale è importante. Consente il monitoraggio continuo del rapporto rischi / benefici del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sito di segnalazione del Coronavirus Yellow Card https://coronavirus-yellowcard.mhra.gov.uk oppure cerca il cartellino giallo MHRA in Google Play o nell'App Store di Apple e includere il marchio del vaccino e il numero di lotto / lotto, se disponibile.

4.9 Sovradosaggio

I partecipanti che hanno ricevuto 58 microgrammi di vaccino mRNA COVID-19 negli studi clinici non hanno segnalato un aumento della reattogenicità o eventi avversi. In caso di sovradosaggio, si raccomanda il monitoraggio delle funzioni vitali e l'eventuale trattamento sintomatico.

5. PROPRIETÀ FARMACODINAMICHE

5.1 Proprietà farmacodinamiche

Categoria farmacoterapeutica: {group}, codice ATC: non ancora assegnato

Meccanismo di azione
L'RNA messaggero modificato con nucleosidi nel vaccino COVID-19 mRNA BNT162b2 è formulato in nanoparticelle lipidiche, che consentono il rilascio dell'RNA nelle cellule ospiti per consentire l'espressione dell'antigene SARSCoV-2

S. Il vaccino stimola sia gli anticorpi neutralizzanti che le risposte immunitarie cellulari all'antigene spike (S), che possono contribuire alla protezione contro la malattia COVID-19.

Efficacia nei partecipanti di età pari o superiore a 16 anni

L'efficacia del vaccino COVID-19 mRNA BNT162b2 è stata valutata in partecipanti di età pari o superiore a 16 anni in due studi clinici condotti negli Stati Uniti, Europa, Turchia, Sud Africa e Sud America. Lo studio 1 ha arruolato 60 partecipanti, dai 18 ai 55 anni di età. Lo studio 2 è uno studio di efficacia multicentrico, controllato con placebo su partecipanti di età pari o superiore a 12 anni. La randomizzazione è stata stratificata per età: da 12 a 15 anni di età, da 16 a 55 anni di età o da 56 anni di età e oltre, con un minimo del 40% dei partecipanti nello strato di età ≥ 56 anni. Lo studio ha escluso i partecipanti immunocompromessi e quelli che avevano una precedente diagnosi clinica o microbiologica della malattia COVID-19.

Sono stati inclusi i partecipanti con malattia stabile preesistente, definita come malattia che non richiedeva modifiche significative nella terapia o ospedalizzazione per peggioramento della malattia durante le 6 settimane precedenti l'arruolamento, così come i partecipanti con infezione stabile nota da virus dell'immunodeficienza umana (HIV), virus dell'epatite C (HCV) o virus dell'epatite B (HBV). Non era richiesto l'uso profilattico di paracetamolo o analgesici. I vaccini antinfluenzali potrebbero essere somministrati al di fuori di una finestra di ± 14 giorni dalle dosi del vaccino.

Nello studio 2, circa 44.000 partecipanti di età pari o superiore a 12 anni sono stati randomizzati allo stesso modo e hanno ricevuto 2 dosi di vaccino mRNA COVID-19 o placebo con un intervallo pianificato di 21 giorni. Le analisi di efficacia includevano partecipanti che hanno ricevuto la loro seconda vaccinazione entro 19-42 giorni dalla prima vaccinazione. I partecipanti dovrebbero essere seguiti per un massimo di 24 mesi, per la valutazione della sicurezza e dell'efficacia contro la malattia COVID-19.

La popolazione per l'analisi dell'endpoint primario di efficacia includeva 36.621 partecipanti di età pari o superiore a 12 anni (18.242 nel gruppo COVID-19 mRNA Vaccine e 18.379 nel gruppo placebo) che non avevano evidenza di una precedente infezione da SARS-CoV-2 a 7 giorni dopo la seconda dose.

Le caratteristiche demografiche erano generalmente simili per quanto riguarda età, sesso, razza ed etnia tra i partecipanti che hanno ricevuto il vaccino COVID-19 mRNA BNT162b2 e quelli che hanno ricevuto il placebo. Complessivamente, tra i partecipanti che hanno ricevuto il vaccino mRNA COVID-19, il 51,1% era di sesso maschile e il 48,9% di sesso femminile, l'82,8% era bianco, l'8,9% era nero o afroamericano, il 26,8% era ispanico / latino, il 4,5% era asiatico e lo 0,6% erano nativi americani / nativi dell'Alaska. Il 57,2% aveva un'età compresa tra 16 e 55 anni, il 42,6% aveva un'età> 55 anni e il 21,8% aveva un'età ≥ 65 anni.

