COVID-19 vaccine candidates

March 1, 2021

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Table of contents

Summary of changes since last publication (update: March 1, 2021)

- Added information from the FDA advisory committee briefing document on the efficacy and safety of JNJ-78436735 (Ad26.COV2.S) (vaccine table and white paper)
- Added emergency use authorization prescribing information for JNJ-78436735 (Ad26.COV2.S) (vaccine table)
- Added information on Moderna and Pfizer/BioNTech plans to address variants (vaccine table)
- Added demographic data for Novavax's U.S./Mexico phase 3 trial (vaccine table)
- Added CPT codes for JNJ-78436735 (Ad26.COV2.S) (vaccine table)
- Added real world study evaluating asymptomatic cases of SARS-CoV-2 with mRNA-BNT162b2 (white paper)

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
FDA status (if authorized, indication)	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 18 y	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 16 y	Investigational	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 18 y	Investigational
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	EUA approval of Pfizer and Moderna vaccines		No[b]	Yes (EU Ebola)	Yes
Platform differentiators	Potential advantages: • 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: • Previous use in immunocompromised populations • Demonstrated immunogenicity in older adults in another disease states (influenza A) • Circumvents existing antivector immunity (novel vector) Potential disadvantages: • No commercial vaccine precedent in humans	Potential disadvantages: • Possibility of pre-existing antivector immunity	Potential advantages: • Safety – non-infectious, non-integrating • Scalable production – engineered production facilitates large-scale vaccine production • Potency – capable of generating humoral and cellular immunity • Adjuvanted –provides enhanced immune response, allowing for vaccine dose-sparing effect Potential disadvantages: • Local and systemic inflammatory responses
Targeted SARS-CoV-2 antigen	Full-length, prefusion stabilized SARS-CoV-2 spike protein		SARS-CoV-2 spike protein	Full-length, stabilized SARS-CoV-2 spike protein	Full-length, prefusion stabilized SARS-CoV-2 spike protein

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Pharmacology	• mRNA encoding for the SARS-CoV-2 spike glycoprotein is delivered to cells in a lipid capsule • Using mRNA, cells manufacture the spike protein (antigen) • Spike protein stimulates the body's immune response and production of antibodies against SARS-CoV-2		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.		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. 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					
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 and dose)	√
Manufacturing	Genetically engineered				
Distribution					
Vaccine	• Moderna ships to central distributor at -20° C • Central distributor ships to States and Jurisdictions	• Pfizer ships directly to facilities or hubs • Shipped in thermal shipper, which utilizes dry ice to maintain ULT • Thermal shipper keeps ULT up to 10 d if stored at 15°C to 25°C without opening	NR	• Johnson and Johnson ships to central distributor at 2°C to 8°C • Central distributor ships to States and Jurisdictions	NR

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Ancillary supply kits	From kitting facility to central distributor to States and Jurisdictions, at RT	Direct to site from kitting facility, at RT	NR	From kitting facility to central distributor to States and Jurisdictions, at RT	NR
How supplied					
Multidose vial	10 to 11 doses/vial[c] Vial size: 5 mL (Does not contain latex)	5 to 7 doses/vial[c] Vial size: 2 mL (Does not contain latex)	• 10 doses/vial (C Dube, oral communication, 9/2020) • 8- and 10-doses/vial (UK EUA)	5 doses/vial (Does not contain latex)	NR
Anticipated commercial vaccine storage conditions – unopened vial (investigational conditions may differ)					
Frozen or ultra-cold	Store at -20°C±5°C	**Two options for storage:** • Transfer to a ULT freezer (-70°C±10°C) immediately upon receipt (shelf-life: up to 6 mo) • If a ULT freezer is not available, the thermal shipper may be used as temporary storage for up to 30 d, provided instructions in the re-icing guidelines (packed in the original thermal container) are carefully followed **Highlights for using the thermal shipper as temporary storage:** *See Pfizer Re-icing Guidelines provided in thermal container* • Upon receipt and after opening, replenish with dry ice (filled to top of container) within 24 h • Store at 15-25°C	Do not freeze (UK EUA, EMA EUA)	• Stored at -20° C, stable for 2 y • Stored frozen prior to shipment, but **should not** be stored frozen at vaccination site • If vaccine is frozen upon receipt, thaw at 2°C to 8°C or if needed immediately, thaw at room temperature (2 h to thaw carton of 10 vials, 1 h to thaw individual vial)	Not applicable

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		• Open no more than 2 times a day, for no more than 3 min at a time; assuming this guidance is followed, the shipper should be re-iced every 5 d. This will allow for up to 30 d of storage. • After storage for 30 d in the thermal shipper, the vaccine can be transferred to a refrigerator (2-8°C) for an additional 5 d, for a total of up to 35 d of storage.			
Refrigeration (2-8°C)	Stable for 30 d	Undiluted vial: 5 d	Until date printed on packaging (at least 6 months)	Stable for 3 mo	Store under refrigeration
Room temperature	Stable for 12 h	Undiluted vial: 2 h	NR	Stable for 12 h	NR
BU after vial entry	• 6 h, stored between 2°C to 25°C • USP Compounding Expert Committee added operational considerations for preparing conventionally manufactured COVID-19 vaccines after FDA issued EUA		6 h, stored between 2°C to 25°C (UK EUA, EMA EUA)	• 6 h, stored between 2°C to 8°C **OR** • 2 h, stored at room temperature, up to 25°C	NR
Dosage and administration					
Dose	100 mcg/0.5 mL	30 mcg/0.3 mL	• 5×10^{10} vp dose or 3.5-6.5 x 10^{10} vp dose (phase 3) • UK: $5x10^{10}$ vp/0.5 mL • EMA: $5x10^{10}$ vp/0.5 mL	5×10^{10} vp dose/0.5 mL	5 mcg protein antigen + 50 mcg Matrix-M adjuvant
Number of doses	2-dose series (28 d between doses)	2-dose series (21 d between doses)	• 2-dose series (4-12 wk between doses) (UK	1 dose	2-dose series (21 d between doses)

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	• Second doses administered within 4 d earlier than recommended are considered valid (e.g., Moderna – days 24-27; Pfizer – days 17-20) (per CDC) • The second dose should be administered as close to recommended interval as possible. If not feasible, the second dose of mRNA vaccines may be scheduled for administration up to 6 wk (42 d) after first dose. • Both doses are necessary for protection; efficacy of a single dose has not been evaluated.[d]		EUA, EMA EUA) • WHO recommends 8-12 wk between doses based on efficacy and immunogenicity data		
Co-administration with other vaccines	• Due to insufficient evidence, administer vaccine series alone, with a minimum interval of 14 d before or after administration with any other vaccine. • If inadvertently administered within 14 d of another vaccine, do not repeat doses of either vaccine.		NR	No data to assess concomitant administration with other vaccines	NR
Administration route	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Dilution required	No	Yes	No	No	No
Preparation	*Full details on preparation can be found in the* **Fact Sheet for HCP**. • Frozen vials must be thawed prior to administration – either under refrigeration (2 h and 30 min) or at room temperature (≤25°C for 1 h). • After thawing, do not refreeze • Swirl vial gently after thawing and between each withdrawal • Record date and time of first use on vial label.	*Full details on preparation can be found in the* **Fact Sheet for HCP** • Frozen vials must be thawed to room temperature prior to dilution – either under refrigeration (up to 3 h) or at room temperature (≤25°C; up to 30 min). • Dilute in original vial with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP (Do not use bacteriostatic 0.9% Sodium Chloride Injection). • Record the date and time of dilution on the vaccine vial label.	Not applicable	*Full details on preparation can be found in the* **Fact Sheet for HCP** • Before withdrawing each dose, carefully mix the contents of the vial by swirling gently in an upright position for 10 sec. • Record date and time of first use on vial label.	Not applicable

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Needle selection	• Choice of appropriate needle length and gauge is directed by patient age, gender, weight, injection site and route of administration. Improper selection may inhibit vaccine reaching targeted tissue and possibly efficacy. See **CDC recommendations** for guidance. • The CDC has **indicated** for both the Pfizer and Moderna vaccines that "changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated"				
Considerations in specific populations					
Current or prior history of SARS-CoV-2 infection	• Current infection - vaccination should be deferred until the person has recovered from acute illness and criteria have been met for isolation discontinuation. • Prior infection - there is no recommended minimum interval between infection and vaccination. While vaccine supply remains limited, persons with recent infection can temporarily delay vaccination, if desired.		NR	NR	NR
History of passive antibody therapy	• Vaccination should be deferred for at least 90 d in those that have received monoclonal antibodies or convalescent plasma as a part of COVID-19 therapy. Recommendation applies to first and second doses. • There is no recommended minimum interval between COVID-19 vaccination and other antibody therapies.		NR	NR	NR
Persons with immunocompromise or autoimmune disorder	Immunocompromising and autoimmune conditions – limited data available, but these individuals may receive the vaccine if no contraindications. Stable HIV patients were enrolled in mRNA trials.		NR	NR	NR
Pregnancy or lactation	• Pregnancy – Limited data, but experts believe mRNA vaccines are unlikely to pose a risk. Individual benefit vs. risk assessment should guide vaccination. • Lactation – mRNA vaccines are not thought to be a risk to a breastfeeding infant. Lactation is not a contraindication to vaccination.		NR	NR	NR
Safety considerations					
Contraindications	• Severe allergic reaction (e.g. anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components. • Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol). [e]		NR	Known history of a severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine	NR

