DUTCH SCIENTIFIC BOARD COVID-19 VACCINES

RECOMMENDATIONS ON PFIZER/BIONTECH

VACCINE

21 October 2020

This Note was provided to the Ministry of Public Health, Welfare and Sport and the Program Management COVID-19 on October 21th 2020

PARTICIPANTS

Scientific Board: 5.1.2e, 5.1.2e 5.1.2e, 5.1.2e 5.1.2e, 5.1.2e 5.1.2e.

INTRODUCTION

The Board obtained confidential information via the EC JNT as well as during the July 27th 2020 meeting of the science boards of France, Spain and NL with their JNT-members. The investigational Pfizer/BioNTech COVID-19 vaccine (BNT162b2) is a mRNA vaccine against SARS-CoV-2. The vaccine is designed to present full-length protein S capable of eliciting powerful immune responses when administered within a lipid nanoparticle.

BioNTech developed the investigational vaccine that will be manufactured, commercialized and distributed in collaboration with Pfizer with broad expertise in vaccine research and development, regulatory capabilities, and a global manufacturing and distribution network.

VACCINE PRESENTATION

Description of vaccine candidate

BioNTech has developed RNA-based vaccine candidates based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). BNT162b1 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes the trimerized receptor-binding domain (RBD) of the spike glycoprotein of SARS-CoV-2. BNT162b2 (variant RBP020.2) is a modRNA candidate vaccine encoding P2 mutant prefusion stabilized full length spike glycoprotein S. Both vaccine candidates are formulated in a lipid nanoparticle (LNP) composition.
The vaccine candidate BNT162b2 has been selected for Phase 2/3 evaluation at a dose of 30 µg in a two dose regimen.

Pre-clinical and clinical studies

Immunisation of mice with a single dose of BNT162b2 induced dose level-dependent increases in pseudovirus neutralisation titers. Prime-boost vaccination of rhesus macaques elicited SARS-CoV-2 specific neutralising geometric mean antibody titers, 10 to 18 times that of a SARS-CoV-2 convalescent human serum panel. The vaccine candidate generated strong S-specific TH1 type CD4+ and IFNγ+ CD8+ T-cell responses in mice and rhesus macaques and fully protected the lungs of immunized rhesus macaques from an infectious challenge with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-WA1/2020). After SARS-CoV-2 challenge viral RNA was detected in the nose of BNT162b2-immunised macaques only at day 1 whereas viral RNA was detected in the nose of all control-immunized macaques at day 1, 3 and 6 post challenge (Vogel et al., BioRxiv September 2020).

A Phase 1/2 placebo-controlled, observer-blinded dose-escalation study has been performed in healthy adults (18–55 years of age), who were randomized to receive 2 doses—separated by 21 days—of 10 µg, or 30 µg of vaccine candidate BNT162b1 or BNT162b2 or 100 µg only for BNT162b1 (Mulligan et al., Nature August 2020, Walsh et al. BioRxiv September 2020). Local reactions (primarily pain at injection site) and systemic events were dose-dependent, generally mild to moderate, and transient. Following BNT162b2 second dose treatment, however, unlike with BNT162b1, no subject reported redness or swelling. The overall rate of injection site pain was lower in older subjects compared to younger ones. A second vaccination with 100 µg was not administered because of the increased reactogenicity and a lack of meaningful increased immunogenicity after a single dose compared with the 30-µg dose.
Antigen-binding IgG and neutralizing responses to vaccination with 10 µg to 30 µg of BNT162b1 or BNT162b2 were boosted by dose 2 in both younger and older adults, showing clear benefit of a second dose. Seven days after a second dose of 30µg, BNT162b2 elicited SARS-CoV-2–neutralizing geometric mean titers (GMTs) in younger adults (18-55 years of age) that were 3.8 times the GMT of a panel of 38 sera of SARS-CoV-2 convalescent patients, and in older adults (65-85 years of age) the vaccine candidate elicited a neutralizing GMT 1.6 times the GMT of the same panel. Demonstrating strong immunogenicity in younger and older adults but with lower antigen-binding IgG and neutralizing responses in 65–85 year olds compared to 18–55 year olds. In both younger and older adults, the 2 vaccine candidates elicited similar dose dependent SARS-CoV-2–neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS-CoV-2 convalescent sera. BNT162b2 was associated with less systemic reactogenicity, particularly in older adults.
BNT162b1induced strong cell-mediated immune responses (TH1-biased CD4+ and CD8+), but cellular immune responses elicited by BNT162b2 are not available yet. It is anticipated that the full-length spike encoded by BNT162b2 will present a greater diversity of T-cell epitopes than does the much smaller RBD encoded by BNT162b1. This may lead to stronger and more consistent cellular responses to BNT162b2.

