World Health Organization

mRNA vaccines against COVID-19: Pfizer-BioNTech COVID-19 vaccine BNT162b2

Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines

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General considerations on mRNA vaccines

The advantage of RNA-based vaccines is their potential for rapid development and reduced side effects. mRNA-based vaccines avoid the risk of integration with the host cell genome and are able to produce pure viral protein. mRNA is transiently expressed, therefore allowing protein to be made within the cell. . Lipid nanoparticle (LNP)-formulated mRNA vaccine technology allows the delivery of precise genetic information together with an adjuvant effect to antigen-presenting cells. It is molecularly well defined, free from materials of animal origin, and synthesized by an efficient, cell-free in vitro transcription process from DNA templates. The technology associated with this vaccine is also capable of bypassing time-consuming standardization processes, thus speeding up its commercial production. The fast and highly scalable mRNA manufacturing and LNP formulation processes enable rapid production of many vaccine doses, making it suitable for rapid vaccine development and pandemic vaccine supply.

COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) vaccine characteristics

The Pfizer-BioNTech COVID-19 vaccine, named BNT162b2, encodes a P2 mutant spike protein (PS 2) and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA). BNT162b2 elicits a blunted innate immune sensor activating capacity and thus augments antigen expression. Encapsulation into LNPs enables transfection of the mRNA into host cells after IM injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol. In the cytosol, the RNA is translated into the encoded viral protein. RNA-expressed S is being degraded intracellularly, the resulting peptides can be presented at the cell surface, triggering a specific humoral T cell mediated immune response with activity against the virus.

Development process, contents, formulation

BNT162b2 is a messenger ribonucleic acid (mRNA) vaccine produced as a highly It is a highliy purified single-stranded, 5`-capped mRNA that has been generated through in vitro transcription in cell-free conditions from the corresponding DNA. The mRNA encodes the viral spike (S) from SARS-CoV-2.
The following excipients are included: ALC-0315, ALC-0159 (polyethylene glycole), cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, and water for injections.

Pre-clinical Studies

The BNT162b2 mRNA vaccine against SARS-CoV-2 elicited high neutralizing antibody titers in mice after a single injection. Vaccination of mice also resulted in a robust T helper 1 (T_H1) and T follicular helper (T_{FH}) type $CD4^+$ responses as well as a robust $IFN\gamma^+IL\text{-}2^+$ $CD8^+$ T-cell response. This pattern of cell mediated immunity suggests a low likelihood that the vaccine will induce a hypersensitivity response and resulting vaccine associated enhanced respiratory diseases. In addition, the induction of a T_{FH} response lends support that the vaccine may confers durable immunity. Translation of this immunogenicity profile into protection against viral infection subsequently was tested in a non-human primate (NHP) study.

The immunogenicity of BNT162b2 in rhesus macaques paralleled that observed in the murine model.[1] Seven days after a second dose of two-dose series (at 0 and 21 days) of 100 µg of this mRNA vaccine, 50% virus neutralization titre of antibodies reached 18-times that of a human SARS-CoV-2 convalescent serum panel and remained 3.3-times higher than this benchmark at five weeks after the last immunisation, though the absolute titer had decayed from 1,689 to 310. The T_H1-biased $CD4^+$ T-

cell response and IFNγ^{+} CD8^{+} T-cell response mirrored that of the cellular immunogenicity profile reported in mice. A two-dose series of 100 μg of BNT162b2, separated by a three-week, interval, protected 2-4 year old rhesus macaques against viral infection when challenged, intranasally and intratracheally, with 1x10^{6} plaque forming units (pfu) of SARS-CoV-2 at 55 days after the second vaccination. Viral RNA, as measured by RT-qPCR, in the bronchoalveolar lavage fluid (BAL) and nasopharyngeal (NP) and oropharyngeal (OP) swabs was significantly reduced in the vaccinated animals as compared to the unvaccinated controls. Absence of virus was seen at Day 3 and Day 6 after challenge. Earlier or later time points were not measured. Histopathologic outcomes are not presented in any detail in the context of this NHP study; protective efficacy is limited to virologic outcomes. Overall, thes preclinical data indicate an immunogenic and efficacious vaccine with respect to protection from viral infection in the lower and upper airways of rhesus macaques three days after challenge.