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	• Immediate allergic reaction of any severity to polysorbate.[e]				
Precautions	• Balance risk vs. benefit in persons with a history of any immediate allergic reaction to any other vaccine or injectable therapy. • Balance risk vs. benefit in persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG, another vaccine component, or polysorbate, but in whom it is unknown which component elicited the allergic reaction. • Delayed-onset local reactions to a mRNA vaccination are not a precaution to a second dose		NR	NR	NR
Observation period	• Persons with a history of an immediate allergic reaction of any severity to a vaccine or injectable therapy and persons with a history of anaphylaxis due to any cause, observe for 30 min • All others, observe for 15 min		NR	Observation period the same as for mRNA vaccines	
Adverse events					
Overall	Phase 3 (11/11 dataset, n = 30,350)[f] • FDA analysis – most common solicited ADEs: injection site pain (91.6%), fatigue (68.5%), headache (63%), muscle pain (59.6%), joint pain (44.8%), chills (43.4%) • Occurrence of local events comparable after dose 1 and 2; systemic events dose 2 > dose 1	Phase 2/3 (reactogenicity subset, n = 8,183) • FDA analysis - most common solicited ADEs: injection site pain (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%) • Occurrence of local events comparable after dose 1 and 2; systemic events dose 2 > dose 1 • Occurrence of systemic events greater in < 55 y vs. ≥ 55 y	Phase 1/2 • Limited to non-serious (pain, tenderness, headache, fatigue) • Decreased frequency in patients treated with paracetamol • Decreased reactogenicity in older adults Phase 3 (n = 4 trials) • Serious ADEs occurred in 79 vaccine recipients. • One reported case of transverse myelitis was reported; possibly related	Phase 3 (reactogenicity subset, n = 6,736) • FDA analysis – most common solicited ADEs: injection site pain (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%) • In general, occurrence of ADEs more common in the 18-59 y group vs. the ≥ 60 y group	Phase 1/2 • Some local and systemic reactions reported in phase 1 trial (placebo-controlled) • Absent or mild in majority of patients after both first and second dose • No serious ADEs noted

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Solicited local ADEs	• Most common is injection site pain, comparable incidence after dose 1 and 2 (83.7% and 88.4%, respectively) • Most local ADEs were grade 1 or 2; grade 3 events were more common after dose 2, and the most common grade 3 was injection site pain (4.1% - dose 2)	• Most common is injection site pain, reported less frequently in recipients aged ≥ 55 y (71% after dose 1, 66% after dose 2) than those aged < 55 y (83% and 78%, respectively) • Pain was mostly mild to moderate and resolved within 1-2 d	• In the phase 2 component of 2/3 UK trial, most common were pain and tenderness at the injection site	• Most common is injection site pain (48.6%) • Most events grade 1 or 2 severity; <0.5% incidence of grade 3 events	
Solicited systemic ADEs	• Most common are fatigue and headache, incidence and severity increased after dose 2 (fatigue: 37.2% (dose 1), 65.2% (dose 2); headache: 32.7% (dose 1) and 58.6% (dose 2)) • Most common grade 3 ADEs after dose 2 were fatigue (9.7%), myalgia (8.8%), headache (4.5%), and arthralgia (5.2%)	• Most common are fatigue and headache (59% and 52% in recipients aged < 55 y and 51% and 39% in recipients aged ≥ 55 y) • Frequency of systemic ADEs was higher in aged < 55 y and within each age cohort, severity was higher after dose 2, except for vomiting and diarrhea	In the phase 2 component of 2/3 UK trial, most common were fatigue, headache, feverishness, and myalgia	• Most common are headache (38.9%), fatigue (38.2%), and myalgia (33.2%) • Most events grade 1 or 2 severity • Numeric imbalances, with more events in vaccine vs. placebo group were observed for: TE events; seizures; tinnitus; and non-serious urticaria	
Special populations in phase 3 trials					
Geriatrics	Demographics of per-protocol efficacy population (11/11) in EUA submission (n = 27,817)[f] • Median age: 53 y (range: 18-95 y) • ≥ 65 y: 25.3%	Demographics of evaluable efficacy population in EUA submission (n = 40,277): • Median age: 51 y (range: 12-91 y) • ≥ 65 y: 21.4%	All adult age groups enrolled	Demographics of per-protocol population in EUA submission (n = 39,321) • Median age: 53 y (range: 18-100 y) • ≥ 65 y: 20.4%	Demographics of U.S./Mexico phase 3 trial • ≥ 65 y: 13%
Pregnancy	• 13 pregnancies • 6 in vaccine group	• 23 pregnancies • 12 in vaccine group	Not included in phase 3 trial	• 8 pregnancies • 4 in vaccine group	Not included in phase 3 trial

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Racial/ethnicity	Demographics of per-protocol efficacy population (11/11) in EUA submission (n = 27,817)[f] • Asian: 4.7% • Black: 9.7% • Hispanic/Latino: 20% • Other: <3%	Demographics of evaluable efficacy population in EUA submission (n = 40,277) • Asian: 4.4% • Black: 9.8% • Hispanic/Latino: 26.2% • Other: <3%	In an August 31, press release, AstraZeneca states it "will enroll in excess of 50,000 volunteers including 30,000 in the US, in Latin America, Asia, Europe, Russia, and Africa that will provide data for diverse populations."	Demographics of per-protocol population in EUA submission (n = 39,321) • Asian: 3.5% • Black: 17.2% • Hispanic: 45.1% (U.S. only: 14.2%) • American Indian or Alaska native: 8.3%	Demographics of U.S./Mexico phase 3 trial • Asian: 5% • Black: 13% • Hispanic/Latino: 20%
Pediatrics	• Not included in phase 3 • Phase 2/3 clinical trial (NCT04649151) in adolescents 12 to < 18 y (TeenCove) initiated. • Moderna announced on Dec. 10 that the first adolescent participants were dosed	In EUA submission: • Children aged ≥ 12 y enrolled • Participants aged ≤ 15 y (n = 100) not included in efficacy analysis or EUA request. No primary endpoint occurred in age group. • Adolescents aged 16-18 y (n = 283) included in efficacy analysis. Only 1 primary endpoint in age group.	Children 5-12 y are being recruited in the UK	Not included in phase 3 trial	Not included in phase 3 trial
Other special populations included/considered	Demographics of per-protocol efficacy population (11/11) in EUA submission (n = 27,817)[f,g] • 1 high-risk condition present: 22.3% • ≥ 2 high-risk conditions present: 4%	Demographics of evaluable efficacy population in EUA submission (n = 40,277): • Obesity: 34.8% • Diabetes: 8.4% • Pulmonary Disease: 7.8% • HIV (n = 120) analyzed in all-enrolled population	Stable, pre-existing medical conditions	Demographics of full analysis population in EUA submission (n = 43,783) • ≥ 1 co-morbidity: 40.8% • Most common: obesity (28.5%) and hypertension (10.3%) • HIV: 2.8%	Up to 400 participants will also receive a licensed seasonal influenza vaccine as part of a co-administration sub study

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Phase 3 efficacy endpoints					
Trial characteristics	• Enrollment: July 27 to Oct. 23, 2020 • 30,351 patients • U.S. phase 3 trial • Final analysis (data cutoff, Nov. 21, 2020)	• Enrollment: July 27 to Nov. 14, 2020 • 43,448 patients • International phase 1/2/3 trial (85% sites in U.S.) • Final analysis (data cutoff, Nov. 14, 2020)	• Enrollment: April 23 to Nov. 4, 2020 • 17,177 patients • Phases 1/2, 2/3 and 3 trials: UK (n = 2), Brazil (n = 1), S. Africa (n = 1) • Final analysis (data cutoff, Dec. 7, 2020)	• Enrollment: Sept. 7 to Dec. 18, 2020 • 43,783 patients • International EMSEMBLE trial (46.7% of participants from U.S.) • Interim analysis (data cutoff, Jan. 22, 2021)	• 15,000 patients • UK phase 3 trial • First interim analysis
Symptomatic COVID-19 (without previous SARS-CoV-2 infection)	• Primary endpoint, measured 14 d after dose 2 • 185 cases in placebo group vs. 11 cases in vaccine group • VE: 94.1% (95% CI, 89.3-96.8)	• Primary endpoint, measured 7 d after dose 2 • 162 cases in placebo group vs. 8 cases in vaccine group • VE: 95% (95% CI, 90.3-97.6)	• Primary endpoint, measured ≥ 15 d after dose 2 • 248 cases in control group vs. 84 cases in vaccine group • Overall VE: 66.7% (95% CI, 57.4-74) • SD/SD cohort VE: 63.1% (95% CI, 51.8-71.7) • LD/SD cohort VE: 80.7% (95% CI, 62.1-90.2) • Single dose VE (22-90 d): 76% (95% CI, 59-86)	• Secondary endpoint, measured 14 d and 28 d after vaccine • 14 d: 351 cases in placebo group vs. 117 cases in vaccine group; VE of 66.9% (95% CI, 59.1-73.4) • 28 d: 195 cases in placebo group vs. 66 cases in vaccine group; VE of 66.5% (95% CI, 55.5-75.1)	• Primary endpoint, measured ≥ 7 d after dose 2 • 56 cases in placebo group vs. 6 cases in vaccine group • Overall VE: 89.3% (95% CI, 75.2-95.4%) • VE, against original strain: 95.6% • VE against UK variant strain: 85.6%
Symptomatic COVID-19 (with or without previous SARS-CoV-2 infection)	• Subgroup analysis, measured 14 d after dose 2 • 187 cases in placebo group vs. 12 cases in vaccine group • VE: 93.6% (95% CI, 88.6-96.5)	• Primary endpoint, measured 7 d after dose 2 • 169 cases in placebo group vs. 9 cases in the vaccine group • VE: 94.6% (95% CI, 89.9-97.3)	NR	• Secondary endpoint, measured 14 d and 28 d after vaccine • 14 d: VE of 66.1% (95% CI, 59.7-71.6) • 28 d: VE of 65.5% (57.2-72.4) • Previous infection: 9.6% of participants	NR