A randomized, double-blind, placebo-controlled phase 2/3 study to assess the efficacy and safety of BNT162b2 for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 16 years and older has started and will run in the US, South Africa, Argentina, Brazil and Germany. The vaccine candidate group will receive 2 vaccine doses with an interval of 21 days and will comprise 21,999 vaccine recipients. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo. Safety and tolerability of the candidate vaccine is continuously being analysed.

FDA and EMA have started rolling review. Both regulatory agencies are currently evaluating pre-clinical and clinical phase 1/2 data. Review will continue until enough evidence is available to support a formal marketing authorization application.

Production :

Several manufacturing sites in Europe (Belgium, Germany), including the recently acquired Novartis site in Marburg Germany with a total production capacity of 750 million vaccine doses/year. Expected distribution of 100 million doses 2020 and a total production capacity for 2021 of 1.3 billion doses.

Formulation, packaging, storage

- Formulation and packaging
  - Multi dose vials
  - 0.5 ml/dose
- Delivery by syringe
- Storage
  - At -80 degrees
  - At room temperature half-life is 6 hours.

General considerations

The levels of binding and neutralizing antibodies induced by two doses of vaccine candidate BNT162b2 are, for most participants, slightly higher as found for convalescent sera from human COVID-19 patients. However, one should be careful with the interpretation of this comparison since the neutralizing capacity of convalescent sera varies considerably between batches since it depends on several factors, such as the patients age, disease severity, time of sampling since disease onset and the number of sera included in the batch. Standardization of convalescent sera is urgently needed to also allow comparison of antibody responses elicited by the different candidate COVID-19 vaccines. Lower antigen-binding IgG and neutralizing responses were measured in 65–85 year old compared to 18–55 year old participants.
Risk of ADE during the waning phase of the immune response.

Only limited safety data is available for BNT162b2. Of the participants who received 30 µg BNT162b1 75% of the 18–55 years old group and 33% of the 65-85 years old group reported fever ≥38.0°C after the dose 2,including 1 older participant who reported fever (38.9–40.0°C).

The storage conditions (-80º) as well as a very short half-life at room temperature (six hours) may be a serious inconvenient for the implementation of a huge vaccination campaign.

CONCLUSIONS

BioNTech has developed RNA-based vaccine candidates based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). BNT162b2 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes the prefusion stabilized full length spike glycoprotein S.

At this moment the only human data available are phase1/2 safety and immunogenicity data. The study results showed an acceptable safety profile and the induction of neutralizing antibodies after one vaccine dose. Since no generally accepted correlate of protection has been identified yet, clinical efficacy data are required to provide an indication on the vaccines ability to induce protection against disease and/or infection. Extrapolating the NHP (rhesus macaques) results to humans suggests that vaccination with this vaccine candidate may not or only partially stop transmission of the virus in the community but could protect against severe disease. The vaccine is currently being tested in a phase 3 efficacy trial in the US.

RECOMMENDATIONS OF THE DUTCH SCIENCE BOARD ON COVID-19 VACCINES

The Committee analysed available data. Based on these pre-clinical and preliminary human phase 1/2 safety and immunogenicity data that show that the vaccine seems to be immunogenic with an acceptable safety profile, the Committee considers that the BNT162b2 vaccine can be successful.

NEDERLANDSE SAMENVATTING AANBEVELINGEN VAN HET WETENSCHAPPELIJK ADVIESPANEL COVID-19 VACCINS T.A.V. PFIZER/BIONETECHs mRNA VACCINE

- Pfizer/BioNTechs COVID-19 vaccin BNT162b2 bestaat uit mRNA verpakt in een *Lipid nanoparticle* (LNP). Het mRNA codeert voor het hele SARS-CoV-2 Spike (S) eiwit.
- Er zijn op dit moment alleen beperkte preklinische en preliminaire klinische fase 1/2 data beschikbaar deze beperkte dataset laat zien dat het vaccin een acceptabel veiligheidsprofiel heeft en in staat is neutraliserende antistoffen en een gunstige T-cel respons op te wekken.
- Het feit dat gebruik gemaakt wordt van een technologie waarmee nog geen geregistreerde vaccines gemaakt zijn is een risico.
- Voor het vaccin is productie capaciteit in EU beschikbaar
- De board ziet op dit moment geen reden voor een opt-out uit de deal van de EU-commissie met Pfizer aangaande levering van SARS-CoV-2 vaccin

These recommendations were approved by the Dutch science board COVID-19 vaccines. In application of the code of ethics, the members confirmed that none of them was in a situation of deportation and they all participated in the collegial debate of the committee.
The members of the COVID-19 Vaccine Scientific Committee are available to the Government to provide additional information, if necessary.