Phase 3 study designs COVID-19 vaccines in development.

AstraZeneca/Oxford vaccine:

Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults.

Vaccine:

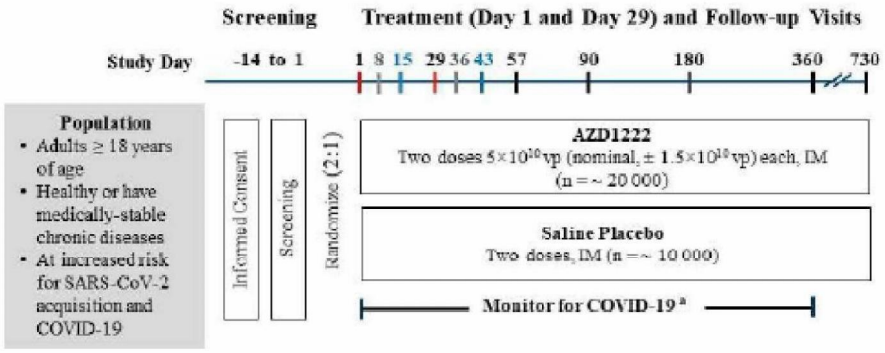
A replication deficient chimapanzee adenovirus-vector based vaccine (ChAdOx1 nCoV-19 or AZD1222) expressing the full length SARS-CoV-2 spike protein.

Pre-clinical and clinical data

In rhesus macaques a single dose of the COVID-19 vaccine candidate provided protection against lower respiratory tract infection in vaccinated animals after a high-dose SARS-CoV-2 challenge (2.6x 10^5 TCID50). Vaccinated animals showed S-protein specific humoral and cellular immune responses (Doremale et al., Nature July 2020).

A phase1/2 single blind, randomized (1:1) controlled trial in healthy adults 18-55 years has been performed in the UK. Participants either received a single im dose of $5x10^{10}$ viral particles test vaccine (n=543) or a single im dose of a control MenACWY vaccine (n=534) (Folegatti et al., *Lancet* 2020; 396: 467–78). Local and systemic reactions were more common in test group, 40% reported fever, no serious adverse events were reported. Reactogenicity was reduced when paracetamol was used prophylactically. In test vaccine group S-protein specific T-cell responses peaked at day 14 and S-protein specific antibodies peaked (157 ELISA units) at day 28 post vaccination and boosted to 639 EU (n=10). Vaccine induced responses were slightly lower/similar to responses following natural exposure. Specific neutralizing antibodies were detected in 91% and 100% with Micro Neutralisatioin Aassay (MNA) or Plaque Reduction Neutralisation assay (PRNT) (n=35) at day 28.

Phase 3 study design:



a Participants who present with qualifying symptoms will be tested for SARS-CoV-2 and if positive, will complete illness visits.

Red bars (Day 1 and Day 29): Administration of study intervention.
Gray bars (Day 8 and Day 36): Visits will be telephone contacts, not study site visits.
Blue bars (Day 15 and Day 43): Visits will only be for participants in the substudy. The first participants randomized in each age group, including 1 500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, will also participate in a substudy assessing the reactogenicity and immunogenicity of AZD1222.

COVID-19 = coronavirus disease 2019; IM = intramuscular; SARS-CoV-2 = severe acute respiratory

D8110C00001 is a Phase III randomized, double-blind, placebo-controlled multicenter study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to placebo for the prevention of COVID-19. Up to approximately 100 sites in the USA will participate in this study. Study sites outside of the USA will also be considered based on predicted transmission rates of SARS-CoV-2 in those locations.

Participants will be adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19.
Approximately 30 000 participants will be randomized in a 2:1 ratio to receive 2 IM doses of either 5 × 10^{10} vp (nominal, ± 1.5 × 10^{10} vp) AZD1222 (n = approximately 20 000) or saline placebo (n = approximately 10 000) 4 weeks apart, on Days 1 and 29. Randomization will be stratified by age (≥ 18 to < 65 years, and ≥ 65 years), with at least 25% of participants to be enrolled in the older age stratum. All participants will be assessed for efficacy and safety. The first participants randomized in each age group, including 1 500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, will also participate in a substudy assessing the reactogenicity and immunogenicity of AZD1222.
A PSRT will provide safety surveillance during the study. Additionally, an independent COVID-19 Vaccine DSMB organized by the National Institutes of Health, National Institute for Allergy and Infectious Diseases, will provide oversight, to ensure safe and ethical conduct of the study.
Participants will remain on study for 2 years following administration of the first dose of study intervention (Day 730). If AZD1222 is proven to be safe and efficacious based on the primary endpoint.

