COVID-19 vaccine candidates

November 20, 2020

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Summary of changes since last publication

- Updated storage conditions for mRNA-1273 to reflect new stability data
- Added interim results from Moderna's phase 3 COVE trial
- Added storage instructions for AZD1222 following vial entry and refrigeration
- Updated information on results of Pfizer/BioNTech's phase 2/3 trial and vaccine efficacy, based on Pfizer press release
- Added that Johnson and Johnson initiated a second phase 3 trial, ENSEMBLE 2 (NCT04614948) to evaluate the efficacy of a 2-dose regimen. Details of ENSEMBLE 2 trial to be added at next update
- Added CPT codes for Moderna and Pfizer vaccine

Late-stage COVID-19 vaccine candidates in United States side-by-side comparison[a]

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	mRNA-BNT162b2 (BioNTech/Pfizer)	AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
Manufacturer	Moderna/NIAID	Pfizer Inc/BioNTech SE	AstraZeneca	Janssen	Novavax
History of bringing vaccine to market?	No	Yes (Pfizer)	Yes	Yes	No
FDA status	Fast track designation	Fast track designation	TBA	TBA	TBA
OWS	Yes	Yes	Yes	Yes	Yes
Vaccine platform technology	LNP-encapsulated, nucleoside-modified mRNA vaccine	LNP formulated, nucleoside-modified mRNA vaccine	Recombinant, replication-defective simian adenovirus vector	Recombinant, replication-defective adenovirus type 26 vector leveraging AdVac technology	Recombinant nanoparticle vaccine technology, leveraging Sf9/BV insect cell platform and Matrix-M™ adjuvant technology
Licensed platform	No		No[b]	Yes (EU Ebola)	Yes
Platform differentiators	Potential advantages:[c,d] • Safety – mRNA is non-infectious and non-integrating. There is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is rapidly degraded by normal cellular processes. • Scalable production - engineered production facilitates large-scale vaccine production. • Potency - capable of generating humoral and cellular immunity. • Efficacy - structural modifications during engineering improves stability and translation efficacy of mRNA. Potential disadvantages: • Lack of commercial vaccine precedent in humans • Local and systemic inflammatory responses • Biodistribution and persistence of the induced antigen expression • Possible development of autoreactive antibodies • Toxic effects of any non-native nucleotides and delivery system components		Potential advantages: • Stability at refrigerated temperatures • Experience with platform Potential advantages: • Replication deficient virus vectors have been used in potentially immunocompromised populations[g] • ChAdOx1 vaccines have demonstrated immunogenicity in older adults in another disease states (influenza A)[g] • Circumvents existing antivector immunity (novel vector)[h] Potential disadvantages: • Lack of commercial vaccine precedent in humans	Potential disadvantages: • Possibility of pre-existing antivector immunity[i]	Potential advantages[e] • Safety – non-infectious, non-integrating • Scalable production – engineered production facilitates large-scale vaccine production • Potency – capable of generating humoral and cellular immunity • Adjuvanted – Matrix-M adjuvant provides enhanced immune response, allowing for vaccine dose-sparing effect Potential disadvantages: • Local and systemic[f] inflammatory responses

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Manufacturing speed	Fast		Medium		Medium to fast
Annualized manufacturing capacity goal	Up to 1 billion doses (in partnership with Lonza)[j]	Up to 50 million doses worldwide by the end of 2020 and ~1.3 billion doses by the end of 2021[k]	Up to 2 billion doses by the end of 2021[l]	Up to 1 billion doses by end of 2021 (J&J owned facilities)[m]	Up to 2 billion doses by mid-2021[n]
Targeted SARS-CoV-2 antigen	Full-length, prefusion stabilized SARS-CoV-2 spike glycoprotein	Full-length, prefusion stabilized SARS-CoV-2 spike glycoprotein	SARS-CoV-2 spike protein	Full-length, stabilized SARS-CoV-2 spike protein	Full-length, prefusion stabilized SARS-CoV-2 spike glycoprotein
Pharmacology	mRNA encoding for the SARS-CoV-2 spike glycoprotein is delivered to cells in a lipid capsule; using this mRNA, cells manufacture the spike protein (antigen), which stimulates the body's immune response and production of antibodies against SARS-CoV-2.[c]		DNA sequence for SARS-CoV-2 spike glycoprotein (antigen) is encoded into a human or non-human adenovirus. Upon delivery to the host cell, host cells manufacture the spike protein (antigen), which stimulates the body's immune response. AZD1222 uses a simian adenovirus and JNJ-78436735 uses a human adenovirus with a low prevalence in humans. Due to genetic alterations, adenovirus vectors are unable to replicate (replication-defective) once in the host cell.[i]		Genetic sequence encoding the antigen (spike protein) is cloned into baculovirus and inserted into Sf9 insect cells, where the antigen is produced and subsequently isolated/extracted.[e] Matrix-M adjuvant boosts immune response and enables vaccine dose-sparing by stimulating entry of antigen-presenting cells into the injection site and enhancing B- and T-cell responses
Immunology[f,g,o-t]					
Humoral	Development of binding and neutralizing antibodies against SARS-CoV-2 spike protein				
Cellular (CD4+)	Th1-biased	Th1-biased	Th1-biased	Th1-biased	Th1-biased
Cellular (CD8+)	√	√	Unknown	√ (varies by age group and by dose)	√
Manufacturing process	Genetically engineered, cell-free, enzymatic reaction – *in vitro* reactions with recombinant enzymes, ribonucleotide triphosphates, and a DNA template[d]		Genetically engineered[r]	Genetically engineered[u]	Genetically engineered[e]

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Distribution – assumptions[v]					
Number of shipped components	2	3	NR	NR	NR
Vaccine	To central distributor at -20° C	Direct to site from manufacturer, on dry ice at –70°C ± 10°C (–94°F)	NR	NR	NR
Diluent	Not applicable	Shipped separately, direct to site from USG, at room temperature	Not applicable	Not applicable	NR
Ancillary supply kits	Direct to site from USG, at room temperature	Direct to site from USG, at room temperature *May include diluent as well as PPE for handling dry ice (e.g. goggles, thermal gloves, scoop)*	NR	NR	NR
How supplied – assumptions[v]					
Multidose vial	10 doses/vial Vial size: 5 mL	5 doses/vial Vial size: 2 mL	10 doses/vial (C.Dube, oral communication, September 2020)	5 doses/vial (ACIP meeting, October 2020)	NR
Anticipated commercial vaccine storage conditions (investigational conditions may differ)[v]					
Frozen or ultra-cold	• Stored at -20° C • Stable for up to 6 mo	• Stored at –70°C±10°C • Thermal shipper keeps ULT up to 10 d if stored at 15°C – 25°C without opening • Thermal shipper can be used as temporary storage for up to 15 d if, within 24 h of receipt and after opening shipper, dry ice is replenished; dry ice must then be replenished every 5 d, for up to 3 total re-icings (including initial replenishment)	Not applicable	• Stored at -20° C • Stable for 2 y	Not applicable
Refrigeration (2 - 8°C) of intact vial	Stable for 30 d	Undiluted: Must use within 5 d	Until date printed on packaging	Stable for 3 mo	Store under refrigeration[t]

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Refrigeration (2 - 8°C) of manipulated vial	NR	BU: 6 h	BU: 4 h (C Dube, written communication, November 2020)	BU: 6 h	NR
Room temperature of intact vial	Stable for 12 h	Undiluted: 2 h	Not applicable	NR	NR
Dosage and administration – assumptions[w-z]					
Dose (phase 3)	100 mcg/0.5 mL	30 mcg/0.3 mL	5×10^{10} vp dose	5×10^{10} vp dose	5 mcg protein antigen + 50 mcg Matrix-M adjuvant
Dilution required	No	Yes	No	No	No
Number of doses (phase 3)	2-dose series (28 d between doses)	2-dose series (21 d between doses)	2-dose series (28 d between doses) (C.Dube, oral communication, September 2020)	1 dose (ENSEMBLE trial) or 2 dose-series (57 d between doses; ENSEMBLE 2 trial)	2-dose series (21 d between doses)
Route of administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Safety considerations					
General safety concerns (non-vaccine specific)	Immunopathological responses that enhance disease severity are a potential concern. Increased immune pathology may occur by: • **Antibody-dependent enhancement:** ADE, defined as an enhancement of disease severity in an infected person when an antibody against a pathogen worsens its virulence by a mechanism that is shown to be antibody-dependent, has been described in SARS-CoV-1, MERS, HIV, Zika, and dengue virus infection and vaccination. In vaccine-related ADE, antibodies enhance or facilitate uptake of the virus via the Fc receptors or complement-binding pathway instead of neutralizing the virus (ie, blocking the interaction of the virus with its cellular receptor).[aa] • **T-helper (Th) 2 response**: Based on SARS research, less severe cases of SARS are associated with an accelerated induction of a Th 1 response while a robust Th 2 response has been associated with enhancement of lung disease following infection. Therefore, any vaccine should polarize the T-cell response toward type 1 immunity and avoid stimulatory cytokine activity indicative of type 2 immunity.[bb] The FDA requires that potential COVID-19 vaccine candidates demonstrate high neutralizing antibody titers and Th1-type T cell polarization prior to proceeding to first in human clinical trials.				
Adverse effects (vaccine specific)	Local and systemic reactions reported in phase 1 trial (not placebo-controlled)[q] • Incidence > 50%: Fatigue, chills, headache, myalgia,	Local and systemic reactions reported in phase 1 trial (placebo-controlled)[p] • Primarily mild to moderate in severity • Most common local reaction: pain at injection site	Phase 3 trials were placed on hold due to a serious adverse event and have been restarted internationally and in the US.[cc] ADEs in phase 1/2 trial were limited to non-serious (pain, tenderness,	• Local and systemic reactions reported in pre-publication manuscript included, but were not limited to: injection site pain, headache, fatigue, and myalgia.[s]	• Some local and systemic reactions reported in phase 1 trial (placebo-controlled)[f] • Absent or mild in majority of patients after both first and