Clinical Studies: phases 1/2

Phase 1/2 trial – Safety

Two candidates of the mRNA vaccine were tested in Phase 1 trials: BNT162b1 and BNT162b2. The latter was ultimately advanced to Phase 3 trials due to greater tolerability and greather breadth of T-cell epitopes represented.[2] Overall, the vaccine, given as a two-dose regimen at one of three doses (10 μg, 20 μg, 30 μg) was tolerated well in two age groups: 18-55 years and 65-85 years. Local and systemic adverse events were generally mild and more frequent in the two higher dose groups. Systemic adverse events were generally milder in the older age group. Perturbations in laboratory values that were deemed related to vaccine administration were also milder in older individuals. No serious adverse events were reported and no stopping rules met, though the trial was ongoing at the time of publication.

Phase 1/2 trial – Immunogenicity

Neutralizing antibody titers (50% neutralizing geometric mean titers (GMT)) elicited by BNT162b2 peaked at one week after the second vaccination and began decaying one week after that. There was a trend toward higher titers among individuals who had received the highest vacine dose of 30 μg. Vaccination with this dose elicited titers that were relatively lower than those seen in animal studies with titers in the 18 to 55 year olds that were 1.7 to 4.6 times than that seen in a convalescent serum panel and 1.1 to 2.2 times the convalescents among the 65 to 85 year olds. Safety and immunogenicity outputs were among an adult population that was stratified by age but relatively skewed toward a Caucasian background (85%). The make-up of the Phase III trial assessing efficacy of BNT162b2 was more diversified.

Clinical studies: Phase 2-3 trials[3]:Efficacy

Trial population

The Phase 2/3 pivotal registration trial of the vaccine was conducted at sites in 6 countries (US, Brazil, Argentina, Turkey, South Africa, and Germany) and involved in total about 43,000 participants aged 16 to 85 years, who were healthy or had stable medical conditions, randomised equally between vaccine and placebo groups. About 6% of participants had serological evidence of a past SARS-CoV-2 infection at entry to the trial. The vaccine was administered in 2 doses separated by 21 days. Most participants were white (83%) and from US sites (77%). Similar numbers of males and females were included and 42 % of the trial population was aged over 55 years, and 22% over 64 years, with a median age at vaccination of 52 years. About 46% of participants were obese or had a comorbid condition that would likely increase their risk of severe Covid-19 and 35% of participants were obese. The primary analysis

of the trial results was conducted when participants had been followed for an average of 2 months after the second vaccine dose and 92% had been followed for at least one month after the second dose.

Efficacy against Covid-19

Two primary endpoints were specified, efficacy among all participants and efficacy among participants who had no evidence of a previous SARS-CoV-2 infection before 7 days after the second vaccine dose. The primary assessment of efficacy was based on the total of 178 cases of symptomatic laboratory-confirmed SARS-CoV-2 infection occurring between 7 days after the second vaccine dose and the end of the follow-up period. Of these cases, 9 were in the vaccinated group and 169 in the placebo group with the estimate of vaccine efficacy (VE) being 94.6% (95% credibility interval (CI) 89.9% - 97.3%). When analysis was confined to participants without evidence of a previous SARS-CoV-2 infection the cases numbers were 8 in the vaccine group and 162 in the placebo group with the estimate of VE being 95.0% (95% CI 90.3% - 97.6%).