The null hypothesis is: VE is equal to 30%. Whereas, the alternative hypothesis is: VE is not equal to 30%.

Objectives:

Primary and secondary objectives and endpoints

Objective [a]	Estimand [b] Description/Endpoint
PRIMARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age	**Population:** Full analysis set, excluding participants who are seropositive at baseline
	Endpoint: A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.
	Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal will be treated as missing (ie, counted as not having met the criteria); participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from primary endpoint analysis.
	Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group.)
2 To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age	a) Incidence of AEs for 28 days post each dose of study intervention
	b) Incidence of SAEs, MAAEs, and AESIs from Day 1 post treatment through Day 730
3 To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only)	Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention
SECONDARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection	The proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time
2 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria
3 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria

	Objective [a]	Estimand [b] Description/Endpoint
4	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention
5	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention
6	To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay)
		b) The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay)
7	To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)
		b) Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)

Intervention Groups and Duration: Study intervention will be administered on Day 1 and Day 29. For the primary efficacy analysis, approximately 150 events meeting the primary efficacy endpoint definition within the population of participants who are not seropositive at baseline are required across the active and control groups to detect a VE of 60% with > 90% power.

An interim efficacy analysis will be conducted when approximately 75 events meeting the primary endpoint definition have been reported across the active and control groups within the population of participants who are not seropositive at baseline, which will give > 70% power to detect a VE of 70% and > 90% power to detect a VE of 75%. A statistically significant finding at the interim analysis will not be considered a reason to stop the study, but instead will be interpreted as early assessment of efficacy.

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Adult, ≥ 18 years of age at the time of consent
- Increased risk of SARS-CoV-2 infection
    - Defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment contemporaneous to enrollment (believed to be at risk/exposure)
- Medically stable such that, according to the judgment of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up
    - A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to enrollment
- Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative) based on the assessment of the investigator
- Contraceptive use by women should be consistent with local regulations regarding the

methods of contraception for those participating in clinical studies

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

- History of allergy to any component of the vaccine
- History of Guillain-Barré syndrome or any other demyelinating condition
- Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the
- day prior to or day of randomization
- History of laboratory-confirmed SARS-CoV-2 infection
- Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia
- Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of study intervention)
- The following exceptions are permitted:
    - Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)
    - Human immunodeficiency virus-positive stable participants on stable antiretroviral therapy, eg, (NIH 2020, Waldrop et al 2016)
- History of primary malignancy except for: Malignancy with low potential risk for recurrence after curative treatment (for example, history of childhood leukaemia) or metastasis (for example, indolent prostate cancer) in the opinion of the site investigator. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. Adequately treated uterine cervical carcinoma in situ without evidence of disease. Localized prostate cancer
- Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet
- disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed)
- Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data
- Receipt of, or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention
- Receipt of immunoglobulins and/or any blood products within 3 months prior to administration of study intervention or expected receipt during the period of study follow-up

Moderna:

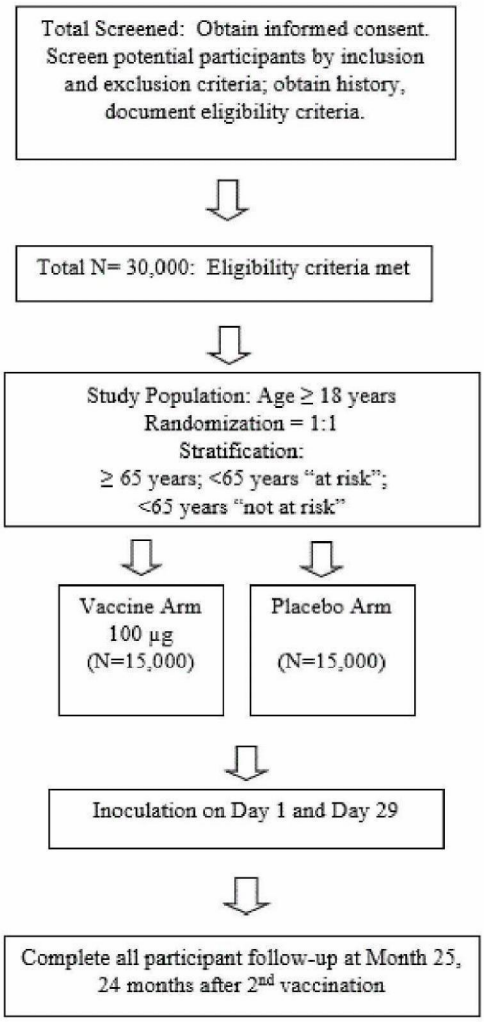
Title: A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older.