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	and pain at the injection site • Majority of events were rated as mild to moderate in severity	• Most common systemic reactions: fatigue and headache • Systemic reactogenicity lower in older population (65 – 85 y)	headache, fatigue) and had decreased frequency in patients treated with paracetamol[g]	• Unsolicited ADEs were reported in both age groups studied and included 1 necessitating drug withdrawal (pyrexia).[s]	second vaccinations. • No serious ADEs were noted.
Special populations in phase 3 trials					
Geriatrics	All adult age groups enrolled[w]	Adults up to 85 y enrolled[x] 40.9% of participants overall (and 45.4% in U.S.) are age 56-85[dd]	All adult age groups enrolled[y]	Adults ≥ 65 y[z]	Adults up to 84 y enrolled Intent is for at least 25% of participants to be 65 years and above
Pregnancy	FDA recommends that all pregnancies that occur within 30 d after vaccination with a COVID 19 vaccine candidate should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital abnormalities.[ee]				
	Not included in phase 3 trial[w]	Not included in phase 3 trial[x]	Not included in phase 3 trial[y]	Not included in phase 3 trial[z]	Not included in phase 3 trial
Racial/ethnicity	As of October 21, the racial/ethnic breakdown is as follows:[ff] • Asian: 4% • Black: 10% • Hispanic/Latinx: 20% • Other: 3%	As of November 18, 42% overall and 30% of U.S. participants have a diverse background[dd] • Asian: 4.5% overall, 5.5% U.S. • Black: 10% overall, 10.1% U.S. • Hispanic/Latinx: 26.1% overall, 13.1% U.S. • Native American: 0.8% overall, 1.0% U.S.	NR	Phase 3 trial includes, "significant representation of Black, Hispanic/Latinx, American Indian and Alaskan Native participants"[gg]	NR, although Novavax has stated that they intend to prioritize groups most affected by COVID-19, including racial and ethnic minorities
Pediatrics	Not included in phase 3 trial[w]	FDA approval to enroll children as young as 12 y[dd]	Children 5-12 y are being recruited in the UK[hh]	Not included in phase 3 trial[z]	Not included in phase 3 trial
Other special populations included/considered	Co-morbidities: Diabetes (36%), severe obesity (25%), cardiac disease (19%), lung disease (18%)[ff]	Chronic, stable HIV, HCV, or HBV[dd]	Stable, pre-existing medical conditions[ii]	Patients with and without comorbidities associated with an increased risk for progression to severe disease.[z]	Up to 400 participants will also receive a licensed seasonal influenza vaccine as part of a co-administration sub study

Phase 3 study endpoints[w-z]					
Primary endpoint	First occurrence of confirmed **symptomatic COVID-19 disease with** onset at least 14 d after second dose.	**COVID-19 incidence** per 1000 person-years of follow-up in participants both with no serological or virological evidence of past SARS-CoV-2 infection or regardless of previous SARS-CoV-2 infection status	First case of SARS-CoV-2 RT-PCR-positive **symptomatic illness** occurring ≥ 15 d post second dose of study intervention.	First occurrence of molecularly confirmed **moderate** to **severe/critical COVID-19**, with onset at least 14 d post-vaccination in seronegative adults.	Two primary endpoints: • First occurrence of PCR-confirmed, **symptomatic COVID-19** with onset at least 7 d after the second dose in volunteers not previously infected with SARS-CoV-2 • First occurrence of PCR-confirmed, **symptomatic moderate or severe COVID-19** with onset at least 7 d after the second dose in volunteers not previously infected with SARS-CoV-2
FDA criteria for approval	Full report: Development and Licensure of Vaccines to Prevent COVID-19 – Guidance for Industry[ee] **Expectations for approval - highlights**: • Compared with placebo, the point estimate for vaccine efficacy of a COVID-19 candidate must be at least 50% with a lower bound of the confidence interval > 30%. • For secondary endpoints, the lower bound of the confidence interval around the point estimate may be between 0% to 30%. • All late phase studies should conduct interim analysis to survey for the development of enhanced respiratory disease. • General safety evaluations should be similar as for other preventative vaccines for infectious diseases and should include ○ Solicited local and systemic adverse events for at least 7 d after each study vaccination to characterize reactogenicity. ○ Unsolicited adverse events in all study participants for at least 21 to 28 d after each study vaccination. ○ Serious and other medically attended adverse events in all study participants for at least 6 mos after completion of all study vaccinations. • Pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure.				
CPT codes	91301	91300	NR	NR	NR
Clinical summary	Minimal clinical data are available. As more data become available, the side-by-side clinical discussion will be expanded. Please view the evidence summary for a discussion of published phase 1 data.				

Abbreviations: ADE = adverse drug event; BU = beyond use; CPT = current procedural terminology; EUA = emergency use authorization; HIV = human immunodeficiency virus; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; NR = not reported; OWS = Operation Warp Speed; PPE = personal protective equipment; TBA = to be announced; ULT = ultra low temperature; USG = United States government; VP = viral particle

Footnotes

[a] Information is rapidly changing and this is a living document. Storage and how supplied information are assumptions and are subject to change as additional information becomes available.

[b] A Chinese vaccine against Ebola that uses a simian adenovirus has been granted an EUA

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Evidence summary: COVID-19 vaccines

Introduction

On May 15, Operation Warp Speed (OWS) – a partnership among the Department of Health and Human Services (HHS), the Department of Defense (DoD), and the private sector – was announced with the goal to advance the development, manufacture, and distribution of vaccines, therapeutics, and diagnostics to combat the COVID-19 pandemic. In addition to providing financial support, the OWS has committed to work in parallel with the U.S. FDA to ensure that safe and effective candidates are taken through the necessary steps to obtain approval or authorization. The goal of the initiative is to deliver 300 million doses of a safe and effective vaccine against COVID-19 by January 2021.[1] To meet this goal, OWS plans to support the development and eventual distribution of the most promising 8 vaccine candidates (2 candidates per vaccine platform technology) produced from 1 of 4 vaccine platform technologies: the mRNA platform, the replication-defective live-vector platform, the recombinant-subunit-adjuvanted protein platform, or the attenuated replicating live-vector platform.[2] These platforms are considered ideal because they support rapid development from viral sequencing to clinical trials (<16 weeks) and are suitable for large-scale manufacture using pathogen agonistic technology.[3] To date, partnerships have been executed with Moderna and Pfizer/BioNTech (both mRNA), AstraZeneca and Janssen (both replication-defective live-vector), and Novavax and Sanofi/GSK (both recombinant-subunit-adjuvanted protein).[2] The federal government has made investments to expand domestic manufacturing capabilities for vaccine candidates and specialized materials (eg, syringes, vials) and is planning/building the necessary infrastructure to support vaccine distribution.

On June 30, the U.S. FDA published **guidance** that outlines key considerations for the development and licensure of a safe and effective vaccine against COVID-19.[4] In its guidance, the FDA recommends that the point estimate for vaccine efficacy against placebo should be at least 50%. The FDA also recommends that all phase 3 vaccine trials employ best methodology for trial design, enroll at least 3,000 patients to ensure the sample is sufficiently large to evaluate prelicensure safety, and enroll diverse patient populations. It is likely that a COVID-19 vaccine will be reviewed in real-time and eventually approved under a Biologics License Application. However, the FDA will consider issuing an Emergency Use Authorization (EUA) for a vaccine candidate on a case-by-case basis. On October 6, the FDA released additional **guidance** to inform industry regarding the data and information needed to support the issuance of an EUA.[5] Notable in this guidance, the FDA suggests that in order to issue an EUA, efficacy data from an interim analysis must meet the prespecified success criteria for the study's primary endpoint and data from phase 3 trials should include, at minimum, a median of 2 months of follow-up after the completion of the full vaccine regimen to provide adequate information to assess safety and efficacy. The FDA's Vaccines and Related Biological Products Advisory Committee is expected to provide an independent review and recommendation to the FDA on the scientific and technical merits of a vaccine candidate.[6] However, the FDA will be solely responsible for making the decision for or against approval of a vaccine candidate.

The average timeline for developing a new vaccine is 10 years.[7] However, most expect a vaccine against COVID-19 to be approved for commercial use in record time. One of the factors that has enabled rapid development is previous

investments in new vaccine technology platforms, such as nucleotide- and adenovirus-based approaches.[7] Both platforms offer theoretical manufacturing advantages compared to established platforms in speed and scalability. Development time has also been reduced by executing vaccine development steps simultaneously (or in parallel) versus in a linear sequence. For example, vaccine platforms that have been previously evaluated in humans may proceed to phase 1 clinical trials without waiting for confirmatory results from animal models.[3] Because of financial and technology investments from the federal government, manufacturers of late-stage vaccine candidates have been able to scale production to commercial levels before proof of substantial safety and immunogenicity data are available.[3] Lastly, maximizing enrollment and location of phase 3 trials ensures that event-driven trials can demonstrate efficacy (or lack thereof) rapidly.

The demand for a COVID-19 vaccine is expected to initially exceed supply. In order to determine equitable allocation, the National Academies of Sciences, Engineering, and Medicine (NASEM) and the National Academy of Medicine (NAM), at the request of the National Institutes of Health and Centers for Disease Control and Prevention (CDC), convened a committee to develop a framework to assist policymakers, including the Advisory Committee on Immunization Practices (ACIP) in planning for equitable allocation. The NASEM/NAM committee released the final draft of its Framework for Equitable Allocation of COVID-19 vaccine to the public on October 2. The allocation framework is based on three ethical principles – maximum benefit, equal concern, mitigation of health inequities – and three procedural principles – fairness, transparency, evidence. The committee recommends a **four-phased approach** for vaccine distribution.[8] Other organizations that have released or proposed frameworks for equitable vaccine distribution include Johns Hopkins, the World Health Organization, and ACIP. An ACIP COVID-19 Vaccine Workgroup was established in April to provide vaccine-specific guidance to the CDC. It is widely expected that the ACIP COVID-19 Vaccine Workgroup will provide recommendations for the use and prioritization of COVID-19 vaccines in the U.S.