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Moderate or severe COVID-19	• Secondary endpoint, prevention of **severe** COVID-19 • 30 cases in placebo group vs. 0 cases in vaccine group (note: 1 vaccine recipient met definition for severe disease, but negative SARS-CoV-2 at hospital, but previously positive) • VE: 100% (95% CI, not estimated)	• Secondary endpoint, prevention of **severe** COVID-19 • After dose 1: 9 cases in placebo group vs. 1 case in vaccine group • After dose 2: 4 cases in placebo group vs. 1 case in vaccine group • After dose 2: VE: 75% (95% CI, -152.6-99.5)	• Subgroup analysis – SD/SD cohort, **hospitalization** or **severe** cases • **Hospitalization**: 22 cases in control group vs. 2 cases in vaccine group • **Severe cases**: 3 cases in control group vs. 0 cases in vaccine group	• Primary endpoint, (**moderate to severe/critical**) measured 14 d and 28 d after vaccine • 14 d: 348 cases in placebo group vs. 116 cases in vaccine group; VE of 66.9% (95% CI, 59-73.4) • 28 d: 193 cases in placebo group vs. 66 cases in vaccine group; VE of 66.1% (95% CI, 55-74.8) • U.S. only: VE of 72% (95% CI, 58.2-81.7) • Planned analysis (**severe/critical**) measured 14 d and 28 d after vaccine • 14 d: 60 cases in placebo group vs. 14 cases in vaccine group; VE of 76.7% (95% CI, 54.6-89.1) • 28 d: 34 cases in placebo group vs. 5 cases in vaccine group; VE of 85.4% (95% CI, 54.2-96.9)	1 severe case reported in placebo group vs. 0 cases in vaccine group
Asymptomatic infection	NR	NR	• Single UK trial • SD/SD cohort VE: 2.0% (95% CI, -50.7-36.2) • LD/SD cohort VE: 49.3% (95% CI, 7.4-72.2)	• Secondary endpoint • Limited interpretation serology assessments were performed in a small subset	NR

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COVID-19-related deaths	• 1 in placebo group • 0 in vaccine group	• 0 in placebo group • 0 in vaccine group	NR	• 7 in placebo group • 0 in vaccine group	NR
Efficacy against variants					
Approach to variants	Moderna is evaluating 3 approaches to boosting for variants: • Variant-specific booster candidate, mRNA-1273.351, based on the B.1.351 variant, at the ≤ 50 mcg dose level • Multivalent booster candidate, mRNA-1273.211, combining mRNA-1273 and mRNA-1273.351at the ≤ 50 mcg dose level • A third dose of mRNA-1273 as a booster at the 50 mcg dose level	• Pfizer is evaluating the safety and immunogenicity of a third dose of mRNA-BNT162b2. Participants enrolled in the phase 1 U.S. study will be offered a 30 mcg booster dose 6 to 12 mo after the initial 2-dose regimen • Pfizer is discussing an additional study to evaluate a modified version of the BNT162b2 vaccine that will target the B.1.351 variant	NR	NR	NR
B.1.1.7 variant (UK variant)	*In vitro*: no impact on neutralizing titers vs. Wuhan reference[h]	*In vitro*: Slightly reduced, but overall, largely preserved neutralizing titers (ratio of GMTs, B.1.1.7 pseudovirus vs. Wuhan reference: 0.80)[i]	• Pre-pub trial results, VE of 74.6% (95% CI, 41.6-88.9)[k] • VE against other lineages was 84.1% (95% CI, 70.7-91.4)[k]	No cases of B.1.1.7 variants identified in ENSEMBLE trial	VE in UK trial: 85.6% (post-hoc analysis)
B.1.351 variant (South African variant)	• *In vitro*: a 2.7 factor reduction in neutralizing antibody titers against the partial panel of mutations and a 6.4 factor reduction in titers against full panel[h] • Variant-specific vaccine candidate, mRNA-1273.351 was shipped to NIH for a phase 1 trial	*In vitro*: Two-thirds reduction in neutralizing titers against recombinant virus with full set of B.1.351 spike protein mutations[j]	South African trial paused due to reported lack of protection against mild-moderate disease caused by B.1.351 variant[l]	• In phase 3 trial, VE for moderate to severe/critical disease was lower in S. Africa at 14 d and 28 d • VE for severe/critical disease was similar in U.S. and S. Africa • 94.5% of sequenced cases in S. Africa were B.1.351 variant	• In phase 2b S. Africa trial, VE in HIV-negative patients: 60% (95% CI, 19.9-80.1) • Approximately 92.6% infected with B.1.351

	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)
CPT codes (Payment allowance)	91301 ($0.010) 0011A – first dose ($16.940) 0012A – second dose ($28.390)	91300 ($0.010) 0001A – first dose ($16.940) 0002A – second dose ($28.390)	91302 ($0.010) 0021A – first dose ($16.940) 0022A – second dose ($28.390)	91303 ($0.010) 0031A – vaccine administration ($28.390)	NR
Clinical summary	Please view the evidence summary for an expanded discussion of data.				

Abbreviations: ADE = adverse drug event; BU = beyond use; CPT = current procedural terminology; EMA = European Medicines Agency; EUA = emergency use authorization; GMT = geometric mean titer; HIV = human immunodeficiency virus; LD = low dose; LNP = lipid nanoparticle; mRNA = messenger ribonucleic acid; NR = not reported; PPE = personal protective equipment; RT = room temperature; SD = standard dose; TE = thromboembolic; ULT = ultra-low temperature; VE = vaccine efficacy; VP = viral particle

Footnotes

[a] Information is rapidly changing; this is a living document that is updated frequently

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

[c] FDA is **advising** that it is acceptable to use every full dose obtainable (6 or 7) from each vial, pending resolution of the issue. However, since the vials are preservative free, it is critical to note that any further remaining product that does not constitute a full dose should not be pooled from multiple vials to create one.

[d] After hearing news reports about reducing the number of doses, extending the length of time between doses, changing the dose (half-dose), or mixing and matching vaccines, the FDA published a **statement** that "the available data continue to support the use of 2 specified doses of each authorized vaccine at specified intervals."

[e] These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safety receive the vaccine (e.g., under observation, in a setting with advanced medical care available).

[f] Two datasets were submitted: November 11, 2020 dataset (interim data) and November 25, 2020 dataset (final data). The FDA validated November 11 dataset only; however, results between datasets were consistent

[g] High risk is defined as patients who meet at least one of the following criteria (protocol-defined): 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; HIV

[h] Wu K, Werner AP, Koch M, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv. Available at **https://www.biorxiv.org/content/10.1101/2021.01.25.427948v1**. Published online ahead of print January 25, 2021.

[i] Muik A, Wallisch AK, Sanger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. *Science*. Published online ahead of print January 29, 2021. doi: 10.1126/science.abg6105.

[j] Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum-preliminary report. *N Engl J Med*. Published online ahead of print February 17, 2021. doi: 10.1056/NEJMc2102017

k Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). *Lancet* preprint. Published online February 4, 2021. **https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160**.

[l] Mahase E. COVID-19: South Africa pauses use of Oxford vaccine after study casts doubt on efficacy against variant. *BMJ*. 2021;372:n372.

Evidence summary: COVID-19 vaccines

Introduction

On May 15, 2020, 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, 2020, 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, 2020, 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. The Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccines Work Group convened an emergency meeting on December 1, 2020, to determine the phased allocation of COVID-19 vaccines in the event of an FDA approval. Using the pillars – science, implementation, and ethics – ACIP approved the following recommendation by a majority vote (13-1) at its emergency meeting: “When a COVID-19 vaccine is authorized by FDA and recommended by ACIP, vaccination in the initial phase of the COVID-19 vaccination program (Phase 1a) should be offered to both 1. health care personnel and 2. residents of long-term care facilities.” The recommendation has been adopted by the Centers for Disease Control and Prevention (CDC) Director.[8] On December 20, 2020, the ACIP updated interim vaccine allocation recommendations to include Phases 1b and 1c. In Phase 1b, COVID-19 vaccine should be offered to persons aged 75 and older and non-health care frontline essential workers. In Phase 1c, the vaccine should be offered to persons aged 65 to 74 years, persons aged 16 to 64 years with high-risk medical conditions, and essential workers not included in Phase 1b.[9]

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.[10] 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, 2020 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.[11]

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.[12]

The phase 3 trial was initiated in July and results were recently published in the ***New England Journal of Medicine***.[13] 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.[14] Additional information on the trial is presented in **Appendix A**.

Efficacy

Published interim results of phase 1 data[15] 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.[15]

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.[16] 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. Moderna submitted an EUA application on November 30 (2 data sets: interim data set with 7 weeks of safety data – November 11; final dataset with 9 weeks of safety data – November 25) and the Vaccines and Related Biological Products Advisory Committee panel voted in favor of EUA approval on December 17. The FDA issued an EUA for mRNA-1273 on December 18, 2020. The primary endpoint of the phase 3 trial evaluated the incidence of protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline. The protocol defined COVID-19 as at least 2 systemic symptoms (fever (≥38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorders) OR at least 1 respiratory sign/symptom (cough,

shortness of breath or difficulty breathing, OR clinical radiographic evidence of pneumonia) AND nasopharyngeal swab, nasal swab, or saliva sample (respiratory sample if hospitalized) positive for SARS-CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a blinded committee. In the per-protocol set (n = 27,817) at the first pre-specified interim analysis, there were 5 and 90 adjudicated COVID-19 cases in the vaccine and placebo groups, respectively (VE of 94.5%; 95% CI, 86.5-97.8%). In the per-protocol set (n = 27,817) at the final scheduled efficacy analysis, there were 11 and 185 adjudicated COVID-19 cases in the vaccine and placebo groups, respectively (VE of 94.1%; 95% CI, 89.3-96.8%). The FDA has not validated the final efficacy results for the EUA submission. Results from the interim and final efficacy analysis of the primary endpoint are consistent and met the prespecified success criterion (true VE > 30%). While the occurrence of COVID-19 in patients with evidence of prior SARS-CoV-2 infection at study enrollment was evaluated as a secondary endpoint, too few patients at baseline had evidence of prior infection (approximately 2.2% of the population) and data are insufficient to draw any conclusions regarding efficacy in those with prior infection. The FDA analyzed results of the primary endpoint at the first pre-specified interim analysis by baseline risk for severe COVID-19, regardless of age and found that VE against COVID-19 was consistent in those at risk for developing severe COVID-19 due to a baseline comorbidity (VE: 95.9%; 95% CI, 69.7-99.4%). While multiple subgroup analyses by high-risk baseline comorbidity were conducted, groups stratified by baseline comorbidity were small and the trial lacked sufficient power to reach conclusions.[17,18]