Efficacia contro la malattia COVID-19

Al momento dell'analisi dello Studio 2, le informazioni presentate si basano sui partecipanti di età pari o superiore a 16 anni. I partecipanti erano stati seguiti per la malattia sintomatica COVID-19 per almeno 2.214 anni-persona per il vaccino mRNA COVID-19 e almeno 2.222 anni-persona nel gruppo placebo. Ci sono stati 8 casi confermati di COVID-19 identificati nel gruppo COVID-19 mRNA Vaccine e 162 casi nel gruppo placebo, rispettivamente. In questa analisi, rispetto al placebo, l'efficacia del vaccino COVID-19 mRNA BNT162b2 dalla prima occorrenza di COVID-19 da 7 giorni dopo la dose 2 nei partecipanti **senza evidenza** di precedente infezione da SARS-CoV-2 è stata del 95,0% (intervallo credibile del 95% di Dal 90,3% al 97,6%). Nei partecipanti di età pari o superiore a 65 anni e di età pari o superiore a 75 anni senza evidenza di precedenti infezioni da SARS-CoV-2, l'efficacia del vaccino COVID-19 mRNA BNT162b2 è stata del 94,7% (intervallo di confidenza bilaterale al 95% dal 66,7% al 99,9%) e 100% (intervallo di confidenza bilaterale al 95% da -13,1% a 100,0%) rispettivamente.

In un'analisi separata, rispetto al placebo, l'efficacia del vaccino COVID-19 mRNA dalla prima occorrenza di COVID-19 da 7 giorni dopo la dose 2 nei partecipanti **con o senza evidenza** di precedente infezione da SARS-CoV-2 è stata del 94,6% (95% intervallo di confidenza compreso tra 89,9% e 97,3%). Non ci sono state differenze cliniche significative

nell'efficacia complessiva del vaccino nei partecipanti che erano a rischio di malattia da COVID-19 grave, compresi quelli con una o più comorbidità che aumentano il rischio di malattia da COVID-19 grave (ad es. asma, BMI ≥ 30 kg / m2, malattia polmonare cronica, diabete mellito, ipertensione).

*I casi confermati sono stati determinati mediante reazione a catena della trascrizione polimerasi-inversa (RT-PCR) e almeno 1 sintomo compatibile con la malattia COVID-19 *.*

** Definizione del caso (almeno 1 di): febbre, tosse nuova o aumentata, mancanza di respiro nuova o aumentata; brividi, dolore muscolare nuovo o aumentato, nuova perdita del gusto o dell'olfatto, mal di gola, diarrea o vomito.*

5.2 Proprietà farmacocinetiche

Non applicabile.

5.3 Dati preclinici di sicurezza

I dati non clinici non rivelano rischi particolari per l'uomo sulla base di uno studio convenzionale di tossicità a dosi ripetute. Gli studi sugli animali sulla potenziale tossicità per la riproduzione e lo sviluppo non sono stati completati.

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

ALC-0315 = (4-idrossibutil) azandiil) bis (esano-6,1-diil) bis (2-esildecanoato),
ALC-0159 = 2 - [(polietilenglicole) -2000] -N, N-ditetradecilacetammide, 9 1,2-distearoil-sn-glicero-3-fosfocolina,
colesterolo,
cloruro di potassio,
diidrogeno fosfato di potassio,
cloruro di sodio,
disodio idrogenofosfato diidrato,
saccarosio,
acqua per preparazioni iniettabili

6.2 Incompatibilità

In assenza di studi di compatibilità, questo medicinale non deve essere miscelato con altri medicinali.

6.3 Data di scadenza

6 mesi da -80 ° C a -60 ° C.

6.4 Speciali precauzioni per la conservazione

Conservare in congelatore a una temperatura compresa tra -80 ° C e -60 ° C. Conservare nel contenitore termico a una temperatura compresa tra -90 ºC e -60 ºC.

Conservare nella confezione originale per proteggere il medicinale dalla luce.

Dopo lo scongelamento, il vaccino deve essere diluito e utilizzato immediatamente. Tuttavia, i dati sulla stabilità durante l'uso hanno dimostrato che, una volta scongelato, il vaccino non diluito può essere conservato per un massimo di 5 giorni a 8 ° C, o fino a 2 ore a temperature fino a 25 ° C, prima dell'uso.

Durante lo stoccaggio, ridurre al minimo l'esposizione alla luce ambientale ed evitare l'esposizione alla luce solare diretta e alla luce ultravioletta.

Le fiale scongelate possono essere maneggiate in condizioni di luce ambientale.

Dopo la diluizione, conservare il vaccino a una temperatura compresa tra 2 ° C e 25 ° C e utilizzarlo immediatamente ed entro 6 ore.

Il vaccino non contiene conservanti. Scartare qualsiasi vaccino inutilizzato.

Una volta diluite, le fiale devono essere contrassegnate con la data e l'ora di diluizione. Una volta scongelato, il vaccino non può essere ricongelato.

6.5 Natura e contenuto del contenitore

Concentrato per soluzione iniettabile per 5 dosi in un flaconcino trasparente da 2 mL (vetro di tipo I) con tappo (bromobutile) e capsula di chiusura a strappo in plastica con sigillo in alluminio.

Confezione: 195 flaconcini

6.6 Precauzioni speciali per lo smaltimento e la manipolazione

Qualsiasi medicinale inutilizzato o materiale di scarto deve essere smaltito in conformità con i requisiti locali.

Per le istruzioni sulla preparazione della dose del medicinale prima della somministrazione, vedere paragrafo 4.2.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

Non applicabile.

8. NUMERO (I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

Non applicabile.

9. DATA DELLA PRIMA AUTORIZZAZIONE / RINNOVO DELL'AUTORIZZAZIONE

Non applicabile.

10. DATA DI REVISIONE DEL TESTO