Vaccine:
mRNA-1273 is a mRNA encoding the stabilized prefusion S protein of SARS-CoV-2 based vaccine formulated in lipid nanoparticles (LNPs) composed of 4 lipids (1 proprietary and 3 commercially available) for transport into cells.

Pre-clinical and clinical data:
Results of a non human primate model showed that two doses of the vaccine induced Th1 type CD4 T cell immunogenicity and had protective capacity in upper and lower respiratory tract. No CD8 T cells could be detected.

In a phase 1 study three groups of 15 participants each received two intramuscular injections 28 days apart of either 25, 100, or 250 µg of mRNA-1273. Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-µg dose group reported one or more severe adverse events. Six participants (40%) in the 100-µg group and 57% in the 250-µg group reported fever after the second vaccination. Antibody responses were higher with higher dose and increased further after the second vaccination. Serum neutralizing activity was detected in all participants after the second vaccination. Values were generally similar to those in the upper half of the distribution of a panel of control convalescent serum samples. (Jackson et al., NEJM July 2020).
The trial was expanded to include 40 older adults, who were stratified according to age (56 to 70 years or ≥71 years). All the participants received two doses of either 25 µg or 100 µg of vaccine administered 28 days apart. Binding-and neutralizing-antibody responses appeared to be similar to those previously reported for adults 18 to 55 years of age. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells but did not evoke detectable CD8+ T-cells.
The 100-µg dose induced higher binding- and neutralizing-antibody titers than the 25-µg dose, which supports the use of the 100-µg dose in a phase 3 vaccine trial (Anderson et al., NEJM September 2020).

Study Design:



The target VE against COVID-19 is 60% (with 95% confidence interval lower bound ruling out 30%, rejecting the null hypothesis H0: VE ≤ 30%).

Objectives:

Primary:

- To demonstrate the efficacy of mRNA-1273 to prevent COVID-19.
- To evaluate the safety and reactogenicity of 2 injections of mRNA-1273 given 28 days apart.

Secondary:

- To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity.
- To evaluate vaccine efficacy (VE) against a secondary definition of COVID-19.
- To evaluate VE to prevent death caused by COVID-19.

• To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of investigational product (IP).
• To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.
• To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection.

Design: randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection.

Participants will be randomly assigned to receive injections of either 100 µg of mRNA-1273 vaccine or a placebo control in a 1:1 randomization ratio. Assignment will be stratified by age and health risk. This is a case-driven study and thus final sample size of the study will depend on the actual attack rate of COVID-19. There will be 3 strata for randomization: ≥ 65 years, < 65 years and categorized to be at increased risk ("at risk") for the complications of COVID-19, and < 65 years "not at risk". Risk will be defined based on the study participants' relevant past and current medical history. At least 25% of enrolled participants, but not more than 40%, will be either ≥ 65 years of age or < 65 years of age and "at risk" at Screening.

Participants who are < 65 years old will be categorized as at risk for severe COVID-19 illness if they have at least 1 of the following risk factors at Screening:

- Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection

Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

- Adults, ≥ 18 years of age at time of consent, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
- Understands and agrees to comply with the study procedures and provides written informed consent.
- Able to comply with study procedures based on the assessment of the Investigator.
- Female participants of nonchildbearing potential may be enrolled in the study.
- Female participants of childbearing potential may be enrolled in the study if the participant fulfills predefined criteria.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

- Is acutely ill or febrile 72 hours prior to or at Screening. Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
- Is pregnant or breastfeeding.
- Known history of SARS-CoV-2 infection.

- Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or current/planned simultaneous participation in another interventional study to prevent or treat COVID-19.
- Demonstrated inability to comply with the study procedures.
- An immediate family member or household member of this study's personnel.
- Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.
- Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.
- Has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any dose of IP).
- Has participated in an interventional clinical study within 28 days prior to the day of enrollment.
- Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV positive participants with CD4 count ≥350 cells/mm3 and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy [ART] are permitted]).
- Has received systemic immunosuppressants or immune-modifying drugs for >14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent).
- Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.
- Has donated ≥ 450 mL of blood products within 28 days prior to Screening.