Analyses were also conducted including all cases from the time of the first dose. There was evidence of protection both between the first and second doses (VE 52.4%, 95% CI 29.5% - 68.4%) and between the second dose and 7 days after the second dose (VE 90.5%, 95% CI 61.05 to 98.9%). More detailed analyses indicated that there was no evidence of protection until about 12 days after the first dose, but subsequently the incidence of Covid-19 was lower among vaccinated participants.

In the period 7 or more days after the second vaccine dose, no significant variations in the estimates of vaccine efficacy were apparent when the primary analyses were stratified according to sex, age, race, ethnicity, country, comorbid conditions or obesity or obesity alone. In particular, among those aged 65 years or older, without evidence of prior infection prior to 7 days after the second dose, there was 1 case in the vaccinated group and 19 cases in the placebo group (VE 94.7%, 95% CI 66.7% to 99.9%).

Efficacy against severe Covid-19

A total of 10 cases of severe Covid-19 occurred in trial participants, 1 in the vaccinated group and 9 in the placebo group (VE 88.9%, 95% CI 20.1%, 99.7%). Of these cases, 5 occurred 7 or more days after the second vaccine dose, 1 in the vaccine group and 4 in the placebo group (VE 75%, 95% CI -152.6% to 99.5%).

Summary of efficacy evidence in phase 2-3 trials

The vaccine was highly efficacious against laboratory-confirmed Covid-19 from 7 days after the second vaccine dose until the end of the follow-up period, which was, on average, 2 months. Evidence of efficacy emerged from about 12 days after the first vaccine dose. No evidence of variations in efficacy were found in the various subgroups that were analyzed and, importantly, in subgroups of participants likely to be at higher risk of severe Covid-19, including those over 65 years and those with comorbid conditions or obesity, the estimates of efficacy were very high. Few participants in the trial developed severe Covid-19, so efficacy against this endpoint is less certain, but measured from the time of the first dose, there was only 1 severe case in the vaccinated group and 9 in the placebo group, consistent with high efficacy.

Clinical studies: Phase 2-3 trials:Vaccine Safety

Safety data from 37,586 participants ≥16 years of age randomized 1:1 to vaccine or placebo with a median of 2 months of follow up after the second dose suggested a favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the 7 days after vaccination, were frequent and mostly mild to moderate. Reactogenicity and adverse events (AEs) were generally milder and less frequent in participants in the older group (≥55 years of age) compared with the younger group (18-55 years of age) and tended to increase after the second dose. Reactogenicity was mostly mild to moderate and short-lived after dosing for both adult age groups (median onset was 0-2 days after either dose for a median duration of 1 - 2 days). The vaccine's AE profile did not suggest any specific safety concerns. The median onset of systemic AEs was 1-2 days after either dose for a median duration of 1 day. Severe adverse reactions occurred in 0.0% - 4.6% of participants. The incidence of serious adverse events (SAEs), deaths, and discontinuations due to AEs were low and comparable for both the vaccine and placebo groups. There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

Adverse Events

The most common solicited adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%). The mean duration of pain at the injection site after Dose 2 was 2.5 days (range 1 to 36 days), for redness 2.6 days (range 1 to 34 days), and for swelling 2.3 days (range 1 to 34 days).

Adverse Events of Special Interest (that would potentially require longer follow up)

Lymphadenopathy

Lymphadenopathy was reported in 64 participants (0.3%). There were more cases in the vaccine group (64) vs. the placebo group (6). In the vaccine group, 54 (0.5%) occurred in the younger (16- 55 years) age group and 10 (0.1%) in the older (>55 years) age group. Lymphadenopathy occurred in the arm and neck region, and was reported within 2 to 4 days after vaccination. The average duration of these events was approximately 10 days, with 11 events ongoing at the time of the data cutoff.