Multiple subgroup analyses of the primary endpoint at the pre-specified interim analysis were performed and are summarized in Table 1. Of note, while the VE against COVID-19 was consistent across age cohorts in the interim analysis, at the final scheduled efficacy analysis (results not shown in the table), the VE in participants aged 65 years and older (VE: 86.4%; 95% CI, 61.4-95.5%) was lower than the VE in those aged less than 65 years (VE: 95.6%; 95% CI, 90.6-97.9%). This may be due to the lower number of COVID-19 cases (n = 33) and participants (n = 7,135) in the ≥ 65 years old cohort. Many subgroups were too small to reach firm conclusions about VE against COVID-19.[17,18]

Table 1: Subgroup analyses of vaccine efficacy, COVID-19 14 days after dose 2 per adjudication committee assessments, per-protocol set (pre-specified interim analysis)[17]

Efficacy endpoint subgroup	Vaccines cases (no. at risk)	Placebo cases (no. at risk)	Vaccine Efficacy % (95% CI)
Age group (years)			
18 to <65	5 (10407)	75 (10384)	93.4% (83.7,97.3)
65 to <75	0 (2904)	12 (2823)	100%
75 and older	0 (623)	3 (676)	100%
Age and risk for severe COVID-19[a]			
18 and <65 and not at risk	4 (8309)	57 (8323)	93% (80.8,97.5)
18 and <65 and at risk	1 (2098)	18 (2061)	94.6% (59.4,99.3)

≥ 65	0 (3527)	15 (3499)	100%
Ethnicity			
Hispanic or Latino	0 (2783)	12 (2769)	100%
Not Hispanic or Latino	5 (11019)	77 (10987)	93.6% (84.1,97.4)
Race			
American Indian or Alaska native	0 (107)	0 (110)	--
Asian	0 (616)	3 (684)	100%
Black or African American	0 (1369)	4 (1338)	100%
White	5 (11078)	80 (11005)	93.8% (84.8,97.5)

[a]High risk is defined as patients who meet at least one of the following criteria (protocol-defined): 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; HIV

Protocol-defined severe COVID-19 disease, defined as a case with at least 1 of the following – clinical signs at rest indicative of severe systemic illness; respiratory failure or Acute Respiratory Distress Syndrome; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death – occurred in 30 participants at the time of the final analysis (0 in the vaccine group and 30 in the placebo group) for a VE point estimate against severe COVID-19 disease of 100%. There was 1 death in the placebo group adjudicated as COVID-19 related. While no COVID-19 cases in vaccine recipients were adjudicated as severe, 1 vaccine recipient met the definition for severe COVID-19 disease based on symptoms, but had a negative SARS-CoV-2 test at hospitalization with evidence of a positive SARS-CoV-2 test at an outside facility.[18]

Cumulative incidence curves for the first COVID-19 occurrence started to diverge between vaccine and placebo recipients around 14 days after dose. While there appears to be some protection after dose 1 (VE: 50.8%; 95% CI, -53.6-86.6%), the durability of VE after a single dose is unknown because most participants received a second dose.[17]

Safety

Phase 1 safety results: All 3 doses of mRNA-1273 were well tolerated in the 18 to 55-year-old cohort.[15] 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.[15]

The reactogenicity profile of mRNA-1273 in the older cohort was not qualitatively different 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 and 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.[15]

Phase 3 safety results: In the pre-specified, safety interim analysis (n = 30,350, median follow-up 7 weeks) the most common local and systemic solicited adverse events that occurred within 7 days of a dose were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). In general, local solicited adverse events occurred at a similar incidence after the first and second dose and the majority were grade 1 to 2 in severity. Most local events occurred within the first 2 days of vaccination and persisted for a median of 1 to 3 days, although some local events persisted for greater than 7 days and were most likely dermal hypersensitivity reactions. Systemic adverse events occurred at a higher incidence and severity after the second dose. Most solicited systemic adverse events occurred within 2 days after an injection and lasted for 1 to 3 days. Grade 3 events that occurred at a 2% or greater frequency after the first dose included injection site pain (2.8%) and after the second dose included fatigue (9.7%), myalgia (8.8%), arthralgia (5.2%), headache (4.5%), injection site pain (4.1%), and erythema/redness at the injection site (2.0%). Severe adverse events were generally less frequent in participants aged 65 years and older.[17,18]

The incidence of unsolicited adverse events (dataset cutoff of November 25, median follow-up of 9 weeks) that occurred up to 28 days after an injection were comparable between vaccine and placebo recipients with the exception of a numeric imbalance in the occurrence of lymphadenopathy (1.1% vaccine, 0.63% placebo) and local hypersensitivity reactions (1.5% vaccine, 1.1% placebo). There were 4 cases of Bell's palsy (3 vaccine, 1 placebo). While there appears to be no causal relationship between the vaccine and Bell's Palsy, the FDA recommends continued surveillance. A total of 13 deaths (6 vaccine, 7 placebo) have been reported up to December 3; none of the deaths are considered related to vaccine or placebo.[17,18]

BNT 162b2

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).[19]

BNT162b2 is 1 of 4 vaccine candidates in the Pfizer/BioNTech BNT162 vaccine platform.[20] 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.[21]

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[21](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.[22]

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.[22]

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.[22]

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.[23,24]

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%.[25]

Pfizer submitted an EUA application on November 20 (data cutoff for EUA submission was November 14) and the Vaccines and Related Biological Products Advisory Committee panel voted in favor of EUA approval on December 10. The FDA granted emergency use on December 11. Pfizer/BioNTech published results from the ongoing phase 2/3 trial in the ***New England Journal of Medicine***[26] and both the FDA[27] and Pfizer/BioNTech presented separate analyses of the phase 2/3 data during the Vaccines and Related Biological Products Advisory Committee meeting. The first and second primary endpoints of the phase 2/3 trial evaluated the occurrence of confirmed COVID-19 with onset at least 7 days after the second dose in participants without and with and without previous SARS-CoV-2 infection, respectively. Confirmed COVID-19 was defined as the presence of at least 1 of the following symptoms - fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting - combined with a respiratory specimen positive for SARS-CoV-2 within ± 4 days of symptom onset. In the cohort of participants without evidence of existing or prior SARS-CoV-2 infection (n = 36,258), a primary endpoint occurred in 8 and 162 vaccine- and placebo-recipients, respectively for a VE of 95% (95% CI, 90.3-97.6). In those participants with and without evidence of prior SARS-CoV-2 infection (n = 40,137), an endpoint occurred in 9 vaccine recipients and 169 placebo recipients for a VE of 94.6% (95% credible interval, 89.9-97.3). Results from the first and second primary endpoints met the prespecified success criterion (true VE > 30%).[25] It should be noted that only 3% of participants had evidence of prior infection at study enrollment and few COVID-19 cases occurred in these participants. Because there were too few COVID-19 cases in patients with evidence of prior SARS-CoV-2, efficacy data cannot be interpreted for this subgroup.[26] The FDA analyzed results of the first primary endpoint (patients without prior SARS-CoV-2 infection) by baseline co-morbidity and found that VE point estimates in patients with any co-morbidity (95.3%, 95% CI, 87.7-98.8), any malignancy (75.7%; 95% CI, -145.8-99.5), cardiovascular disease (100%; 95% CI, -0.8-100), chronic pulmonary disease (93%; 95% CI, 54.1-99.8), diabetes (94.7%, 95% CI, 66.8-99.9), and obesity (95.4%; 95% CI, 86-91) were consistent with the VE point estimate for the overall population; however, many groups were small and the trial lacked sufficient power to reach firm conclusions.[27]

Multiple subgroup analyses of the second primary endpoint (recipients with and without prior SARS-CoV-2 infection) were performed and are summarized in Table 2. In general, VE point estimates were high and comparable to that of the overall population, but some subgroups were too small to confirm efficacy.

Table 2: Subgroup analyses of second primary endpoint: First COVID-19 occurrence ≥ 7 days after second dose in participants with and without evidence of SARS-CoV-2 infection (FDA analysis)[27]

Efficacy endpoint subgroup	BNT162b2 cases (no. at risk)	Placebo cases (no. at risk)	Vaccine Efficacy % (95% CI)
Overall	9 (18,559)	169 (18,708)	94.6 (89.6,97.6)
Age group (years)			
16 to 17	0 (58)	1 (61)	100 (-3969.9,100)
18 to 64	8 (14443)	149 (14566)	94.6 (89.1,97.7)
65 to 74	1 (3239)	14 (3255)	92.9 (53.2,99.8)
≥ 75	0 (805)	5 (812)	100 (-12.1,100)
Ethnicity			
Hispanic or Latino	3 (5074)	55 (5090)	94.5 (83.2,98.9)
Not Hispanic or Latino	6 (13380)	114 (13509)	94.7 (88.1,98.1)
Race			
American Indian or Alaska native	0 (104)	1 (104)	100 (-3511,100)
Asian	1 (796)	4 (808)	74.4 (-158.7,99.5)
Black or African American	0 (1758)	7 (1758)	100 (30.4,100)
White	7 (15294)	153 (15473)	95.4 (90.3, 98.2)

Severe COVID-19 disease, defined as a case with at least 1 of the following - clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death – occurred in 5 recipients at least 7 days after the second dose (1 in the vaccine group and 4 in the placebo group)[26] and in 10 recipients after the first dose (1 in the vaccine group and 9 in the placebo group).[26] Due to the small number of severe COVID-19 disease cases, the numeric trend favored BNT162b2, but efficacy cannot be confirmed (VE: 75%, 95% CI, -152.6-99.5). The single vaccine recipient met the case definition for severe COVID-19 disease because oxygen saturation was 93% on room air. To date, no COVID-19-related deaths have occurred.[27]

Cumulative incidence curves for first COVID-19 illness suggest divergence between vaccine and placebo recipients around 14 days after dose 1. Because most patients received a second dose, the durability of VE after a single dose is unknown. The median follow-up time at EUA submission is 2 months and the VE response has been durable.[27]