Vaccine will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29. Each injection will have a volume of 0.5 mL and contain mRNA-1273 100 µg, or saline placebo.

Primary endpoints efficacy:
To be considered as a case of COVID-19 for the evaluation of the Primary Efficacy Endpoint, the following criteria must be met:
• The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38oC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
• The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
• The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Secondary Efficacy Assessments:
To be considered a severe COVID-19, the following criteria must be met: a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:
• Clinical signs indicative of severe systemic illness, Respiratory Rate ≥ 30 per minute, Heart Rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
• Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
• Significant acute renal, hepatic or neurologic dysfunction OR
• Admission to an intensive care unit or death. The secondary case definition of COVID-19 is defined as the following systemic symptoms: fever (temperature ≥ 38oC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhea, nausea or vomiting or diarrhea AND a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR.

Two interim analyses have been planned in this study, which will be performed when approximately 35% and 70% of the target total number of cases have been observed.

Pfizer/BioNTech:

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Vaccine:
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 full length spike glycoprotein S. Both vaccine candidates are formulated in a lipid nanoparticle (LNP) composition.
The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Pre-clinical and clinical data:
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 45 healthy adults (18–55 years of age), who were randomized to receive 2 doses—separated by 21 days—of 10 µg, 30 µg or 100 µg of BNT162b1 (Mulligan et al., Nature August 2020). Local reactions (primarily pain at injection site) and systemic events were dose-dependent, generally mild to moderate, and transient. A second vaccination with 100 µg was not administered because of the increased reactogenicity and a lack of meaningfully increased immunogenicity after a single dose compared with the 30-µg dose. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titres in sera increased with dose level and after a second dose. Geometric mean neutralizing titres reached 1.9–4.6-fold that of a panel of COVID-19 convalescent human sera, which were obtained at least 14 days after a positive SARS-CoV-2 PCR. In older (65-85 y) subjects, BNT162b1 elicited similar local reactions, with a tendency towards more moderate reactions compared to younger subjects. Mild-moderate injection site pain was also the most common local reaction 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.

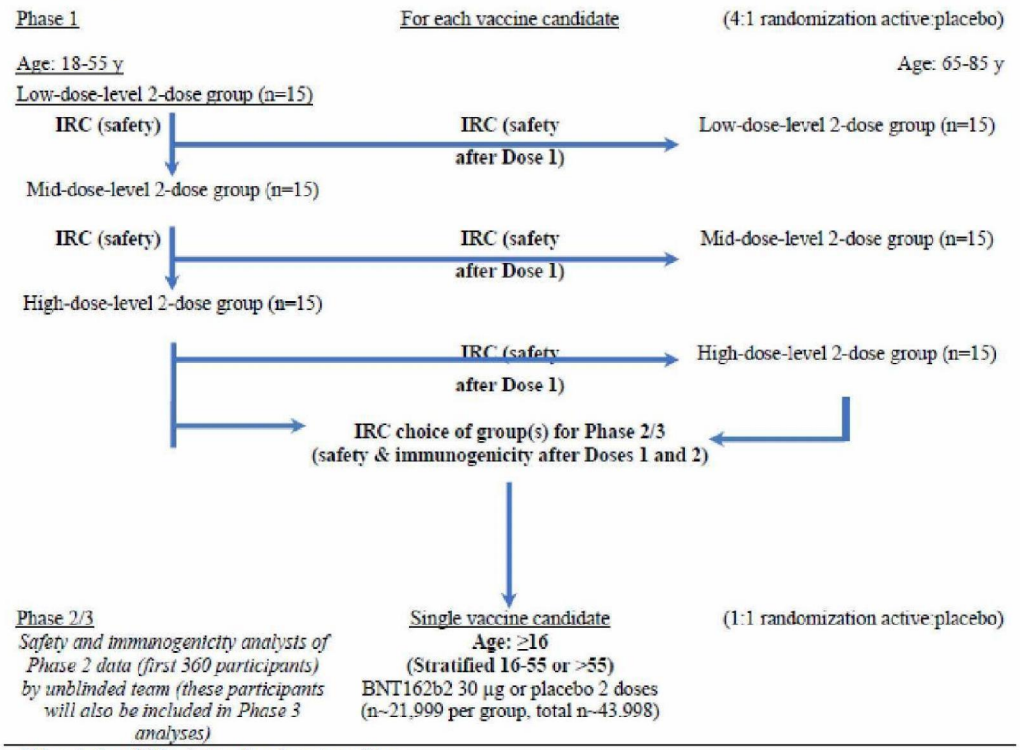
Study design:
The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 (Phase1/2) and the efficacy of 1 candidate (Phase 2/3):