Bell's Palsy

Bell's palsy was reported by four vaccine participants and none in the placebo group. These cases occurred at 3, 9, 37, and 48 days after vaccination. One case (onset at 3 days post vaccination) was reported as resolved with sequelae within three days after onset, and the other three were reported as continuing or resolving as of the November 14, 2020 data cut-off with ongoing durations of 10, 15, and 21 days, respectively. The usual incidence of Bell`s palsy is 15-30/100,000/year.[4] The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population and an association between COVID-19 and Bell's palsy has been reported. At this point in time, there is no clear basis upon which to conclude a causal relationship, but surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations is an absolute requirement. Bell`s palsy has been addressed in the risk management plan.

Allergic reactions

The FDA independently conducted standard MedDRA queries (SMQs) on the phase 2/3 all-enrolled safety population using FDA-developed software. This was to evaluate for constellations of unsolicited adverse event preferred terms that could represent various diseases and conditions, including allergic, neurologic, inflammatory, and autoimmune conditions. The SMQs revealed a slight numerical imbalance of adverse events potentially representing allergic reactions, with more participants reporting hypersensitivity-related adverse events in the vaccine group (137 [0.63%]) compared with the placebo group (111 [0.51%]). No imbalances between treatment groups were evident for any of the other SMQs evaluated. [5]

Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials. Any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer BioNTech vaccine.

Additional adverse reactions may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine.

Serious Adverse Events

Two of the SAE's considered as possibly related to vaccine included shoulder injury possibly related to vaccine administration or to the vaccine itself, and lymphadenopathy involving the axilla contralateral to the vaccine injection site. The lymphadenopathy was temporally associated and biologically plausible.

Special populations

Comorbidities in the Clinical Trial

Across both treatment groups, 20.5% had any comorbidity (per the Charlson Comorbidity Index). The most frequently reported comorbidities were diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%) and were reported at similar frequencies in each group. More participants had comorbidities in the older population (31.1%) than the younger population (12.8%), including diabetes (14.6% and 3.8%), malignancy (7.4% and 1.0%), and pulmonary disease (8.8% and 7%).

Overall, 0.3% of participants were HIV-positive and were evenly distributed between treatment groups. The HIV-positive participants were included in the safety population and are shown as part of the study demographics and disposition but did not have safety data available to contribute to the safety analyses at the time of the data cutoff.

Pregnancies in the Clinical Trial

Female study participants of childbearing potential were screened for pregnancy prior to each vaccination. A positive test resulted in their exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occurred after vaccination, or before vaccination and were not detected by pre-vaccination screening tests. Twenty-three inadvertent pregnancies were reported through the data cut-off date of November 14, 2020 (12 vaccine, 11 placebo).

Pregnancy outcomes are currently not known. Available data on the BNT162b2 vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy

Special considerations

PEGylation ((or pegylation)

The Pfizer BioNTech BNT162b2 vaccine contains four lipids. The lipids encapsulate the mRNA in the form of a lipid nanoparticle to aid cell entry and stability of the RNA/lipid nanoparticles.

Two of the lipids are used in approved medicinal products (cholesterol and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)) and two have not been commonly used in an authorised medicinal product

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

ALC-0159 is a polyethylene glycol (PEG) lipid conjugate (i.e. PEGylated lipid). The primary function of the PEGylated lipid ALC-0159 is to form a protective hydrophilic layer that sterically stabilises the lipid nanoparticle, which contributes to storage stability and reduces nonspecific binding to proteins.

Severe allergies

From the excipients officially declared, ALC-0159 has the ability to cause allergic reactions since it contains polyethylene glycol (PEG) or macrogol.

Summary of vaccine safety aspects

Reactogenicity and adverse events (AEs) associated with the vaccine were generally milder and less frequent in participants in the older group (≥55 years of age) compared with the younger group (18-55 years of age) and tended to increase after the second dose. Reactogenicity was mostly mild to moderate and short-lived after dosing for both adult age groups (median onset was 0-2 days after either dose for a median duration of 1 - 2 days). Available data on the vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Adverse events of special interest (that would potentially require longer follow up) include lymphadenopathy, Bell's Palsy and Allergic reactions.