In the reactogenicity subset (n = 8,183) solicited local and systemic adverse events that occurred within 7 days after the receipt of vaccine or placebo were evaluated by self-report in an e-diary.[26] The most common solicited adverse drug reactions were injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), and fever (14.2%).[27] Pain at the injection site was the most common local adverse event and occurred more frequently in the recipients aged ≤ 55 years old compared to those aged > 55 years old. Pain was mild to moderate in severity with less than 1% of recipients reporting severe pain. Most injection site pain resolved within 1 to 2 days. The frequency and severity of systemic adverse drug reactions were higher in recipients aged ≤ 55 years old (vs. > 55 years old). Within all age groups, systemic events occurred more frequently after dose 2 (vs. dose 1) except for vomiting and diarrhea.[26,27] Although the frequency of severe systemic adverse drug reactions was generally less than 2% after any dose, 2 grade 3 adverse reactions were reported at a frequency greater than or equal to 2% after the second dose: fatigue (3.8%) and headache (2.0%).[26] In the main safety population that was followed for at least 2 months after the second dose (n = 37,706), reports of lymphadenopathy (64 vaccine, 6 placebo) and Bell's Palsy (4 vaccine, 0 placebo) were imbalanced between groups.[26,27] While there appears to be no causal relationship between the vaccine and Bell's Palsy, FDA recommends continued surveillance. Four serious adverse events were considered related to vaccine administration by a site investigator including shoulder injury, lymphadenopathy, ventricular arrhythmia, and leg paresthesia. A total of 6 participants (2 vaccine, 4 placebo) died during the follow-up period; none of the deaths were considered related to vaccine or placebo.[26, 27]

Real-world evidence

Between December 19, 2020 and January 24, 2021, rates of SARS-CoV-2 infection were **compared** in a retrospective cohort of 9,109 Israeli health care works (HCWs) deemed eligible to receive the BNT162b2 vaccine. HCWs who tested positive for the SARS-CoV-2 virus on PCR, but remained asymptomatic were defined as cases of SARS-CoV-2 infection, while symptomatic HCWs were defined as COVID-19 cases. There was a total of 170 SARS-CoV-2 infections within the study period, 99 of which (58%) were symptomatic cases. Of the 170 HCWs who became infected, n = 81 (48%) were vaccinated, with 46% (n = 78) testing positive after the first dose and only 2% (n = 3) testing positive after the second dose.[28]

Adjusted rate reductions of SARS-CoV-2 infection (all cases) were 30% (95% CI, 2-50) within the first 14 days of receiving the first vaccine dose and 75% (72-84) 15 to 28 days after receiving the first dose. Adjusted rate reductions for symptomatic SARS-CoV-2 infection were 47% (95% CI, 17- 66) within the first 14 days of receiving the first vaccine dose and 85% (71-92) 15 to 28 days after receiving the first dose.[28]

While this study helps to shed light on prevention of asymptomatic SARS-CoV-2 infection with the COVID-19 vaccine, there are a number of limitations to note. A description of this study was published in the form of "Correspondence" in *The Lancet*, with less than 2 pages of descriptive material (full publication of the study design and results needed). This was an observational study, and it appears testing occurred based on daily symptom reporting by participants and known exposure; thus, asymptomatic cases may not have been fully captured (underestimated). The authors were able to trace 125 of the 170 infections, and noted that 87 (70%) of these were community acquired; however, it bears noting that the study took place in hospital HCWs, who by nature have a higher exposure risk than the general public.

mRNA vaccines – Anaphylaxis reactions

The CDC has received numerous reports of anaphylaxis outside of clinical trials after vaccination with BNT162b2 and mRNA-1273. Between December 14 and December 23, 2020, the incidence of anaphylaxis with BNT162b2 was 11.1 cases per million doses; 71% of the 29 cases occurred within 15 minutes of vaccination.[29] Between December 21, 2020 and January 10, 2021, the incidence of anaphylaxis with mRNA-1273 was 2.5 cases per million doses; 90% of the 10 cases occurred with 15 minutes of vaccination.[30] Due to the risk of anaphylaxis, the CDC recommends the following emergency equipment be available for assessing and managing anaphylaxis at any site where the vaccine is administered: epinephrine prefilled syringe or autoinjector, H1 antihistamine, blood pressure cuff, stethoscope, and timing device to assess pulse. While not required, if feasible, the CDC additionally recommends that sites have a pulse oximeter, oxygen, bronchodilator, H2 antihistamine, intravenous fluids, intubation kit, and an adult-sized pocket mask with one-way valve.[31] For more information on managing anaphylaxis associated with mRNA COVID-19 vaccines, please consult the CDC's **interim guidance**.

The CDC currently advises that mRNA COVID-19 vaccines should not be administered to individuals who have experienced a severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or an immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol and polysorbate).[32] Inactive components of the mRNA COVID-19 vaccines are listed in Table 3. Although the specific vaccine component(s) responsible for anaphylaxis is/are unknown, both vaccines contain polyethylene glycol, which has been known to cause anaphylaxis. Further study is required to establish causality between polyethylene glycol and anaphylaxis; however, immediate allergic reactions to polyethylene glycol or polysorbate (due to potential cross-reactive hypersensitivity) are considered a contraindication to vaccination with an mRNA COVID-19 vaccine.[32] While neither the CDC or the American College of Allergy, Asthma, and Immunology (ACAAI) consider a history of allergic reactions to any other vaccine or injectable therapy a contraindication to vaccination with an mRNA COVID-19 vaccine, both advise that vaccination should be undertaken using professional judgement and in consultation with the patient. Patients with common allergies to medications, foods, inhalants, insects and latex are not assumed to be at greater risk for experiencing anaphylaxis compared to the general public.[32,33] As information is rapidly changing, the CDC and ACAAI will update guidance.

Table 3: Ingredients in mRNA COVID-19 vaccines[32]

Description	BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)	mRNA-1273 (Moderna COVID-19 vaccine)
mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	
Lipids	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol,methoxypolyethylene glycol
	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-e-phosphocholine
	Cholesterol	Cholesterol

	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102: heptadecane-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
Salts, sugars, buffers	Potassium chloride	Tromethamine
	Monobasic potassium phosphate	Tromethamine hydrochloride
	Sodium chloride	Acetic acid
	Dibasic sodium phosphate dihydrate	Sodium acetate
	Sucrose	Sucrose

Neither vaccine contain eggs, gelatin, latex, or preservative

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.[34] The tPA component has been demonstrated to enhance immunogenicity in another ChAdOx1 vectored CoV vaccine (ChAdOx1 MERS).[34] Clinical trials consist of 2 phase 1/2 trial (**NCT04324606 & NCT04568031**; active, not recruiting), a phase 2 trial (**NCT0444674**; recruiting), a phase 2/3 trial (**NCT04400838**; recruiting), 4 phase 3 trials (NCT04540393 [suspended], **ISRCTN89951424** not recruiting; and **NCT04516746** & **NCT04536051** recruiting) and are being completed in various ages and populations. Summaries of the published phase 1/2 trial, interim phase 2 UK trial, and the phase 3 U.S. trial are in **Appendix C**. The UK 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 Japan phase 1/2 trial targets enrollment of 256 patients ≥18 years of age. 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 10,300 patients..

Efficacy

Data published in the phase 1/2 trial in adults 18-55 years of age 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.[34] 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.

Interim (phase 2) data published from the phase 2/3 UK trial evaluated a ChAdOx1 standard dose (3.5-6.5 X10^{10} vp) or low dose (2.2 X10^{10} vp) intramuscular injection in 1 or 2 doses (separated by 28 days) in 3 adult age groups (18-55, 56-69, ≥70 y) and found cellular and humoral activity in all groups as indicated by T-cell response (Interferon-gamma ELISpot), SARS-CoV-2 live virus microneutralization PHE MNA80, and IgG response by ELISA. Fourteen days after a second dose, 99% of participants mounted neutralizing antibody responses in the standard dose group.[35]

In a **press release** published on November 23, AstraZeneca announced top line efficacy data in the UK and Brazil trials. The primary endpoint of preventing symptomatic COVID-19 was demonstrated in 62% and 90% of 2 different dosing regimens: a half dose followed by a full dose or 2 full doses, respectively resulting in an average efficacy of 70%.[36] No hospitalizations or severe cases of disease were noted in patients who received vaccine. The subsequent interim analysis of 4 phase 3 trials was published on December 8, 2020 and included results from **ISRCTN89951424, NCT04324606, NCT04400838, NCT04444674** completed in Brazil, the UK, and South Africa.[37] Participants received 2 doses: standard or low dose AZD1222 followed by standard dose AZD1222 in the treatment arm, vs. saline or meningococcal vaccine in the placebo arm (see specific protocols for details). When all dosing schemas were included, VE as measured by the primary endpoint (symptomatic COVID-19 ≥ 15 days after the second dose) was 70.4% (95 CI, 54.8-80.6). Two standard doses produced a vaccine efficacy of 62.1% (95% CI, 41-75.7) and a low dose followed by a standard dose produced a vaccine efficacy of 90% (95% CI, 67.4- 97).[37]

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.[34]

Interim (phase 2) data published from the phase 2/3 UK trial reported 13 serious adverse drug events at time of publication; however, none were attributed to the vaccine. The most common local adverse events were pain and tenderness at the injection site with the most common systemic adverse events of fatigue, headache, feverishness, and myalgia. Decreased reactogenicity was observed in older adults. Refer to pages 16-31 of the **supplement** for detailed information regarding local and systemic effects.[35]

The interim analysis of 4 phase 3 trials with results from I**SRCTN89951424**, **NCT04324606**, **NCT04400838**, **NCT04444674** completed in Brazil, the UK, and South Africa reported serious adverse events occurred in 79 AZD1222 vaccine recipients. One case of transverse myelitis was reported following a booster dose and was thought to be possibly related to vaccination. An unmasked patient experienced a high fever (> 40°C) after a first dose, but not a second. One additional case of transverse myelitis was determined likely unrelated to vaccine administration.
Four non-COVID-19-related deaths (1 in AZD1222 group) were all considered to be unrelated to the vaccine.[37]

Approvals

AZD1222 was granted temporary approval for use in the United Kingdom on December 30, 2020 and **authorization** in the European Union on January 29, 2021. India and Mexico have also approved AZD1222 for use. On February 10, the World Health Organization issued **interim recommendations** for use.