Side-by-side document

The side-by-side document is a living document intended to provide the most up-to-date clinical information. As information is changing rapidly, the document will be updated frequently. The document provides a brief summary of safety and efficacy of late-stage vaccine candidates.

Efficacy and safety considerations

In order to meet the criteria for FDA approval, initial vaccine candidates will need to demonstrate a reduction in the rate of symptomatic COVID-19 disease by 50%.[4] Of note, the FDA has not historically recommended numerical end point estimates for licensure, but the agency has developed endpoint criteria prospectively for COVID-19 vaccines to increase confidence in the efficacy of a COVID-19 vaccine.[6] Secondarily, most trials will assess vaccine efficacy to prevent severe COVID-19. Once it is known which immune responses are reasonably likely to predict protection against COVID-19, it is expected that COVID-19 vaccines will be approved based on surrogate immunogenicity endpoints, similar to other vaccines against respiratory pathogens.[3] In collaboration with the National Institute of Allergy and Infectious Diseases, the

Coronavirus Prevention Network, and sponsor companies, OWS has harmonized trial endpoints and assay readouts to permit the indirect comparison among findings from phase 3 trials – with the caveat that indirect comparisons have limitations.[2]

Preclinical experience with vaccine candidates for Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) has raised concerns about exacerbating lung disease, which is likely mediated through antibody-dependent enhancement or a type 2 helper T-cell response.[7] Therefore, rigorous safety monitoring of all COVID-19 vaccine candidates is required. The FDA recommends that only vaccine candidates that demonstrate robust neutralizing antibody titers and Th1-type T cell polarization proceed to human trials and that all late phase COVID-19 vaccine studies conduct interim analysis to survey for the development of enhanced respiratory disease, which may be indicative of vaccine-induced immunopathology.[4]

Late-stage vaccine candidates

mRNA-1273

mRNA-1273 is a nucleotide-based vaccine candidate that utilizes Moderna's mRNA technology platform. It encodes for a prefusion stabilized form of the full-length SARS-CoV-2 spike (S) protein. Due to the labile nature of mRNA, it is encapsulated and delivered via a lipid nanoparticle (LNP) carrier. Once the vaccine is injected into the muscle, myocytes take up the LNP carrier and release the mRNA into the cytoplasm for translation into the S protein. Subsequent development of anti-S protein antibodies by the immune system may prevent infection by blocking the S protein from binding to its receptor.[9] While none of Moderna's mRNA vaccine candidates are FDA approved for commercial use, multiple mRNA vaccines that use its platform are currently in human clinical trials.

The clinical development program for mRNA-1273 consists of 3 trials: a phase 1 (**NCT04283461**), phase 2 (**NCT04405076**), and a phase 3 (**NCT04470427**) trial. All trials have been initiated and are currently active. Descriptions of the study methodology and results (if available) are presented in **Appendix A**. Moderna entered its phase 1 clinical trial on March 16, less than 10 weeks after the first genetic sequence for SARS-CoV-2 was released. Two of the expected 3 reports from the phase 1 trial have been published –interim analyses of the safety and immunogenicity of mRNA-1273 in the 18 to 55 years of age old cohort and in the 56 years of age or older cohort through day 57 – and results are briefly summarized in the next section. The third and final report will summarize the safety and durability of immunity for both study cohorts for up to 1 year after the second dose of the vaccine.[10]

A phase 2 trial was initiated in May and is expected to enroll 600 healthy participants aged 18 years and older. Participants will be randomized to receive mRNA-1273, given as 2 doses of 50 mcg or 100 mcg, or a matching placebo. The primary outcome measures are the occurrence of solicited and unsolicited safety events and the titer of SARS-CoV-2-specific binding antibodies up to 1 year after the final dose.[11]

The phase 3 trial was initiated in July and top-line results from the first interim analysis were posted in November. Enrollment is complete and the final sample size is 30,000 participants. Assuming an attack rate of 0.75% in the placebo

group, 151 symptomatic COVID-19 cases will provide 90% power to demonstrate 60% vaccine efficacy (VE) against symptomatic COVID-19 illness (with a lower bound of the VE confidence interval to exceed 30%). Two interim analysis are planned once 35% and 70% of total target cases occur. The primary efficacy objective of the trial can be achieved if the corresponding confidence for VE rules out less than 30% efficacy at either of the interim analyses or at the primary analysis.[12] Additional information on the trial is presented in **Appendix A**.

Efficacy

Published interim results of phase 1 data[13] from the 18 to 55 year old cohort suggest that all participants achieved seroconversion for binding antibodies, regardless of dose administered (25 mcg, 100 mcg, 250 mcg) by day 15 after the first dose of vaccine; however, the magnitude of the antibody response was time and dose dependent. The median magnitude of the antibody response in the 100-mcg and 250-mcg dose group was similar to the median magnitude of response in human convalescent plasma samples (HCS) after the first dose of the vaccine and in all dose groups, the median magnitude of the antibody response after the second dose was in the upper quartile of the values seen with convalescent plasma. Antibody neutralizing activity, measured by pseudovirus and live virus neutralization assays, was achieved in all participants after the second dose of the vaccine. Similarly, the magnitude of neutralization activity was also dose dependent. In the 100-mcg and 250-mcg dose groups, the magnitude of neutralizing activity after the second dose was similar to values seen in the upper half of the distribution of values for HCS. In addition to evaluating humoral response (ie, neutralizing antibody titers), cellular immunity was also evaluated. mRNA-1273 demonstrated Th1-type T cell polarization with minimal Th2 cytokine expression.[13]

Moderna published interim reactogenicity and immunogenicity results from its phase 1 data from the 56 years or older cohort. The cohort was small; only 20 patients received 2-doses of the 100-mcg phase 3 dose (results from the 25-mcg older cohort are not discussed here.). Similar to the younger cohort, the magnitude of antibody response was time and dose dependent. Additionally, binding antibody responses, though based on a small sample size, appeared to be age independent. At day 57, the GMTs for binding antibody responses in participants between 56 and 70 years of age and those 71 years of age or older far exceeded the responses observed among those who donated HCS. Antibody neutralizing activity, measured by 3 live-virus neutralization methods, was undetectable at baseline in all 20 participants. By day 43 (14 days after the second dose), all participants experienced a robust neutralizing response that was age independent in 2 of 3 assays. In the plaque reduction neutralization test (80% neutralization), neutralization responses were higher in those 56 to 70 years of age compared to those 71 years of age or older.[14] Like the younger cohort, older cohorts also demonstrated Th1-type T cell polarization after vaccination with mRNA-1273.

Results from the phase 3 trial are necessary to confirm that the humoral and cellular responses elicited by mRNA-1273 confer protection against COVID-19. Top-line results from the first interim analysis of the COVE phase 3 trial were released on November 16.[15] The first interim analysis was based on 95 cases of confirmed, symptomatic COVID-19 illness, of any severity. Of these, 90 cases occurred in the placebo cohort versus 5 cases in the mRNA-1273 cohort, resulting in a VE point estimate of 94.5% ($P < .0001$). The 95 COVID-19 cases included 15 participants aged 65 and older and 20 participants identified as being a member of a diverse community. Severe COVID-19-related illness, defined per

the **study protocol**, was analyzed as a secondary endpoint. All 11 confirmed cases of severe COVID-19 occurred in the placebo group. The point estimate for VE may change as additional data are analyzed.

Safety

Phase 1 safety results: All 3 doses of mRNA-1273 were well tolerated in the 18 to 55-year-old cohort.[13] In general, solicited systemic and local adverse events were more commonly reported after the second dose. After the first dose, solicited systemic adverse events (arthralgia, fatigue, fever, chills, headache, myalgia, nausea) were mild to moderate in severity. Solicited local adverse events (redness/erythema, induration/swelling, pain at injection site) were mostly rated as mild to moderate in severity after both the first and second doses; however, size of erythema/redness was rated as severe in a small proportion of participants in the 100-mcg and 250-mcg groups after the first and second doses. No participant had a fever after the first dose. A fever after the second dose was documented in 40 to 57% of participants in the 100-mcg and 250-mcg groups, respectively. Across both vaccine doses, adverse events that occurred in greater than 50% of participants included fatigue, chills, headache, myalgia, and pain at the injection site. There were no potential safety signals based on reports of unsolicited adverse events or clinical laboratory values.[13]

The reactogenicity profile of mRNA-1273 in the older cohort was not qualitatively differ from its profile in the younger cohort. In the older cohorts, the most common solicited adverse events were headache, fatigue, myalgia, chills, and injection-site pain. The occurrence of adverse events was more common after the second dose. All the 10 solicited local adverse events and all but 2 of the systemic events that were rated as moderate in severity occurred after the administration of the second dose. Most symptoms occurred within 1 to 2 days of vaccination and resolved quickly; however, 3 patients experienced erythema for 5 to 7 days and 1 participant reported myalgia for 5 days. There were no potential safety signals based on reports of unsolicited adverse events or clinical laboratory values.[13]

Phase 3 safety results: The interim analysis of the available safety data from the COVE trial did not reveal any unexpected or significant safety concerns.[15] Solicited adverse events occurred more commonly after the second dose and the majority of reported events resolved quickly. Grade 3 events that occurred at a 2% or greater frequency after the first dose included injection site pain (2.7%) and after the second dose included fatigue (9.7%), myalgia (8.9%), arthralgia (5.2%), headache (4.5%), pain (4.1%), and erythema/redness at the injection site (2.0%).

Emergency Use Authorization

Moderna expects to submit an EUA to the FDA. The exact timeframe for submission is unknown, but Moderna expects the EUA to be based on the final analysis of 151 COVID-19 cases and median follow-up time of at least 2 months.