- As a 2-dose (separated by 21 days) schedule;
- In 3 age groups Phase 2/3: ≥16 years of age [stratified as ≤55 or >55 years of age]).

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, 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, ie. randomized in a 1:1 ratio.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as VE = 100 × (1 – IRR), where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90% power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being non evaluable.

1.2. Schema



Abbreviation: IRC = internal review committee.

Primary efficacy objectives and endpoints:

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Secondary efficacy objectives and endpoints:

Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Primary safety objectives and endpoints:

Objectives[a]	Estimands	Endpoints
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
To define the safety profile of prophylactic BNT162b2 in all participants randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the last dose • SAEs from Dose 1 to 6 months after the last dose	• AEs • SAEs • In a subset of at least 6000 participants: o Local reactions (pain at the injection site, redness, and swelling) o Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85
- Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
- Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study. Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)
- Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).
- Capable of giving personal signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
- Receipt of medications intended to prevent COVID-19.
- Previous clinical or microbiological diagnosis of COVID-19.
- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding.
- Previous vaccination with any coronavirus vaccine.
- Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.
- Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.
- Previous participation in other studies involving study intervention containing lipid nanoparticles.
- Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Janssen:

Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of
Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older.

Vaccine:
Ad26.COV2.S (previously known as Ad26COVS1) is a monovalent vaccine composed of a recombinant, replication-incompetent adenovirus type 26 (Ad26) vector, constructed to encode the SARS-CoV-2 spike (S) protein.

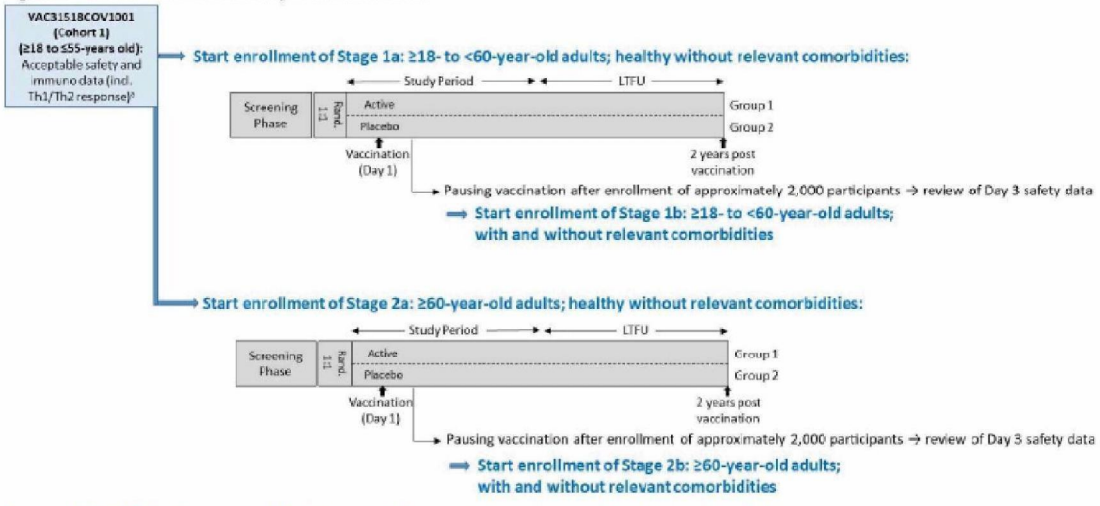
Pre-clinical and clinical data
A single dose of Ad26.COV2.S elicited strong immune responses in all 6 rhesus macaques. None of the vaccinated animals had a detectable viral load in the lung, in 1 animal virus could be detected in the nose after a challenge with SARS-CoV-2 ($1.0x10^5$ TCID50). Protective efficacy strongly correlated with the presence of neutralizing antibodies in serum of the animals, which was dose dependent. The vaccine also provided protective immunity, no signs of enhanced respiratory tract pathology, in vaccinated hamsters, a model for severe respiratory disease (Mercado et al., Nature July 2020).