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.[38] Clinical trials consists of a phase 1 trial **(NCT04509947**; active), a phase 1/2a trial (**NCT04436276**; active, recruiting), a phase 2 trial (**NCT04535453**; active, recruiting) and 2 phase 3 trials (**NCT04505722**; active; **NCT04614948**; active, recruiting). Summaries of the published manuscript of the phase 1/2a trial and the description of the phase 3 trials are in **Appendix C**. The phase 1/2a trial started enrolling patients in June of 2020 and interim results were published in the ***New England Journal of Medicine*** in January 2021.[38] The ENSEMBLE phase 3 trial was initiated in September and enrollment of participants (n = 45,000) was completed in mid-December 2020.

Efficacy and safety: Phase 1/2a

Interim data from a multicenter, randomized, double-blind, placebo-controlled phase 1/2a trial describe interim safety and immunogenicity of JNJ-78436735. Healthy adults aged 18 to 55 years (cohort 1, n = 402) and ≥ 65 years (cohort 3, n = 403) received JNJ-78436735 at a dose of either 5 x 10^{10} viral particles (low dose) or 1 x 10^{11} viral particles (high dose) per mL administered in a single-dose or 2-dose series 56 days apart. In each of the 2 cohorts, there were 5 vaccination groups (low dose followed by low dose; low dose followed by placebo; high dose followed by high dose; high dose followed by placebo; placebo followed by placebo). The interim report presents results from cohort 1 after the first and second dose and cohort 3 after the first dose. The primary endpoint was solicited and unsolicited adverse reactions that occurred up to 7 and 28 days after a vaccine dose, respectively. Solicited local adverse events (erythema, injection site pain, swelling) were reported in 64% (n = 103) and 78% (n = 123) of low dose and high dose recipients, respectively vs. 9% in placebo recipients in cohort 1 (18-55 years). In cohort 3 (≥ 65 years), the respective percentages were 41% (low dose), 42% (high dose), and 14% (placebo). Most local adverse events were of grade 1 or 2 severity and injection-site pain was the most common local adverse event. In both cohorts, the majority of solicited systemic adverse events (fatigue, headache, myalgia, nausea, pyrexia) were of grade 1 or 2 severity; the most frequent events were fatigue, headache, and myalgia. In cohort 1, systemic adverse events were reported in 65%, 84%, and 26% of low dose, high dose, and placebo recipients, respectively. In cohort 3, the respective percentages for solicited systemic adverse events were 46% (low dose), 55% (high dose), and 23% (placebo). A fever was reported in 15% and 4% of low dose recipients in cohort 1 and 3, respectively and in 39% and 9% of high dose recipients in cohort 1 and 3, respectively.[38] In cohort 1, safety information was available after the second dose in 363 participants. One or more solicited adverse events were reported in 77% and 80% of low and high dose recipients, respectively after the second dose versus 34% and 31% of those who received placebo as a second dose after a first dose of vaccine. In those that received 2 doses of placebo, 22% reported a solicited adverse event after the second dose. Five serious adverse events occurred; none were judged to be related to vaccine administration.

In cohort 1, 57 days after the first dose, the incidence of seroconversion was 100% in all groups except for the high dose/placebo group (97%). Fourteen days after the second dose, all groups had 100% seroconversion. A second dose increased the titer of neutralizing antibodies by a factor of 2.6 to 2.9. In cohort 3, at day 29 after the first dose, the

incidence of seroconversion was 96%. Cellular response was demonstrated through Th1 cytokine producing CD4+ T cell (S-specific) response (cohort 1: 76-83%; cohort 3: 60-67%) and CD8+ T cell (S-specific) response (cohort 1: 51-64%; cohort 3: 24-36%) 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. Two participants had a measurable Th2 response, but Th1/Th2 ratio indicated it was a Th-1 skewed response; hence, VAERD risk is expected to be low.[38]

Phase 3 Study

The phase 3 ENSEMBLE trial evaluated a single dose approach using 5 X 10^{10} virus particles in adult patients (n = 45,000). Primary and secondary outcome measures are listed in **Appendix D**. Johnson and Johnson announced in November 2020 the initiation of the 2-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.

Johnson & Johnson submitted an EUA application on February 4, 2021 (data cutoff for EUA submission was January 22, 2021) and the Vaccines and Related Biological Products Advisory Committee panel unanimously voted in favor of EUA approval on February 26, 2021. The FDA issued an EUA for J&J's COVID-19 vaccine on February 27, 2021. Results from the phase 3 ENSEMBLE trial met the predefined success criteria delineated in the study protocol (VE point estimate ≥ 50% for both co-primary endpoints). The co-primary endpoints of the phase 3 trial were incidence of protocol-defined moderate to severe/critical COVID-19, confirmed by the central laboratory, occurring at least 14 days and at least 28 days after vaccination in participants without prior evidence of SARS-CoV-2 infection. In the per-protocol population (n = 39,321) at data cutoff, there were 464 centrally confirmed moderate to severe/critical COVID-19 cases. The VE against moderate to severe/critical COVID-19 with onset ≥ 14 days after vaccination was 66.9% (95% CI, 59-73.4) and the VE against moderate to severe/critical COVID-19 with onset ≥ 28 days after vaccination was 66.1% (95% CI, 55-74.8). The VE against moderate to severe/critical COVID-19 in patients with evidence of prior SARS-CoV-2 infection could not be estimated because only 9.6% of participants were seropositive at baseline.[39]

While multiple subgroup analyses of the co-primary endpoints were performed based on demographic characteristics and individual comorbid conditions, many subgroups were small and underpowered to draw firm efficacy conclusions. VE point estimates were similar with overlapping 95% CIs between participants aged 18 to 59 years and those aged ≥ 60 years (VE at 14 days: 63.7% vs. 76.3% for participants aged 18 to 59 years and those aged ≥ 60 years, respectively; VE at 28 days: 66.1% and 66.2% for participants aged 18 to 59 years and those aged ≥ 60 years, respectively). Vaccine efficacy appeared to be consistent across gender, race, and ethnicity. The VE point estimates for the co-primary endpoints varied by geographic region. Vaccine efficacy against moderate to severe/critical COVID-19 was lower in South Africa (VE of 52% and 64% at 14 days and 28 days, respectively) than in the U.S. (VE of 74.4% and 72% at 14 days and 28 days, respectively) and Brazil (VE of 66.2% and 68.1% at 14 days and 28 days, respectively). In South Africa, 66.9% of cases have been sequenced and of those, 94.5% were identified as the B.1.351 variant. In the U.S., 73.5% of cases have been sequenced and of those, 96.4% were identified as the SARS-CoV-2 Wuhan-H1 variant D614G. Due to selection bias in how cases are prioritized to be sequenced, VE against specific SARS-CoV-2 variants cannot be ascertained at this time.[39]

Protocol-defined severe/critical COVID-19 disease, defined as a case with at least 1 of the following – clinical signs at rest indicative of severe systemic illness; respiratory failure or Acute Respiratory Distress Syndrome; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death – was adjudicated by a blinded, severity committee. At the cutoff date for adjudication, there were 14 and 60 confirmed severe/critical COVID-19 cases with an onset at least 14 days after vaccination in the vaccine and placebo groups, respectively (VE: 76.7%; 95% CI, 54.6-89.1) and 5 and 34 confirmed severe/critical COVID-19 cases with an onset at least 28 days after vaccination in the vaccine and placebo groups, respectively (VE: 85.4%; 95% CI, 54.2-96.9). While VE against severe/critical COVID-19 appeared lower in participants aged 60 years and older compared with those aged 59 years and younger, CIs were wide. An additional analysis was performed to assess the impact of the vaccine on all COVID-19 related medical interventions, defined as a participant requiring hospitalization, ICU admission, mechanical ventilation, and/or ECMO due to COVID-19. Fewer COVID-19 cases that occurred at least 14 days after vaccination in the vaccine group required medical intervention compared with those that occurred in the placebo group (2 vs. 8 cases, respectively). No COVID-19 cases that occurred at least 28 days after vaccination in the vaccine group required medical intervention (vs. 5 cases for placebo). There were 7 deaths during the follow-up that were adjudicated as COVID-19 deaths; all occurred in placebo recipients in South Africa.[39]

Cumulative incidence curves for the first COVID-19 occurrence started to diverge between vaccine and placebo recipients around 14 days after vaccination.[39]

In the reactogenicity subset (n = 6,736) the most common solicited adverse events were injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and myalgia (33.2%). These were predominantly mild to moderate in severity, with 0.7% and 1.8% of the local and systemic solicited adverse reactions, respectively, reported as grade 3. Reports of solicited reactions were less common among participants aged 60 years and older. Most solicited adverse events resolved 1 to 2 days post-vaccination.[39]

Among all adverse events collected through the January 22,2021 data cutoff, numerical imbalances were observed between vaccine and placebo recipients for non-serious urticaria events (5 vs. 1), thromboembolic events (15 versus 10) and tinnitus (6 versus 0). Data currently are insufficient to determine a causal relationship between these events and the vaccine. There was 1 serious event of hypersensitivity, not classified as anaphylaxis, that occurred 2 days after vaccination that was likely vaccine related.[39]

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.[40] 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.[40] 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[40] (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, 2020, Novavax **announced** that it launched its phase 3 trial for NVX-CoV2373 in the United Kingdom. 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.[41] The protocol for this phase 3 study was published October 27, 2020.

On January 28, 2021, Novavax **announced** an interim analysis of phase 3 trial data from the UK.[42] This analysis is based on 62 cases, of which 56 cases were observed in the placebo group and 6 cases were observed in the NVX-CoV2373 group. Of these cases, 61 were mild or moderate and 1 (in the placebo group) was severe. Preliminary results show that the UK variant was detected in over 50% of the cases. Efficacy by strain was calculated to be 95.6% against the original COVID-19 strain and 85.6% against the UK variant (post-hoc analysis). The overall efficacy of the vaccine in preliminary data was shown to be 89.3%.