BNT 16262

BNT162b2 is an LNP formulated, nucleoside-modified messenger RNA (modRNA) vaccine. While the LNPs help protect the mRNA against enzymatic degradation and ensure efficient cellular uptake, the N-methyl pseudouridine (m1Ψ) nucleoside modification dampens immune sensing and assists in providing increased RNA translation in vivo. The vaccine encodes the SARS-CoV-2, full-length, spike glycoprotein, stabilized in its prefusion confirmation (P2 S).[16]

BNT162b2 is 1 of 4 vaccine candidates in the Pfizer/BioNTech BNT162 vaccine platform.[17] Two of the vaccine candidates—BNT162b1 and BNT162b2—were included in phase 1 of the ongoing phase 1/2/3, randomized, placebo-controlled, observer-blind clinical trial (**NCT04368728**). The study has been conducted in 2 parts—phase 1 and phase 2/3. The goal of phase 1 was to examine immuno- and reactogenicity of the vaccines and to identify the preferred vaccine candidate and dose level, while phase 2/3 is an expanded cohort with the primary goal of determining VE.[18]

Efficacy and safety: Phase 1

Results from the phase 1 trial were published **online** on October 14, 2020. Healthy adults (n = 195), aged 18 to 55 and 65 to 85, were randomized to receive placebo or 1 of the vaccine candidates: BNT162b1 or BNT162b2, at dose levels of either 10 mcg, 20 mcg, or 30 mcg. Study participants received 2 doses of their assigned intervention (placebo or vaccine candidate), 21 days apart. One group of 18 to 55-year-old participants was randomized to receive a single dose of 100 mcg BNT162b1. In total, there were 13 groups with 15 participants each[18] (refer to **Appendix B** for further detail).

Investigators examined antigen (receptor binding domain or S1)-binding IgG and neutralizing antibody responses in participants at days 0, 21, 28, and 35 (sera were obtained prior to vaccination on days 0 and 21). Immunogenicity data from a human convalescent serum (HCS) panel (n = 38 donors with PCR-confirmed SARS-CoV-2) served as a benchmark against which the immune response in trial participants was evaluated.[19]

Ultimately, BNT162b1 and BNT162b2 were found to elicit similar dose-dependent SARS-CoV-2 neutralizing geometric mean titers (GMTs), comparable to or higher than GMTs in the HCS panel. Antigen-binding IgG and neutralizing responses were boosted by the administration of dose 2 with both vaccine candidates at the 30-mcg dose level, providing justification for administration of a second dose of vaccine. Lower antigen-binding IgG and neutralizing responses were observed in the 65 to 85 year old age group as compared to the 18 to 55 year old age group; specifically, in looking at neutralization titers for both vaccine candidates at the 30 mcg dose level on days 28 and 35 (the days on which the highest neutralization titers were observed), the 50% neutralizing GMTs ranged from 1.7 – 4.6 times the GMT of the HCS panel for participants age 18 – 55 years and from 1.1 – 2.2 times the GMT of the HCS panel for participants age 65 – 85 years.[19]

From a safety standpoint, local reactions reported within 7 days of vaccination were largely mild to moderate and consisted primarily of pain at the injection site; local reactions were more frequent after the second dose. No older adults who received BNT162b2 reported redness or swelling and there were no reports of a grade 4 local reaction (e.g. necrosis or exfoliative dermatitis) in any group. As far as systemic events, only 17% of participants in the 18 to 55 year old group and 8% of participants in the 65 to 85 year old group experienced a fever with dose 2 of 30 mcg BNT162b2 as compared to 75% and 33% of participants receiving dose 2 of 30 mcg BNT162b1 in those same respective age groups. Ultimately, the milder systemic reactogenicity of BNT162b2—along with the comparable antibody responses noted between the 2 vaccine candidates—led to the selection of BNT162b2 to move into phase 2/3 studies.[19]

Phase 2/3 Study

The BNT162b2 vaccine trial moved into phase 3 in July 2020, with the initial intent of enrolling 30,000 participants aged 18 to 85 years; however, in subsequent months, the protocol was amended to expand enrollment to 44,000 participants—including persons as young as 12 years of age and participants with chronic, stable HIV, Hepatitis C, or Hepatitis B.[20,21]

For Phase 2/3, evaluation of VE is the primary objective. Under the assumption of a true VE of 60% and an attack rate of 1.3% illness rate per year in the placebo group, it was estimated that a total of 164 COVID-19 cases (estimated accrual: 6 months) would provide 90% power to conclude a true VE >30% with high probability. It was noted that if the attack rate were much higher, the case accrual could be more rapid, allowing for the study's primary endpoint to be assessed much sooner. There were 4 interim analyses (IAs) planned, which will occur after accrual of 32, 62, 92, and 120 cases; however, the first planned IA was not conducted for operational reasons, leaving the remaining 3 IAs (at 62, 92, and 120 cases) to be completed. Vaccine efficacy for the first primary objective (see **Appendix B** for further detail on hierarchical analysis of endpoints) was to be evaluated at each IA, with the potential for efficacy to be declared if the VE point estimate for the current number of cases were met, which would be indicative of VE>30%.[22]

While publication of trial results is still pending, it was **announced** on October 18, 2020 that Pfizer and BioNTech had concluded the phase 3 study of BNT162b2. There were 170 confirmed cases of COVID-19 evaluated (162 in the placebo group and 8 in the vaccine group). The vaccine was found to be 95% effective, beginning 28 days after receipt of the first dose, with Pfizer claiming consistent efficacy across age, gender, race, and ethnicity and an observed efficacy greater than 94% in adults over the age of 65.[23]

There were no serious safety concerns observed, and only 2 grade 3 (severity: "serious") adverse reactions were reported at a frequency greater than or equal to 2%: fatigue (3.8%) and headache (2.0%), after the second dose. Similar to reports from the Phase 1 study, older adults reported fewer and milder solicited adverse events.[23]

AZD1222

AZD1222 is Astra Zeneca's replication defective simian (chimpanzee) adenovirus vaccine containing a full-length spike protein and a leading tissue plasminogen activator (tPA) sequence that produces both a cellular and humoral response to the SARS-CoV-2 virus.[24] The tPA component has been demonstrated to enhance immunogenicity in another ChAdOx1 vectored CoV vaccine (ChAdOx1 MERS).[24] Clinical trials consist of a phase 1/2 trial (**NCT04324606**; active, not recruiting), a phase 2 trial (**NCT0444674**; recruiting), a phase 2/3 trial (**NCT04400838**; recruiting), 4 phase 3 trials (**NCT04540393**, **ISRCTN89951424** & **NCT04516746**; not recruiting; **NCT04536051** recruiting) and are being completed in various ages and populations. Summaries of the published phase 1/2 trial and the phase 3 U.S. trial (on hold) are in **Appendix C**. The phase 1/2 trial started enrolling patients in April of 2020 in the UK through May of 2020 and results were published in August. The phase 2 trial was initiated in June in South Africa and is recruiting 2,000 patients with and without HIV infection. The phase 2/3 trial began in the UK in May of 2020 and is estimating enrollment of 12,330 patients including ages 5 to 12 years and ≥ 18 years. A phase 3 trial currently enrolling patients is being conducted in Brazil in healthcare workers or other adults at high risk of contracting infections and is projected to be completed in 5,000 patients.

Efficacy

Data published in the phase 1/2 trial indicate ChAdOx1 nCoV-19 5 X 10^{10} virus particles (0.5 mL intramuscularly) produced a humoral response as indicated by anti-spike IgG and a cellular response by spike-specific T-cell response. Boosting with a second dose at day 29 occurred in a small number of patients (n = 10) and produced an increase in anti-spike IgG MNA_{80} is defined as titers inducing 80% virus neutralization. MNA_{80} was achieved in 32/35 (91%) patients after a single dose and 9/9 after a booster dose (100%). Pending phase 3 and 2/3 trials are generally focusing on a 2-dose approach.

Safety

No serious adverse events were reported in the phase 1/2 trial. Local and systemic reactions were reported the ChAdOx1 nCov-19 group and were reduced in patients instructed/allowed to use paracetamol prophylactically (1 g every 6 h for 24 h) including but not limited to pain, feeling feverish, chills, muscle ache, headache, and malaise. Immunogenicity in patients advised to take paracetamol prophylactically was similar to those who were not advised to do so; however, these data were not reported.[24]

JNJ-78436735

JNJ-78436735 is Janssen's non-replicating adenovirus 26 (Ad26) based vaccine expressing a stabilized pre-fusion full-length spike protein that produces both a cellular and humoral response to the SARS-CoV-2 virus.[25] Clinical trials consists of a phase 1 trial (**NCT04509947**; active, recruiting), a phase 1/2a trial (**NCT04436276**; active, recruiting), a phase 2 trial (**NCT04535453**; active, recruiting) and a phase 3 trial (**NCT04505722**; recruiting). Summaries of the prepublication manuscript of the phase 1/2a trial and the description of the phase 3 trial are in **Appendix C**. The phase 1/2a trial started enrolling patients in June of 2020 and interim results were released in pre-publication form in September.[25] The phase 3 trial was initiated in September.

Efficacy and safety: Phase 1/2a

Interim data was presented in a pre-publication manuscript of a multicenter, randomized, double-blind, placebo-controlled phase 1/2a trial and describes interim safety and immunogenicity following a single dose in two age cohorts (18-55 yo and ≥65 yo). These preliminary data indicate a single dose of JNJ- 78436735, 5 X 10^{10} virus particles or 1 X 10^{11} virus particles produced a humoral response as demonstrated by spike-specific ELISA geometric mean titers (GMT) and presence of neutralizing titers by wild-type virus neutralization assay (wtVNA) GMT. GMT in human convalescent plasma overlapped in the 95% CI range of the two aforementioned humoral response tests. Cellular response was demonstrated through Th1 cytokine producing CD4+ T cell (S-specific) response (cohort 1a: 80%; cohort 3: 83%) and CD8+ T cell (S-specific) response (varied by age group and dose: 33-64%). Regarding safety, local adverse events were reported in 58% of patients in cohort 1 (18-55 yo) and 27% of patients in cohort 3 (≥ 65 yo). The most common local adverse effect was injection site reaction and most frequent systemic reactions were headache, fatigue, and myalgia. Fever was reported in 64% of cohort 1 patients and 36% of cohort 3 patients. Assessment for vaccine associated enhanced respiratory disease (VAERD) was completed by measuring CD4+ Th1 and Th2 responses to the vaccine evaluating for Th2 skewed

response. One participant in the 1a cohort had a Th2 response and the Th1/Th2 ratio indicated it was a Th-1 skewed response; hence, VAERD risk is expected to be low. Additional detail regarding safety and efficacy is expected when the full results are published.