A phase 1/2a randomized, double-blinded, placebo controlled clinical study to assesses the safety, reactogenicity and immunogenicity of Ad26.COV2.S started on July 22nd 2020 in Belgium and US (NCT04436276). The study evaluates a one- and two-dose (8-week interval) schedule with two different vaccine doses ($5x10^{10}$ or $1x10^{11}$ viral particles (vp)) per intramuscular vaccination in adults 18–55 or >65 years of age. Interim analysis showed solicited local and systemic adverse events in 27-64% of participants that resolved within a few days. Fever has been reported by 19% of participants mostly mild to moderate, 5% grade 3, resolved in 1-2 days. After only a single dose, seroconversion rate in wt virus neutralisation assay at day 29 after immunization reached 83-100%. On day 14 post immunization, Th1 cytokine producing S-specific CD4+ T cell responses were measured in 80% of a subset of participants with no or very low Th2 responses, indicative of a Th1-skewed phenotype. CD8+ T cell responses were also robust for both dose levels. They concluded that the safety profile and immunogenicity after a single dose are supportive for further clinical development of Ad26.COV2.S at a dose level of $5x10^{10}$ vp, as a potentially protective vaccine against COVID-19 (Sadoff et al., MedRxiv Sptember 2020).

A phase 2 trial comparing 1 dose and 2 homologous doses, with different intervals and schedules in participants age 18-55 years and 65 and older (n=375) is ongoing. Sites in the Netherlands (Leiden, Utrecht, Groningen), Germany and Spain.

Study design phase 3 trial:
This is a multicenter, randomized, double-blind, placebo-controlled, Phase 3, pivotal efficacy and safety study in adults ≥18 to <60 years of age and ≥60 years of age including participants with comorbidities that are associated with increased risk of progression to severe COVID-19. The efficacy, safety, and immunogenicity of Ad26.COV2.S will be evaluated in participants living in, or going to, locations with high risk for acquisition of SARS-CoV-2 infection after administration of study vaccine. Efforts will be made to ensure good representation in terms of race, ethnicity, and gender. Participants will be randomized in parallel in a 1:1 ratio to receive intramuscular (IM) injections of Ad26.COV2.S or placebo. Ad26.COV2.S will be administered at a dose level of $5×10^{10}$ vp.

Figure 1: Schematic Overview of Study VAC31518COV3001



Active = Ad26.COV2.S; incl. = including; LTFU = long-term follow-up; rand. = randomization; Th = T-helper cell type 1/2.

* At the time of protocol Amendment 1 writing, immunogenicity and safety data from Cohort 1a (≥18-≤55 years of age) and Cohort 3 (≥65 years of age) of study VAC31518COV1001 have become available. The data demonstrated that a single dose of Ad26.COV2.S at a dose level of 5×10^{10} vp is sufficient to induce an acceptable immune response that meets prespecified minimum criteria and that the dose is considered safe. Stage 2a can therefore be enrolled in parallel to Stage 1a, unless this is not allowed per local Health Authority guidance.

A screening phase of up to 28 days is included, however, screening may also be performed prior to randomization on the day of vaccination.

In Stage 1a and 1b combined, the enrollment of participants aged ≥18 to <40 years will be limited to approximately 20% of the total study population. Stage 2, including participants aged ≥60 years, will enroll a minimum of approximately 30% of the total study population. The analysis of the data will not be staggered: the primary analysis will be based on pooled data from both stages of the study.

Comorbidities (or risk factors) that are or might be associated with an increased risk of progression to severe COVID-19a include: moderate to severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1, type 2, or gestational); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (body mass index [BMI] ≥30 kg/m2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; uncontrolled human immunodeficiency virus (HIV) infection and other immunodeficiencies hepatitis B infection; sleep apnea; Parkinson's disease; seizures; ischemic strokes; Intracranial hemorrhage; Guillain-Barré syndrome; encephalopathy; meningoencephalitis; and participants who live in nursing homes or long-term care facilities.

The study is designed to test the primary hypothesis of vaccine efficacy (VE) in the PP population: H0: VE ≤30% versus H1: VE >30% and will be evaluated at a 2.5% one-sided significance level. Assumed VE: 60%.