In late December, Novavax announced the initiation of PREVENT-19 (PRE-fusion protein subunit Vaccine Efficacy Novavax Trial | COVID-19, **NCT04611802**), the phase 3 study in the United States and Mexico to evaluate the NVX-CoV2373 vaccine for safety, efficacy and immunogenicity. PREVENT-19 is a randomized, placebo-controlled, observer-blinded study of up to 30,000 subjects aged 18 years and older. Two thirds of study volunteers will be assigned to receive

intramuscular injections of the study vaccine to be administered 21 days apart. The other one third of participants will receive placebo. The primary endpoint is the prevention of PCR-confirmed, symptomatic COVID-19 with a secondary endpoint of the prevention of PCR-confirmed symptomatic moderate or severe COVID-19 to be assessed at least 7 days after the second study vaccination in patients who have not been previously infected by SARS-CoV-2. Participants will be followed for 24 months after the second injection.[43] In an update on February 1, 2021, Novavax announced that 19,438 participants have been enrolled in the PREVENT-19 trial. The company expects enrollment to be complete by mid-February. Of the participants, 16% are over the age of 65 years, 13% are African American, and 16% are LatinX. Due to the availability of vaccine, the protocol of the PREVENT-19 was amended to allow for blinded crossover.[44]

References

1. Fact sheet: Explaining operation warp speed. HHS website. https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html. Published June 16, 2020. Accessed September 16, 2020.
2. Slaoui M, Hepburn M. Developing safe and effective Covid vaccines – Operation Warp Speed's strategy and approach. *N Engl J Med*. 2020;383(18):1701-1703.
3. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. *N Engl J Med*. 2020;382(21):1969-1973.
4. Development and licensure of vaccines to prevent COVID-19: Guidance for industry. Food and Drug Administration website. https://www.fda.gov/media/139638/download. Published June 2020. Accessed September 16, 2020.
5. Emergency use authorization for vaccines to prevent COVID-19: Guidance for industry. Food and Drug Administration website. https://www.fda.gov/media/142749/download. Published October 2020. Accessed October 7, 2020.
6. Shah A, Marks PW, Hahn SM. Unwavering regulatory safeguards for COVID-19 vaccines. *JAMA*. 2020;324(10):931-932.
7. Mullard A. COVID-19 vaccine development pipeline gears up. *Lancet.* 2020;395(10239):1751-1752.
8. Dooling K, McClung N, Chamberland M, et al. The Advisory Committee on Immunization Practices' interim recommendation for allocating initial supplies of COVID-19 vaccine – United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1857-1859.
9. Dooling K, Marin M, Wallace M, et al. The Advisory Committee on Immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine – United States, December 2020. *MMWR Morb Mortal Wkly* Rep. 2021;69:1657-1660.
10. Wang F, Kream RM, Stefano GB. An evidence-based perspective on mRNA-SARS-CoV-2 vaccine development. *Med Sci Monit*. 2020;26:e924700.
11. Heaton PM. The Covid-19 vaccine-development multiverse. *N Engl J Med*. 2020;383(20):1986-1988.
12. Dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 COVID-19 vaccine in adults aged 18 years and older. ClinicalTrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT04405076?term=NCT04405076&draw=2&rank=1. Published May 28,2020. Updated July 10, 2020. Accessed September 23, 2020.
13. Baden LR, El Sahly HM, Essink B, et al for the COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New Engl J Med*. 2021;384(5):403-416.
14. Moderna clinical study protocol. Moderna website. https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf. Published August 20, 2020. Accessed September 23, 2020.
15. Jackson LA, Anderson EJ, Rouphael NG et al for the mRNA-1273 Study Group. An mRNA vaccine against SARS-CoV-2 – Preliminary Report. *N Engl J Med*. 2020;383(20):1920-1931.
16. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020;383(25):2427-2438.

17. U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. FDA Briefing Document. Moderna COVID-19 vaccine. FDA website. https://www.fda.gov/media/144434/download. Published December 15, 2020. Accessed December 15, 2020.
18. U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. Sponsor Briefing Document. Moderna COVID-19 vaccine. FDA website. https://www.fda.gov/media/144452/download. Published December 15, 2020. Accessed December 15, 2020.
19. Vogel AB, Kanevsky I, Che Y, et al. A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. Published online ahead of print on September 8, 2020. Available online at https://doi.org/10.1101/2020.09.08.280818.
20. A trial investigating the safety and effects of four BNT162 vaccines against COVID-2019 in healthy adults. U.S. National Library of Medicine (ClinicalTrials.gov) website. https://clinicaltrials.gov/ct2/show/NCT04380701?term=BNT162b2&draw=2&rank=1. Published May 8, 2020. Updated September 11, 2020. Accessed September 15,2020.
21. Study to describe the safety, tolerability, immunogenicity, and efficacy of RNA vaccine candidates against COVID-19 in healthy adults. U.S. National Library of Medicine (ClinicalTrials.gov) website. https://clinicaltrials.gov/ct2/show/NCT04368728?term=BNT162b2&draw=2&rank=2. Published April 30, 3030. Updated September 4, 2020. Accessed September 15,2020.
22. Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. *N Engl J Med*. 2020;383(25):2439-2450.
23. Pfizer. Pfizer and BioNTech propose expansion of pivotal COVID-19 vaccine trial. Pfizer website. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-propose-expansion-pivotal-covid-19. Published September 12, 2020. Accessed September 15, 2020.
24. Pfizer. Our progress in developing a potential COVID-19 vaccine. Pfizer website. https://www.pfizer.com/science/coronavirus/vaccine. Updated October 26, 2020. Accessed October 27, 2020.
25. Pfizer. A phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals: Clinical Protocol. Pfizer website. https://www.pfizer.com/clinicalprotocol. Accessed November 18, 2020.
26. Polack FP, Thomas SJ, Kitchin N, et al for the C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
27. U.S. Food and Drug Administration. Vaccine and Related Biological Products Advisory Committee December 10, 2020 Meeting Briefing Document – FDA. FDA website. https://www.fda.gov/media/144245/download. Published December 8, 2020. Accessed December 8, 2020.
28. Amit S, Regev-Yochay G, Afek A, et al. Correspondence: Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet*. Published online ahead of print February 18, 2021. doi: https://doi.org/10.1016/S0140-6736(21)00448-7.
29. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14-23, 2020. *MMWR Morb Mortal Wkly Rep*. Published online ahead of print January 6, 2021. http://dx.doi.org/10.15585/mmwr.mm7002e1.
30. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine – United States, December 21,2020-January 10, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:125-129.
31. Centers for Disease Control and Prevention. Interim considerations: Preparing for the potential management of anaphylaxis at COVID-19 vaccination sites. CDC website. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/anaphylaxis-management.html. Updated December 31, 2020. Accessed January 6, 2021.
32. Centers for Disease Control and Prevention. Clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. CDC website. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Updated January 6, 2021. Accessed January 6, 2021.
33. ACAAI provides further guidance on risk of allergic reactions to mRNA COVID-19 vaccines. ACAAI website.https://college.acaai.org/acaai-guidance-on-risk-of-allergic-reactions-to-mrna-covid-19-vaccines/ Updated December 21, 2021. Accessed January 6, 2021.

34. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 n CoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet*. 2020;396(10249):467-478.
35. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomized, controlled, phase 2/3 trial. *Lancet*. 2021;396(10267):1979-1993.
36. AstraZeneca. AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19. AstraZeneca website. https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html. Published November 23, 2020. Accessed December 9, 2020.
37. Voysey M, Clemens SA, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. *Lancet.* 2021;397(10269):99-111.
38. Sadoff J, Le Gars M, Shukarev G, et. al. Interim results of a phase 1-2a trial of Ad26.CoV2.S COVID-19 vaccine. *N Engl J Med*. Published online ahead of print January 13, 2021. doi: 10.1056/NEJMoa2034201.
39. U.S. Food and Drug Administration. Vaccines and Related Biological Products Advisory Committee Meeting. February 26, 2021 – FDA Briefing Document. FDA website. https://www.fda.gov/media/146217/download. Published February 24, 2021. Accessed February 24, 2021..
40. Keech C, Albert G, Cho I, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *New Engl J Med*. 2020;383(24):2320-2332.
41. Novavax. Novavax initiates phase 3 efficacy trial of COVID-19 vaccine in the United Kingdom. Novavax website. https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-3-efficacy-trial-covid-19-vaccine-united**.** Published September 24, 2020. Accessed October 5, 2020.
42. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK phase 3 trial. Novavax website. https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3. Published January 28, 2021. Accessed February 4, 2021.
43. Novavax. Novavax announces initiation of PREVENT-19 pivotal phase 3 efficacy trial of COVID-19 vaccine in the United States and Mexico. Published December 28, 2020. Accessed January 5, 2020.
44. Efficacy data updates from Novavax' protein-based vaccine candidate. Novavax website. https://www.novavax.com/sites/default/files/2021-02/20210202-NYAS-Novavax-Final.pdf. Published February 2, 2021. Accessed February 4, 2021.