Phase 3

The phase 3 ENSEMBLE trial will focus on a single dose approach using 5 X 10^{10} virus particles in adult patients (goal n = 60,000). Primary and secondary outcome measures are listed in **Appendix D**. Johnson and Johnson announced in November 2020 the initiation of the two-dose regimen ENSEMBLE 2 trial. The ENSEMBLE 2 trial will run in parallel to the ENSEMBLE trial and is expected to enroll 30,000 patients worldwide.

NVX-CoV2373

NVX-CoV2373 is a recombinant protein nanoparticle vaccine, consisting of purified protein antigen—specifically, the full-length SARS-CoV-2 spike glycoprotein, synthesized using Novavax' Sf9/BV insect cell platform—and Matrix-M1 adjuvant.[26] The phase 1 trial (**NCT04368988**) was comprised of 131 healthy adults, aged 18 to 84 years, who received rSARS-CoV-2 in 1 of 2 doses (5 mcg or 25 mcg), either with (n = 83) or without (n = 25) Matrix-M1 adjuvant, or placebo (n = 23). Vaccination consisted of 2 intramuscular injections, administered 21 days apart. Primary outcomes in the phase 1 trial included reactogenicity and IgG anti-spike protein response; secondary outcomes included wild-type virus neutralization and T-cell responses.[26] Currently, only phase 1 clinical trial data have been published (summarized in **Appendix E**); publication of results from the phase 1/2 trial continuation in the U.S. and Australia (**NCT04368988**) are still pending.

Efficacy and safety: Phase 1

Phase 1 clinical trial data[26] (summarized in **Appendix E**), demonstrated that NVX-CoV2373 elicits a Th1-dominant response and produces spike-specific IgG and neutralizing antibodies in levels exceeding those found in COVID-19 convalescent serum. The addition of Matrix-M1 adjuvant was found to produce a dose-sparing effect, with similar magnitudes of response seen with administration of 5 mcg and 25 mcg doses of rSARS-CoV-2. Specifically, the 2-dose 5 mcg adjuvanted regimen produced 63,160 EU/mL of anti-spike IgG (vs. 8,344 EU/mL [mean, overall] and 53,391 EU/mL [mean, hospitalized patients] of anti-spike IgG found in human convalescent serum) and a GMT neutralizing antibody response of 3,906 as compared to 984 (overall mean) in human convalescent plasma.

Reactogenicity was absent or mild in most patients and no serious adverse events were reported. Localized adverse events consisted primarily of pain and tenderness and the most common systemic adverse events were fatigue, headache, and myalgia. Only 1 participant experienced a fever. The mean duration of reactogenicity events was 2 days or less after both first and second vaccinations.

Phase 3

On September 24, Novavax **announced** that it launched its phase 3 trial for NVX-CoV2373 in the UK. The trial will enroll up to 10,000 healthy adults between the ages of 18 and 84 years, both "with and without relevant comorbidities."

Participants will be randomized to receive 2 intramuscular injections, 21 days apart, of either the vaccine (5 mcg protein antigen + 50 mcg Matrix-M adjuvant) or placebo. Up to 400 participants will also receive a licensed seasonal influenza vaccine as part of a co-administration sub-study. The primary efficacy analysis will be an event-driven analysis based on the number of participants with symptomatic or moderate to severe COVID-19, and an interim analysis will be performed when 67% of the desired number of cases is reached. The primary endpoints will be first occurrence of either symptomatic COVID-19 OR symptomatic moderate or severe COVID-19, with an onset of at least 7 days after the second dose in participants not previously infected with SARS-CoV-2.[27] The protocol for this Phase 3 study was published October 27, 2020.

On October 27, Novavax provided an **update** on the UK phase 3 trial. The trial currently has 5,500 individuals enrolled and has expanded its target enrollment from 10,000 to 15,000 participants. The increased enrollment is expected to "facilitate assessment of safety and efficacy in a shorter time period." Novavax predicts full enrollment by the end of November with interim data available in early Q1 2021. Additionally, the update indicated that phase 3 trials in the U.S. and Mexico are expected to begin by the end of November.[28]

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Appendix A – mRNA-1273 trials

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Jackson LA, et al. mRNA-1273 study group Phase 1, dose-escalation, open-label clinical trial Interim analysis through day 57 (28 d after second dose of vaccine)	45	Healthy adults 18 to 55 y Baseline characteristics • Male, n = 22 (49%) • Age, mean (SD): 33.0 y (8.5) • White, n = 40 (89%) • BMI, mean (SD): 25.3 (3.2)	**Intervention group** 2 injections of mRNA-1273 given 28 d apart at 3 different dose levels: • 25 mcg (n = 15) • 100 mcg (n = 15) • 250 mcg (n = 15) Vaccine administered as a 0.5-mL injection in deltoid muscle on days 1 and 29 **Control group** Convalescent serum specimens (n = 38 samples) • Mild infection (63%) • Moderate infection (22%) • Severe infection (15%)	**SARS-CoV-2 antibody response** Seroconversion, measured by ELISA, defined as a 4-factor or more increase in antibody titer over baseline. All patients achieved seroconversion by day 15. **Anti-S-2P ELISA mean GMTs (95% CI) at day 57** • 25-mcg group: 299,751 (206,071 – 436,020) • 100-mcg group: 782,719 (619,310 – 989,244) • 250-mcg group: 1,192,154 (924,878 – 1,536,669) • Convalescent serum: 142,140 (81,543 – 247,768) **Anti-receptor-binding domain GMT (95% CI) at day 57** • 25-mcg group: 183,652 (122,763 – 274,741) • 100-mcg group: 371,271 (266,721-516,804) • 250-mcg group: 582,259 (404,019 – 839,134) • Convalescent serum: 37,857 (19,528 – 73,391) **Pseudovirus neutralization assay (PsVNA)** • No participant had detectable PsVNA responses before vaccination • < 50% had a PsVNA response after first dose • 100% had a PsVNA response after second dose with higher responses seen in the 100-mcg and 250-mcg group vs. the 25-mcg group at day 43 **Live SARS-CoV-2 PRNT** • Before vaccination, no participant had detectable 80% live-virus neutralization activity • At day 43, all participants had neutralizing activity capable of reducing infectivity by 80% **SARS-CoV-2 T-cell responses** (data available only for 25-mcg and 100-mcg doses) • Both doses elicited CD4 T-cell responses – strongly biased toward expression of Th1 cytokines, with minimal type 2 helper T-cell cytokine expression • CD8 T-cell responses were detected at low levels after the second dose in the 100-mcg group	Discontinuations due to safety (n = 1) • 25 mcg group - discontinued due to transient urticaria, judged to be related to the first vaccination Incidence of solicited systemic AEs, first dose • 25-mcg group, n = 5 (33%) • 100-mcg group, n = 10 (67%) • 250-mcg group, n = 8 (53%) Incidence of solicited systemic AEs, second dose • 25-mcg group, n = 7 (54%) • 100-mcg group, n = 15 (100%) • 250-mcg group, n = 14 (100%); 3 (21%) reported ≥ 1 severe AE Solicited systemic and local AEs with incidence ≥ 50% • Fatigue, chills, headache, myalgia, and pain at the injection site No patterns of concern for unsolicited AEs or for clinical laboratory values of grade 2 or higher

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Anderson EJ, et al. mRNA-1273 study group Phase 1, dose-escalation, open-label clinical trial Interim analysis through day 57 (28 d after second dose of vaccine)	40	Healthy adults aged ≥ 56 y old Baseline characteristics • Male, n = 19 (48%) • Age, mean: 68.7 y • White, n = 39 (98%) • BMI, mean (SD): 25 (3)	**Intervention group** 2 injections of mRNA-1273 given 28 d apart at 3 different dose levels: 56-70 y old cohort • 25 mcg (n = 10) • 100 mcg (n = 10) ≥71 y old cohort • 25 mcg (n = 10) • 100 mcg (n = 10) Vaccine administered as a 0.5-mL injection in deltoid muscle on days 1 and 29 **Control group** Convalescent serum specimens (n = 38 samples) • Mild infection (63%) • Moderate infection (22%) • Severe infection (15%)	**Binding antibody response** **Anti-S-2P ELISA mean GMTs (95% CI) at day 57** • 25-mcg group, 56-70 y: 323,945 (182,202-575,958) • 25-mcg group, ≥ 71 y: 1,128,391 (636,087-2,001,717) • 100-mcg group, 56-70 y: 1,183,066 (379,698-3,686,201) • 100-mcg group, ≥ 71 y: 3,638,522 (1,316,233-10,058,130) • Convalescent serum: 138,901 (82,876-232,799) **Neutralizing antibody response** • Measured by pseudovirus, PRNT, nLuc HTNA, and FRNT-mNG • Pseudovirus neutralization: Age-independent responses induced as early as 7 d after second dose • nLuc HTNA and FRNT-mNG: Age-independent responses induced by 14 d after second dose • PRNT: Age-dependent responses induced by 14 d after second dose with higher response in 56-70 y cohort **SARS-CoV-2 T-cell responses** • 100-mcg group elicited CD4 T-cell responses – strongly biased toward expression of Th1 cytokines, with minimal type 2 helper T-cell cytokine expression – in both age groups • 25-mcg group only elicited a T-cell response in the 56-70 y cohort	Most common solicited AEs: • Headache • Fatigue • Myalgia • Chills • Injection-site pain All 10 solicited local AEs that were classified as moderate occurred after the second dose All but 2 systemic AEs classified as moderate occurred after the second dose
Phase 3 trial – ongoing COVE trial (NCT04470427) 2 interim analysis planned	30,000 Event-driven, final number will depend on number of events	For full inclusion/exclusion criteria, see **clinical trial protocol** Inclusion • ≥ 18 y • Healthy adults or adults with pre-existing medical conditions who are in stable condition	Intervention • mRNA-1273 – 100 mcg injection given on Day 1 and on Day 29 Control • Placebo – 0.9% sodium chloride injection	For most up-to-date information, please visit: **modernatx.com/cove-study** • Participants enrolled: 30,000 (date: 10/22); 25,654 have received second vaccination ○ 20% Hispanic/Latinx, 10% Black, 4% Asian, 3% Other • Primary outcomes ○ Number of participants with a first occurrence of COVID-19 starting 14 days after second dose of mRNA-1273 [time frame: 29 d up to 2 y after second dose] ○ Number of participants with AEs or medically attended AEs leading to withdrawal [time frame: up to 2 y after second dose] ○ Number of participants with solicited local and systemic adverse reactions [time frame: Up to day 8 and up to day 36 (7 d after the first and second doses, respectively) ○ Number of participants with unsolicited AEs [time frame: up to day 57]	