Objectives and endpoints

For the primary endpoint, all moderate and severe/critical COVID-19 cases will be considered

The primary and secondary objectives and endpoints are:

Objectives	Endpoints
Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical coronavirus disease-2019 (COVID-19)[b], as compared to placebo, in SARS-CoV-2 seronegative adults	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15)
Secondary[e] *(The method used to perform hypothesis testing preserving the family-wise error rate [FWER] will be specified in the Statistical Analysis Plan [SAP])*	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe/critical COVID-19[b], as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset 1 day post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a] moderate to severe/critical COVID-19[b] as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe/critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) or linked to any

Objectives	Endpoints
	molecularly confirmed[a], COVID-19[b,c] at least 14 days post-vaccination (Day 15)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe/critical COVID-19[b]	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed[a], moderate to severe/critical COVID-19[b] by serial viral load measurements during the course of a COVID-19 episode
To assess the effect of Ad26.COV2.S on molecularly confirmed[a] mild COVID-19[c]	First occurrence of molecularly confirmed[a], mild COVID-19[c], at least 14 days post-vaccination (Day 15)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	First occurrence of molecularly confirmed[a] COVID-19[d] at least 14 days post-vaccination (Day 15)
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19[b,c], as compared to placebo	Burden of disease (BOD) endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe/critical COVID-19 case definition) with onset at least 14 days post-vaccination (Day 15).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre-vaccination), Day 71, 6 months, and 1-year post-vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 14 days after vaccination (Day 15)
Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days post-vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following vaccination and of unsolicited AEs during 28 days post-vaccination

Objectives	Endpoints
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	– Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA – SARS-CoV-2 neutralization as measured by virus neutralization assay (VNA; wild-type virus and/or pseudovirion expressing SARS-CoV-2 S protein)

No Interim evaluation will be done until the following conditions are met, monitoring will occur at least once a week by the SSG of the DSMB until the prespecified boundaries have been crossed:
1. The first 50% of planned participants had at least 2 months of follow-up after vaccination
2. A minimum of 6 COVID-19 cases for the ≥60 years age group
3. At least 20 cases meeting the primary endpoint definition of moderate to severe/critical COVID-19
4. A subset of at least 5 cases meeting the primary endpoint definition of severe/critical COVID-19

Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

- Participants must provide consent indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.
- Participant is willing and able to adhere to the prohibitions and restrictions specified in this protocol.
- Stages 1a and 1b: Participant is ≥18 to <60 years of age on the day of signing the ICF.
  Stages 2a and 2b: Participant is ≥60 years of age on the day of signing the ICF.
- Stages 1a and 2a: In the investigator's clinical judgement, participant must be either in good or stable health, including a BMI <30 kg/m2.
  Stages 1b and 2b: In the investigator's clinical judgement, participant may have a stable and well-controlled comorbidity associated with an increased risk of progression to severe COVID-19 (eg, stable/well-controlled HIV infection)
- Contraceptive (birth control) use should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.
- All participants of childbearing potential must:
  - Have a negative highly sensitive urine pregnancy test at screening
  - Have a negative highly sensitive urine pregnancy test on the day of and prior to study vaccine administration.
- Participant agrees to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving the study vaccine.
- Must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

- Participant has a clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination; randomization at a later date is permitted at the discretion of the investigator and after consultation with the sponsor.
- Participant has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine; refer to the IB).

- Participant has abnormal function of the immune system resulting from: Clinical conditions (eg, autoimmune disease, potential immune mediated disease or known or suspected immunodeficiency, chronic kidney disease [with dialysis]) expected to have an impact on the immune response of the study vaccine. Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) may be enrolled at the discretion of the investigator. Nonimmunomodulator treatment is allowed as well as steroids at a nonimmunosuppressive dose or route of administration.
- Chronic (>10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent. *Note: Ocular, topical or inhaled steroids are allowed.*
- Administration of antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study.
- Participant received treatment with Ig in the 3 months or blood products in the 4 months before the planned administration of the study vaccine or has any plans to receive such treatment during the study.
- Participant received or plans to receive:
    - Licensed live attenuated vaccines - within 28 days before or after planned administration of study vaccine.
    - Other licensed (not live) vaccines - within 14 days before or after planned administration of study vaccine.
- Participant previously received a coronavirus vaccine.
- Participant received an investigational drug (including investigational drugs for prophylaxis of COVID-19, such as remdesivir) or used an invasive investigational medical device within 30 days or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.
- Participant is pregnant or planning to become pregnant within 3 months after study vaccine administration.
- Participant has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the wellbeing) or that could prevent, limit, or confound the protocol-specified assessments.
- Participant has a contraindication to IM injections and blood draws, eg, bleeding disorders.
- Participant has had major psychiatric illness which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.
- Participant cannot communicate reliably with the investigator.
- Participant who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.
- Stages 1a and 2a: Participants with comorbidities that are or might be associated with an increased risk of progression to severe COVID-19a
- Stages 1a and 2a: Participant has a history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence).
- Stages 1a and 2a: Participant has a history of acute polyneuropathy (eg, Guillain-Barr syndrome).
- Stages 1a and 2a: Participant had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12 weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or has surgery requiring hospitalization planned during the time the participant is expected to participate in the study or within 6 months after study vaccine administration.