Abbreviations: AE = adverse event; CI = confidence intervals; FRNT-mNG = focus reduction neutralization test mNeonGreen; GMT = geometric mean titers; nLuC HTNA = nanoluciferase high-throughput neutralization assay; PRNT = plaque reduction neutralization test; SD = standard deviation

Appendix B – BNT162b2 trials

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Walsh EE, et al. Phase 1, randomized, placebo-controlled, observer-blinded, dose-escalation study (NCT04368728) *Note: The data set presented here guided Pfizer and BioNTech's decision to advance BNT162b2 at the 30-mcg dose level into the Phase 2/3, global safety and efficacy evaluation*	195	For full inclusion and exclusion criteria, see **NCT04368728** Inclusion • Healthy adults age 18-55 or 65-85	**Study Design** 13 groups, 15 participants each (n = 195): • Two vaccine candidate "arms": BNT162b1 and BNT162b2 • Each arm further subdivided by age range (18-55 and 65-85) and vaccine dose (10 mcg, 20 mcg, or 30 mcg) • Participants received two 0.5-mL injections to the deltoid of either BNT162b1, BNT162b, or placebo, 21 d apart • One additional group of 18-55 y participants randomized to receive 1 dose of 100 mcg vs. placebo • In each of the 13 groups, n=12 received vaccine and n=3 received placebo *Note: Participants were primarily white (67 – 100%) and non-Hispanic (89 – 100%), depending on intervention group; there was a higher proportion of females than males in the 65-85 y age groups*	Immunogenicity assessments: • RBD- or S1-binding IgG direct Luminex immunoassay and SARS-CoV-2 serum neutralization assay • Sera obtained/assessed—prior to vaccine or placebo administration—on days 1 (dose 1), 21 (dose 2), 28, and 35 • Immunogenicity data from a human convalescent serum (HCS) panel served as benchmark ○ n = 38 donors, age 18-83 y (median age, 42.5 y), who had recovered from SARS-CoV-2 infection Note: Immunogenicity responses for 30 mcg dose (selected to move into phase 2/3 study) reported out here. See Figure 4 in NEJM for full report out of dose-dependent immunogenic responses GMCs (U/mL) of recombinant S1-binding IgG • Placebo: 0.9; HCS: 631 • BNT162b1 (18 – 55 y vs. 65 – 85 y) ○ D0: 0.8 vs. 0.7 ○ D21: 853 vs. 86 ○ D28: 23,516 vs. 6,580 ○ D35: 13,940 vs. 4,798 • BNT162b2 (18 – 55 y vs. 65 – 85 y) ○ D0: 0.6 vs. 0.6 ○ D21: 1,265 vs. 329 ○ D28: 9,136 vs. 7,985 ○ D35: 8,147 vs. 6,014 50% SARS-CoV-2-neutralizing GMT • Placebo: 10; HCS: 94 • BNT162b1 (18 – 55 y vs. 65 – 85 y) ○ D0: 10 vs. 10 ○ D21: 29 vs. 12 ○ D28: 267 vs. 101 ○ D35: 437 vs. 105 • BNT162b2 (18 – 55 y vs. 65 – 85 y) ○ D0: 10 vs. 10 ○ D21: 14 vs. 12 ○ D28: 361 vs. 149 ○ D35: 163 vs. 206	**Local events** • Primarily mild to moderate in severity • Pain at injection site most common; percentage reported with 30 mcg dose are as follows (dose 1 vs. dose 2): ○ BNT162b1 (18-55y): 100% vs. 100% ○ BNT162b1 (65-85y): 92% vs. 75% ○ BNT162b2 (18-55y): 92% vs. 83% ○ BNT162b2 (65-85y): 75% vs. 67% • 8% of participants age 18-55 reported redness with dose 1 of 30 mcg BNT162b2; no other reports of redness or swelling reported with the 30 mcg dose (more common with the BNT162b1 candidate) **Systemic events** BNT162b1 • 18-55 y: frequently reported mild-moderate fever and chills, with 75% reporting a fever ≥38°C after dose 2 of 30 mcg • 65-85 y: systemic events milder as compared to younger group (i.e. only 33% reported fever after dose 2), though many reported fatigue, headache after dose 1 or 2 BNT162b2 • Systemic events were milder for BNT162b2 vs. BNT162b1 ○ Only 17% of 18-55 y and 8% of 65-85 y experienced fever with dose 2 of 30 mcg BNT162b2 • Severe systemic events (i.e. fatigue, headache, chills, muscle/joint pain) reported in a small number 18-55 y; none in 65-85 y

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 2/3 trial (NCT04368728) *Note:* *Although 4 interim analyses (IAs) were originally planned (after accrual of 32, 62, 92, and 120 cases), the first planned IA was not performed for operational reasons.* *The remaining 3 IAs (62, 92, and 120 cases) remained in place, with VE for the first primary objective evaluated at each IA.* *Efficacy could be declared if the VE point estimate for the current number of cases was met, which would be indicative of VE>30%.*	43,661	For full inclusion and exclusion criteria, see **NCT04368728** Inclusion • Healthy individuals aged ≥12 y, stratified: ○ 12-15 y ○ 16-55 y ○ >55 y Exclusion • Immunocompromised • Prior coronavirus vaccination • Receipt of blood/plasma products or immunoglobulin in 60 days prior to study or planned during study *Note:* *HIV-positive participants in phase 3 not included in analyses of objectives (plan to include in specific exploratory objective)*	2 doses of BNT162b2 (30 mcg) or placebo, administered 21 d apart	*Evaluation of VE is the primary objective; VE=100 x (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* **Primary objectives** *Primary efficacy objectives will be evaluated sequentially, in the order presented below (after the first objective is met, then the second primary endpoint will be evaluated):* • Ratio* of confirmed COVID-19 from 7 days after the second dose in participants without evidence of infection (prior to 7 days after receipt of the second dose) • Ratio* of confirmed COVID-19 from 7 days after the second dose in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) ** active vaccine group vs placebo group, per 1000 person-years of follow-up* **Secondary objectives:** *A description of secondary efficacy objectives (which were also to be evaluated in a sequential manner, after the primary objectives were evaluated/met), can be found in the trial **protocol**. However, it was **announced** that Pfizer and BioNTech have concluded the final efficacy analysis for the Phase 3 study, and thus far commentary has only been made on the primary objectives, as well as safety data.*	
				Results reported by Pfizer/BioNTech (*publication of Phase 3 data pending*)	
				• N=170 cases of COVID-19 (n=162 in placebo group, n=8 in BNT162b2 group) • Both primary efficacy endpoints (above) met, demonstrating **95% VE** (p<0.0001), **beginning 28 days after first dose** • Efficacy consistent across age, gender, race, and ethnicity • >94% observed efficacy in adults over age 65	• No serious safety concerns observed • Fatigue (3.8%) and headache (2.0%) after dose 2 were the only Grade 3 (severe) AE reported at a frequency ≥2% • Older adults experienced fewer and milder AE

Abbreviations: AE = adverse event; GMC = geometric mean concentration; GMT = geometric mean titer; SAE = serious adverse event; VE = vaccine efficacy

Appendix C – AZD1222 trials

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Folegatti PM et al. Adenovirus vector AZD1222 (ChAdOx1 nCov-19) Phase 1/2 clinical trial	1077	Inclusion criteria • 18-55 y • Healthy adults Exclusion criteria • Hx of laboratory confirmed SARS-CoV-2 infection • At higher risk for SARS-CoV-2 exposure (later amendment allowed for HCW with negative antibodies to be recruited) • New onset fever, cough, SOB, anosmia, or ageusia	**Intervention group** ChAdOx1 nCoV-19 vaccine 5 X 10^{10} VP in 0.5 mL administered intramuscularly • Initial dose (n = 543) • Booster dose after 28 d (n = 10) • Prophylactic paracetamol (n = 56) **Control group** MenACWY (meningococcal) vaccine 0.5 mL administered intramuscularly (n = 534) • Prophylactic paracetamol (n = 56)	**Note:** Patients were divided into groups and not all received the same assessments. **Spike-specific T cell response: IFN-gamma ELISpot response against SARS-CoV-2 peptides (Spot forming cells)** • Day 14: o ChAdOx1 Prime (n = 43): 856 [IQR:493.3, 1802] o ChAdOx1 Prime-Boost (n = 10): 1642.3 [IQR: 1423.7, 2009.5] o MenACWY (n = 44): 55.3 [48, 99.3] • Day 28: o ChAdOx1 Prime (n = 68): 554.3 [IQR: 311.3, 1017.7] o ChAdOx1 Prime-Boost (n = 10): 528.7 [IQR: 376.3. 603] o MenACWY (n = 69): 61.3 [48, 88] • Day 56: o ChAdOx1 Prime (n = 43): 424 [IQR: 221.3, 798.7] o ChAdOx1 Prime-Boost (n = 10): 614 [IQR: 437.3, 666] o MenACWY (n – 42): 66.7 [48, 123.3] **Anti-spike IgG using standardized ELISA (EU)** • Day 14: o ChAdOx1 Prime (n = 44): 102.7 [IQR:43.7, 186] o ChAdOx1 Prime-Boost (n = 10): 137 [IQR: 46.4, 206.8] o MenACWY (n = 44): 1 [1, 1] • Day 28: o ChAdOx1 Prime (n = 127): 157.1 [IQR: 96.2, 316.9] o ChAdOx1 Prime-Boost (n = 10): 210.7 [IQR: 149.4. 321.6 9] o MenACWY (n = 130): 1 [1, 1] • Day 56: o ChAdOx1 Prime (n = 43): 119 [IQR: 70.3, 203.4]	• No serious AEs reported. • Local and systemic reactions were reported in the ChAdOx1 nCoV-19 group and were reduced in patients instructed/allowed to use paracetamol prophylactically (1 g every 6 h for 24 h) including pain, feeling feverish, chills, muscle ache, headache, and malaise. • Immunogenicity in patients advised to take paracetamol prophylactically was similar to those who were not advised to do so; however, these data were not reported. • Pain o ChAdOx1 + paracetamol: n = 28 (50%) o ChAdOx1: n = 328 (67%) o MenACWY+ paracetamol: n = 18 (32%) o MenACWY: n = 180 (38%) • Tenderness o ChAdOx1+ paracetamol: n =43 (77%) o ChAdOx1: n = 403 (83%) o MenACWY+ paracetamol: n = 26 (14%) o MenACWY: n = 276 (58%) • Chills o ChAdOx1+ paracetamol: n = 15 (27%) o ChAdOx1: n = 272 (56%) o MenACWY: n = 5 (9%)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				○ ChAdOx1 Prime-Boost (n = 10): 639.2 [IQR: 360, 792.2] ○ MenACWY (n = 44): 1 [1, 2.6] ***Note:*** EU values were obtained from CP and were not reported in text. However, ChAdOx1 Prime & ChAdOx1 Prime-Boost responses at 14-56 d were visually within the range of values obtained from CP. **Anti-SARS-CoV-2 neutralizing antibodies: PHE MNA_{80}** • Day 28: ○ ChAdOx1 Prime (n = 35): 51 [IQR:32, 103]; **Note:** Neutralizing antibodies were detected in 32/35 (91%) with the PHE MNA_{80} assay ○ ChAdOx1 Prime-Boost (n = 10): 70 [IQR: 32.8, 168] ○ MenACWY (n = 2): 10 [10, 10] **Anti-SARS-CoV-2 neutralizing antibodies: PHE $PRNT_{50}$** • Day 28: ○ ChAdOx1 Prime (n = 35): 218 [IQR: 122, 395]; **Note:** Neutralizing antibodies were detected in 35/35 (100%) with the PHE $PRNT_{50}$ assay ○ MenACWY (n = 2): 36.5 [30.8, 42.3]	○ MenACWY + paracetamol: n = 46 (10%) • Fatigue ○ ChAdOx1 + paracetamol: n = 40 (71%) ○ ChAdOx1: n = 340 (70%) ○ MenACWY+ paracetamol: n = 26 (46%) ○ MenACWY l: n = 227 (48%) • Headache ○ ChAdOx1+ paracetamol: n = 24 (61%) ○ ChAdOx1: n = 331 (68%) ○ MenACWY+ paracetamol: n = 21 (37%) ○ MenACWY: n = 195 (41%) • Muscle ache ○ ChAdOx1 + paracetamol: n = 27 (48%) ○ ChAdOx1: n = 294 (60%) ○ MenACWY+ paracetamol: n = 15 (26%) ○ MenACWY: n = 118 (25%) • Malaise ○ ChAdOx1 + paracetamol: n = 27 (48%) ○ ChAdOx1: n = 296 (61%) ○ MenACWY+ paracetamol: n = 6 (11%) ○ MenACWY: n = 83 (17%)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 3 trial ChAdOx1 nCov-19 (AZD1222) (NCT04516746)	30,000	Inclusion • ≥ 18 y • Increased risk of SARS-CoV-2 infection Exclusion • Confirmed or suspected immunosuppressive state • Significant disease, disorder, or finding • Prior or concomitant vaccine therapy for COVID-19	Treatment • ChAdOx1 nCoV-19 vaccine 5 X 10^{10} vp (nominal ± 1.5 X 10^{10}) administered intramuscularly X 2 (separate doses by 4 wks) Placebo • Saline intramuscularly X 2 (separate doses by 4 wks)	Primary outcomes to be measured • First SARS-CoV-2 positive illness (by PCR) ≥ 15 d post second dose of study intervention • AE incidence • SAE incidence • Local and systemic solicited AEs Secondary outcomes to be measured • Asymptomatic infection measured by proportion of patients positive for SARS-CoV-2 nucleocapsid antibodies • Symptomatic COVID-19 infection using CDC criteria • University of Oxford defined symptomatic COVID-19 • Severe or critical symptomatic COVID-19 • Emergency department visits • S antigen antibody response • GMTs and GMFRs in SARS-CoV-2 neutralizing antibodies	

Abbreviations: AE = adverse events; CP = convalescent plasma; EU = elisa units; GMFR = geometric mean fold rise; GMT = geometric mean titers; IFN: interferon; MNA = microneutralization assay; PRNT= Plaque reduction neutralization test; NAAT = nucleic acid amplification test; SAE = serious adverse event; VE = vaccine efficacy; VP: viral particles

Appendix D – JNJ-78436735 trials

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 1/2a	796	For full inclusion and exclusion criteria, see **NCT04436276** Inclusion criteria • Healthy patients ≥ 18-55 y • Good or stable health patients ≥ 65 y • BMI ≤ 30 kg/m^2 Exclusion criteria • Clinically significant acute illness • Malignancy ≤ 5 y prior to screening (some exceptions) • Neurological disorders • Positive SARS-CoV-2 • infection at screening Comorbidities associated with increased risk for progression to severe COVID-1	Treatment • $5X10^{10}$ vp or $1X10^{11}$ vp administered intramuscularly as a single dose or 2 doses separated by 8 wks Placebo • Sodium chloride 0.9% 1 mL administered intramuscularly as a single dose or 2 doses separated by 8 wks Note: For single dose treatment arms, a second placebo dose was administered after 8 wks.	See **preprint** for full description of cohorts and results. Humoral response by Spike-specific ELISA against SARS-CoV-2 *Cohort 1a (18-55 yo; 1 or 2 doses)* • $5X10^{10}$ vp dose ○ Baseline GMT: EU/mL <LLOQ in 94% of participants ○ Day 29 GMT: 528 EU/mL (95% CI: 442, 630) • $1X10^{11}$ vp dose ○ Baseline GMT: EU/mL <LLOQ in 98% of participants ○ Day 29 GMT: 695 EU/mL (95% CI: 596, 810) • Observed in HCS: GMT: 899 EU/mL overlapping in the 95% CI of both above doses *Cohort 3 (≥ 65yo; 1 or 2 doses [results are for the first 15 participants])* • $5X10^{10}$ vp dose ○ Baseline GMT: EU/mL <LLOQ ○ Day 29 GMT: 507 EU/mL (95% CI: 181, 1418) • $1X10^{11}$ vp dose ○ Baseline GMT: EU/mL <LLOQ ○ Day 29 GMT: 248 EU/mL (95% CI: 122, 506) • Observed in HCS: GMT: 899 EU/mL overlapping in the 95% CI of both above doses Humoral response by neutralizing titers by wtVNA (50% IC) *Cohort 1a (18-55 yo; 1 or 2 doses; [results are for a subset n = 50 participants])* • $5X10^{10}$ vp dose ○ Baseline GMT: <LLOQ ○ Day 29 GMT: 214 (95% CI: 177, 259) • $1X10^{11}$ vp dose ○ Baseline GMT: <LLOQ ○ Day 29 GMT: 243 (95% CI: 200, 295) • Observed in HCS: GMT: 522 overlapping in the 95% CI of both above doses *Cohort 3 (≥65 yo; 1 or 2 doses; n = 375 [results are for the first 15 participants])* • $5X10^{10}$ vp dose ○ Baseline GMT: <LLOQ	Solicited Local AE • Cohort 1: 58% • Cohort 3: 27% • Most frequent local AE was injection site pain SAEs • Cohort 1: ○ Total:64% ○ Fever: 19% ○ Grade 3 fever: 5% • Cohort 3: ○ Total:36% ○ Fever: 4% ○ Grade 3 fever: 0% • Most frequent SAEs were headache, fatigue, and myalgia Unsolicited AE • Cohort 1a: 12 reported; 8 deemed related to treatment including WBC increase, malaise, back pain, hypotensive crisis, insomnia, fever, and lightheadedness;1 necessitating drug withdrawal (pyrexia) • Cohort 3: 6 reported; 4 deemed related to treatment including: systolic hypertension, hypertension, vomiting, and dizziness Assessing risk for VAERD: CD4+ Th1 & Th2 responses *Cohort 1a Th1 responses* • Baseline: undetectable • 15 days post vaccination ○ $5X10^{10}$ vp dose: 0.08% (95% CI: 0.05, 0.16) ○ $1X10^{11}$ vp dose: 0.11% (95% CI: 0.07, 0.16) *Cohort 3 (first participants) Th1 responses* • Baseline: undetectable • 15 days post vaccination ○ $5X10^{10}$ vp dose: 0.36% (95% CI: 0.15, 0.89)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				○ Day 29 GMT: 196 (95% CI: 69, 560) • $1X10^{11}$ vp dose ○ Baseline GMT: <LLOQ ○ Day 29 GMT: 127 (95% CI: <LLOQ, 327) • Observed in HCS: GMT: 522 overlapping in the 95% CI of both above doses Cellular response by Th1 cytokine producing CD4+ Tcell (S-specific) *Cohort 1a (subset)* • Positive response on day 14: 80% *Cohort 3 (subset)* • Positive response on day 14: 83% Cellular response by CD8+ Tcell (S-specific) *Cohort 1a* • Positive response ○ $5X10^{10}$ vp dose: 51% (95% CI: 39, 63) ○ $1X10^{11}$ vp dose: 64% (95% CI: 52, 75) • Response magnitude 15 days post vaccination ○ $5X10^{10}$ vp dose: 0.07% (95% CI: 0.03, 0.19) ○ $1X10^{11}$ vp dose: 0.09% (95% CI: 0.05, 0.19) *Cohort 3 (first participants)* • Positive response ○ $5X10^{10}$ vp dose & $1X10^{11}$ vp dose: 33% (95% CI: 4, 78) • Response magnitude 15 days post vaccination ○ $5X10^{10}$ vp dose: 0.05% (95% CI: 0.02, 0.24) ○ $1X10^{11}$ vp dose: 0.07% (95% CI: 0.02. 0.14)	○ $1X10^{11}$ vp dose: 0.13% (95% CI: 0.04, 0.5) *Th2 responses* • One patient in cohort 1a $5X10^{10}$ group exhibited a response and the Th1/Th2 ratio was 28.9, indicative of a Th1-skewed response *Th1/Th2 ratio (all)* • Range: 1-68.5