- Stages 1a and 2a: Participant has chronic active hepatitis B or hepatitis C infection per medical history.

Sanofi

Vaccine:
Sub-unit vaccine (preS dTM). The candidate vaccine is composed of Sanofi Pasteur's recombinant SARS-CoV-2 stabilized pre-fusion Spike protein without transmembrane or intracytoplasmic domains– based on Baculovirus Expression System Technology- and GSK's squalene-based ASO3 adjuvant. To achieve better stabilization and promote the formation of trimers the S protein is recombinantly mutated (2 Prolines and furin cleavage site) .

Pre-clinical and clinical data:
Preclinical data showed an acceptable reactogenicity profile. Data based on two injections of the adjuvanted recombinant vaccine showed high levels of neutralizing antibodies that are comparable to levels in humans who recovered from a COVID-19 infection. Pre-clinical results will be published later this year.

The Phase 1/2 clinical trial that started on September 3rd is a randomized, double blind and placebo-controlled trial designed to evaluate the safety, reactogenicity and immunogenicity of the vaccine candidate. Two dose levels (5 µg and 15 µg), with and without adjuvant will be compared in participants of 18 years and older. Safety, neutralizing antibody titers and T helper (Th1 and Th2) cytokines will be measured. A total of 440 healthy adults are being enrolled in the trial across 11 investigational sites in the United States.
First results are anticipated to be available early December 2020 which will support the initiation of a Phase 3 trial in December 2020. There is no protocol available yet.
If data are sufficient for licensure application, the plan is to request regulatory approval in the first half of 2021.

CurVac

Vaccine:
Unmodified full length stabilized S-protein mRNA vaccine (CVnCoV) transported into cells by lipid nanoparticle. The vaccine consists of natural, not modified, nucleotides. The sequence has been optimized to increase translation to reach high levels of S-protein.

Pre-clinical and clinical data:
The limited preclinical data for the Curevac product in mice indicate strong induction of neutralizing antibodies and both Th1 type CD4+ T-cell responses and IFNg+TNFa+ CD8+ T cell responses already after 2 vaccinations with a low dose. Th1 skewed response. Monkey data with rabies and flu vaccine, 1 and 10 ug, show that neutralizing antibody response remains stable for more then 1 year, rabies vaccine for 550 days. Virus specific memory plasma B-cells have been shown to be present in the bone marrow. Pre-clinical data with CVnCoV in mice and challenge data in hamster and non human primates should become available soon.

Phase I partially blinded, placebo-controlled, dose-escalation study to evaluate safety, reactogenicity and immunogenicity of 4 different vaccine concentrations (2, 4, 6, 8 ug) administered intramuscularly. In total, more than 200 healthy participants, 18-60 years old, received 2 doses of the vaccine candidate a month apart, with escalating dose levels, staggered over time. First results are expected to be reported early Q4 2020.
Based on initial phase 1 data phase 2a trials to test safety and confirm dosage have started September 30th in Panama and Peru. A total of 690 participants age 18-60 and 60 years and older will be enrolled. Racial diversity will be increased by using the study to determine whether there are differences between the European and Latin American populations. Each participant will be administered with two CVnCoV vaccines, 28 days apart. The study will test different dose levels, starting from 6µg. The goal is to analyse the safety and reactogenicity of the vaccine as well as antibody responses.
CureVac plans to start the combined Phase 2b/3 study for safety and efficacy in Q4 2020, with the first part vaccinating about 30,000 volunteers globally, involving several thousands of people in Europe, as well as in several countries in Latin America.