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 3 trial Ad26.COV2.S (JNJ-78436735) ENSEMBLE	60,000	For full inclusion and exclusion criteria, see **NCT04505722** Inclusion • ≥ 18 y	Treatment • $5X10^{10}$ vp administered intramuscularly X 1 Placebo • Placebo administered intramuscularly X 1	Primary outcomes to be measured • Molecularly confirmed moderate to severe COVID-19 (onset at least 14 d post vaccination) in SARS-CoV-2 seronegative adults Secondary outcomes to be measured • Molecularly confirmed moderate to severe COVID-19 (day 2-end of study) regardless of serostatus • Molecularly confirmed moderate to severe COVID-19 (onset at least 14 d post vaccination through end of study) regardless of serostatus • Molecularly confirmed moderate to severe COVID-19 (day 2-end of study) • Patients requiring medication intervention (i.e. hospitalization, ICU admission, mechanical ventilation, ECMO) • SARS-CoV-2 viral load • Molecularly confirmed mild COVID-19 • Molecularly confirmed COVID-19 by FDA harmonized case definition • Burden of disease based on first occurrence of confirmed symptomatic COVID-19 • Serologic conversion by ELISA • Occurrence of SARS-CoV-2 infection • SAE • Medically attended AE • Medically attended AE leading to study discontinuation • Solicited local AE • Solicited systemic AE • Unsolicited local AE • SARS-CoV-2 neutralizing antibody titers • SARS-CoV-2 binding antibodies	
Phase 3 trial Ad26.COV2.S (JNJ-78436735) ENSEMBLE 2	30,000	For full inclusion and exclusion criteria, see **NCT04614948** Inclusion • ≥ 18 y	Treatment • Vaccine administered intramuscularly X 2, separated by 57 d Placebo • Placebo administered intramuscularly X 2, separated by 57 d	Primary outcomes to be measured • Number of participants with first occurrence of molecularly confirmed moderate to severe/critical COVID-19 and who were seronegative at baseline	

Abbreviations: AE = adverse events; CP = convalescent plasma; ECMO = extracorporeal membrane oxygenation; EU = elisa units; IC = inhibitory concentration; HCS = human convalescent serum; ICS = intracellular cytokine staining; IFN: interferon; LLOQ = lower limit of quantification; MNA = microneutralization assay; PRNT= Plaque reduction neutralization test; NAAT = nucleic acid amplification test; SAE = serious adverse event; VAERD = vaccine associated enhanced respiratory disease; VE = vaccine efficacy; VP: viral particles; wtVNA = wild type virus neutralization assay

Appendix E – NVX-CoV2373 trials

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
Keech C, et al. SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine Randomized, placebo-controlled, phase 1/2 trial (*only phase 1 results reported here*)	134	Healthy adults 18 to 59 y For inclusion/exclusion criteria, see **NCT04368988** Baseline characteristics • Male, n = 66 (50.4%) • Age, mean (SD): 30.8 y (10.2) • White, n = 103 (78.6%) • Hispanic or Latino, n = 19 (14.5%) • Asian, n = 17 (13.0%) • AI or AN, n = 7 (5.3%) • Black or AA, n = 2 (1.5%) • BMI, mean (SD): 25.19 (3.672)	**Intervention groups** 2 injections, 21 d apart: rSARS-CoV-2 (5 or 25 mcg) ± adjuvant (Matrix-M1) and/or placebo • Group A: Placebo x 2 (n = 23) • Group B: 25 mcg x 2 (n = 25) • Group C: 5 mcg + Matrix-M1 x 2 (n = 29*) • Group D: 25 mcg + Matrix-M1 x 2 (n = 28*) • Group E: 25 mcg + Matrix-M1 (dose 1) then Placebo (Dose 2) (n = 26) *Including 3 "sentinels", which were individuals administered vaccine as part of an initial open-label investigation to assess reactogenicity, prior to 1:1:1:1:1 randomization **Control group** Convalescent serum samples • GMT IgG (n = 29) GMT neutralizing antibody (n = 32)	**GMT (95% CI) IgG responses (reported in EU/mL) to rSARS-CoV-2 at day 28:** • Group A: 110.6 (89.7, 136.3) • Group B: 206.9 (138.9, 308.1) • **Group C: 15318.8 (9486.8, 24736.0)** • **Group D: 20429.2 (11974.4, 34853.6)** • Group E: 3503.2 (2378.4, 5160.1) • **Convalescent serum: 8343.7 (4420.9, 15747.5)** **GMT (95% CI) IgG responses (reported in EU/mL) to rSARS-CoV-2 at day 35:** • Group A: 113.5 (93.6, 137.6) • Group B: 575.5 (331.7, 998.5) • **Group C: 63160.4 (47117.3, 84666.0)** • **Group D: 47521.0 (33803.7, 66804.6)** • Group E: 2932.0 (1987.7, 4324.8) • **Convalescent serum: 8343.7 (4420.9, 15747.5)** **GMT (95% CI) neutralizing antibody responses (MN $IC_{>99\%}$) to rSARS-CoV-2 at day 21:** • Group A: 20.0 (20.0, 20.0) • Group B: 21.7 (19.2, 24.6) • **Group C: 103.3 (74.8, 142.6)** • **Group D: 126.2 (79.5, 200.4)** • Group E: 117.8 (74.2, 187.0) • **Convalescent serum: 983.8 (579.4,1670.5)** **GMT (95% CI) neutralizing antibody responses (MN $IC_{>99\%}$) to rSARS-CoV-2 at day 35:** • Group A: 20.0 (20.0, 20.0) • Group B: 41.4 (27.5, 62.4) • **Group C: 3906.3 (2555.9, 5970.0)** • **Group D: 3305.0 (2205.3, 4953.2)** • Group E: 127.6 (81.8, 199.1) • **Convalescent serum: 983.8 (579.4,1670.5)** **SARS-CoV-2 T-cell responses** • T-cell responses investigated in 16 participants randomly selected from groups A-D	Discontinuations due to safety (n = 1) • 25 mcg + Matrix-M1 group – second vaccine in series not received due to unsolicited AE (mild cellulitis associated unrelated IV placement) Local and systemic reactogenicity was absent or mild in majority of participants* after first vaccination • Local: 100%, 96%, 89%, 84%, and 88% of participants in groups A, B, C, D, and E, respectively • Systemic: 91%, 92%, 96%, 68%, and 89% • 2 participants (1 each in groups D and E) had severe AE (headache, fever, and malaise) Local and systemic reactogenicity was absent or mild in majority of participants* after 2nd vaccination • Local: 100%, 100%, 65%, 67%, and 100% • Systemic: 86%, 84%, 73%, 58%, and 96% • 1 participant in group D had a severe local event (tenderness) and 8 participants (1-2 in each group) had severe systemic events (most commonly joint pain and fatigue) • 1 participant in group D had fever, and only on day 1 Lab values (serum chemistry and hematology) assessed at days 7 and 28, according to FDA toxicity scoring. • 13 participants (10%) experienced lab abnormalities of grade 2 or higher

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				• Adjuvanted regimens were shown to induce antigen-specific polyfunctional CD4+ T-cell responses, with a “strong bias” toward Th1 phenotype and minimal Th2 responses	• Not associated with any clinical manifestations; no worsening with repeat vaccination • N = 6 had transient reductions in Hgb from baseline with resolution within 7-21 d • N = 4 (including n = 1 who received placebo) had elevated LFTs that resolved in 7-14 d (prior to second vaccination)
Phase 3 trial – ongoing Randomized, placebo-controlled , observer-blinded study	5,500 enrolled in UK Up to 15,000 Event-driven, final number will depend on number of events	Healthy adults 18 to 84 y	Intervention • 5 mcg NVX-CoV2373 + 50 mcg Matrix-M injection given on Day 1 and on Day 21 Control • Placebo – 0.9% sodium chloride injection Up to 400 participants will also receive a licensed seasonal influenza vaccine as part of a co-administration sub-study	The primary efficacy analysis will be an event-driven analysis based on the number of participants with symptomatic or moderate to severe COVID-19. An interim analysis will be performed when 67% of the desired number of cases is reached. There will be 2 primary endpoints: • First occurrence of PCR-confirmed, **symptomatic COVID-19** with onset at least 7 d after the second dose in volunteers not previously infected with SARS-CoV-2 • First occurrence of PCR-confirmed, **symptomatic moderate or severe COVID-19** with onset at least 7 d after the second dose in volunteers not previously infected with SARS-CoV-2	

Abbreviations: AA = African American; AE = adverse events; AI = American Indian; AN = Alaska Native; BMI = body-mass index; ELISA = enzyme-linked immunosorbent assay; GMEUs = geometric mean ELISA units; GMT = geometric mean titer; MN $IC_{>99\%}$ = microneutralization assay with an inhibitory concentration >99%; VE = vaccine efficacy; rSARS-CoV-2 = recombinant severe acute respiratory syndrome coronavirus 2

Vizient, Inc.
290 E. John Carpenter Freeway
Irving, TX 75062-5146
(800) 842-5146