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	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	Primary outcome • 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] ○ Interim analysis, per-protocol (n = 27,817); VE:94.5% (95% CI, 86.5-97.8%) ○ Primary analysis, per-protocol (n = 28,207); VE: 94.1% (95% CI, 89.3-96.8%) Secondary outcome • Cases of severe COVID-19 based on adjudication committee assessment starting 14 days after the second injection ○ Primary analysis (n = 28,207): VE: 100% (95% CI, not estimable -100%) Adverse events • Most common local and systemic solicited events occurring up to 7 days after injection: Injection-site pain (91.6%), fatigue (68.5%), headache (63%), muscle pain (59.6%), joint pain (44.8%), chills (43.4%)		

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)	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 Demographics of main safety population (n = 37,706) • Male: 50.6% • Median age at vaccination: 52 (range: 16-91) • White: 82.9% • Black: 9.3% • Hispanic/Latino: 28% • Obese: 35%	2 doses of BNT162b2 (30 mcg) or placebo, administered 21 d apart	**Primary efficacy endpoints** **First**: Efficacy of BNT162b2 against confirmed COVID-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose (n = 36,523) • n =170 cases of COVID-19 (n = 162 in placebo group, n = 8 in BNT162b2 group) • VE: 95% (95% credible interval, 90.3-97.6) **Second**: Efficacy of BNT162b2 against confirmed COVID-19 with onset at least 7 days after the second dose in participants with and without prior SARS-CoV-2 infection (n = 40,137) • n = 178 cases of COVID-19 (n = 169 in placebo group, n = 9 in BNT162b2 group) • VE: 94.6% (95% credible interval, 89.9-97.3) **Secondary efficacy endpoint** Severe COVID-19 disease: 10 cases observed after the first dose (1 vaccine; 9 placebo) **Safety efficacy endpoints** Reactogenicity subset (n = 8,183) – Vaccine recipient reported events • Mild to moderate pain at injection site most common local reaction in ≤55 y (83% dose 1, 78% dose 2) and >55 y (71% dose 1, 66% dose 2) • Most common systemic reactions were fatigue and headache. More common in the ≤ 55 y cohort (59% and 52% after dose 2) vs. > 55 y cohort (51% and 39% after dose 2). In all age cohorts, frequency and severity higher after dose 2. • Severe (grade 3) systemic events of fatigue and headache reported in 3.8% and 2.0% of recipients, respectively. • Fever (temp ≥ 38°C) reported after second dose in 16% and 11% of those ≤ 55 y and > 55 y, respectively. • Fever (temp 38.9-40◦) reported in 0.2% after first dose (vs. 0.1% in placebo group) and 0.8% after second dose (vs. 0.1% in placebo). • Younger cohort more likely to take use antipyretic or pain medication (28% after first dose; 45% after dose 2) vs. older cohort (20% after dose 1; 38% after dose 2) Main safety population (n = 37,706) • Imbalances in Bell's Palsy (4 vaccine; 0 placebo) and lymphadenopathy (64 vaccine, 6 placebo) • 6 deaths (2 vaccine; 4 placebo). None considered related to treatment • 4 related serious adverse events in vaccine recipients (shoulder injury, lymphadenopathy, ventricular arrhythmia, leg paresthesia)	

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. Replication deficient simian 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]	**Note:** Patients were divided into groups and not all received the same assessments. • 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** • ChAdOx1 + paracetamol: n = 28 (50%) • ChAdOx1: n = 328 (67%) • MenACWY+ paracetamol: n = 18 (32%) • MenACWY: n = 180 (38%) Tenderness • ChAdOx1+ paracetamol: n =43 (77%) • ChAdOx1: n = 403 (83%) • MenACWY+ paracetamol: n = 26 (14%) • MenACWY: n = 276 (58%) **Chills** • ChAdOx1+ paracetamol: n = 15 (27%) • ChAdOx1: n = 272 (56%) • MenACWY: n = 5 (9%) • 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%)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				• 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] o ChAdOx1 Prime-Boost (n = 10): 639.2 [IQR: 360, 792.2] o 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: o ChAdOx1 Prime (n = 35): 51 [IQR:32, 103]; **Note:** Neutralizing antibodies were detected in 32/35 (91%) with the PHE MNA_{80} assay o ChAdOx1 Prime-Boost (n = 10): 70 [IQR: 32.8, 168] o MenACWY (n = 2): 10 [10, 10] **Anti-SARS-CoV-2 neutralizing antibodies: PHE $PRNT_{50}$** • Day 28:	**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
				○ 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]	

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
Ramasamy MN et al. Replication deficient simian a**denovirus vector** **AZD1222 (ChAdOx1 nCov-19)** **Phase** 2/3 **clinical trial** (phase 2 interim results reported here) NCT04400838	560	For full inclusion and exclusion criteria, see **NCT04400838**	**Intervention group** Standard dose ChAdOx1 nCoV-19 vaccine 3.5-6.5 X 10^{10} VP in 0.5 mL administered intramuscularly for 1 or 2 doses (separated by 28 d) Low dose ChAdOx1 nCoV-19 vaccine 2.2 X 10^{10} VP in 0.22 or 0.5 mL administered intramuscularly for 1 or 2 doses (separated by 28 d) **Control group** MenACWY (meningococcal) vaccine 0.5 mL administered intramuscularly in 1 or 2 doses separated by 28 d Patients were stratified into 3 age groups • 18-55 y • 56-69 y • ≥ 70 y For the full break down of dosing groups with stratification, refer to interim trial **publication** or NCT04400838	**Spike-specific T cell response: IFN-gamma ELISpot response against SARS-CoV-2 peptides (Spot forming cells)** ***18-55 yo (SD/SD):*** Day 14: • ChAdOx1 two doses (n = 24): 1187 [IQR: 841, 2428] Day 28: • ChAdOx1 two doses (n = 10): 292 [IQR: 178, 803] Day 42: • ChAdOx1 two doses (n = 23):413 [IQR: 245, 675] ***56-69 yo (LD/LD):*** Day 14: • ChAdOx1 single dose (n = 30): 1001 [IQR:662, 1965] • ChAdOx1 two doses (n = 30): 1341 [IQR: 536, 2029] Day 28: • ChAdOx1 single dose (n = 28): 511 [IQR:264, 790] • ChAdOx1 two doses (n = 29): 488 [IQR: 255,1043] Day 42: • ChAdOx1 two doses (n = 29): 501 [IQR: 253, 905] ***56-69 yo (SD/SD):*** Day 14: • ChAdOx1 single dose (n = 21): 677 [IQR:411, 1503] • ChAdOx1 two doses (n = 29): 797 [IQR: 383, 1817] Day 28: • ChAdOx1 single dose (n = 29): 335 [IQR: 162, 523] • ChAdOx1 two doses (n = 30): 591 [IQR: 238, 922] Day 42: • ChAdOx1 two doses (n = 28): 798 [IQR: 462, 1186] ***≥ 70 yo (LD/LD):*** Day 14:	Thirteen serious ADEs were reported; none were attributed to the vaccine. The most common local ADEs were pain and tenderness at the injection site with the most common systemic ADEs of fatigue, headache, feverishness, and myalgia. Decreased reactogenicity was observed in older adults. Refer to pages 16-31 of the **supplemen**t for details.

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
				• ChAdOx1 single dose (n = 49): 1009 [IQR:485, 2265] • ChAdOx1 two doses (n = 44): 921 [IQR: 400, 1733] Day 28: • ChAdOx1 single dose (n = 47): 420 [IQR:232, 721] • ChAdOx1 two doses (n = 43): 397 [IQR: 203, 715] Day 42: • ChAdOx1 two doses (n = 43): 285 [IQR: 172, 554] ***≥ 70 yo (SD/SD):*** Day 14: • ChAdOx1 single dose (n = 48): 975 [IQR: 442, 1530] • ChAdOx1 two doses (n = 48): 977 [IQR: 458, 1914] Day 28: • ChAdOx1 single dose (n = 47): 567 [IQR: 357, 1018] • ChAdOx1 two doses (n = 49): 300 [IQR: 157, 492] Day 42: • ChAdOx1 two doses (n = 47): 307 [IQR: 161, 516] Comparison across all three age groups in SD: *P <.0001* **SARS-CoV-2 micro-neutralization: PHE MNA_{80}** ***18-55 yo (LD/LD):*** Day 28: • ChAdOx1 two doses (n = 45): 79 [IQR: 47, 127] Day 42: • ChAdOx1 two doses (n = 41): 161 [IQR: 99, 233] Day 56: • ChAdOx1 two doses (n = 39):110 [IQR: 74, 184] ***18-55 yo (SD/SD):*** Day 28:	

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
				• ChAdOx1 two doses (n = 43): 47 [IQR: 5, 124] Day 42: • ChAdOx1 two doses (n = 39): 193 [IQR: 113, 238] Day 56: • ChAdOx1 two doses (n = 37):185 [IQR:129, 359] ***56-69 yo (LD/LD):*** Day 28: • ChAdOx1 single dose (n = 18): 64 [IQR: 41, 93] • ChAdOx1 two doses (n = 21): 55 [IQR: 25, 79] Day 42: • ChAdOx1 two doses (n = 28): 143 [IQR: 79, 220] Day 56: • ChAdOx1 one dose (n = 29): 45 [IQR: 27, 67] • ChAdOx1 two doses (n = 27): 127 [IQR: 74, 183] ***56-69 yo (SD/SD):*** Day 28: • ChAdOx1 single dose (n = 9): 76 [IQR: 46, 179] • ChAdOx1 two doses (n = 15): 72 [IQR: 35, 102] Day 42: • ChAdOx1 two doses (n = 20): 144 [IQR: 119, 347] Day 56: • ChAdOx1 one dose (n = 10): 32 [IQR: 11, 63] • ChAdOx1 two doses (n = 22): 178 [IQR: 124, 416] ***≥ 70 yo (LD/LD):*** Day 28: • ChAdOx1 single dose (n = 21): 47 [IQR: 23, 82] • ChAdOx1 two doses (n = 34): 33 [IQR: 13, 65] Day 42:	

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				• ChAdOx1 two doses (n = 34): 150 [IQR: 103, 255] Day 56: • ChAdOx1 one dose (n = 20): 31 [IQR: 13, 84] • ChAdOx1 two doses (n = 36): 111 [IQR: 61, 251] ***≥ 70 yo (SD/SD):*** Day 28: • ChAdOx1 single dose (n = 49): 58 [IQR: 20, 120] • ChAdOx1 two doses (n = 42): 48 [IQR: 21, 121] Day 42: • ChAdOx1 two doses (n = 47): 161 [IQR: 73, 323] Day 56: • ChAdOx1 one dose (n = 47): 44 [IQR: 22, 76] • ChAdOx1 two doses (n = 43): 146 [IQR: 56, 239] Comparison across all age groups at day 42 in LD (*P = 0.899)* and SD (*P = .4)* Comparison between LD and SD at day 42: • 18-55yo: *P = .3287* • 56-69yo: *P = .124* • ≥70yo: *P = .6195* **Anti-spike IgG using standardized ELISA (EU)** Refer to page 13 of **supplementary material** for detailed results	

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; LD = low dose; MNA = microneutralization assay; PRNT= Plaque reduction neutralization test; NAAT = nucleic acid amplification test; SAE = serious adverse event; SD = standard dose; 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	Cohort 1 (n = 402) Cohort 3 (n = 403)	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 (low dose) or $1X10^{11}$ vp (high dose) 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.	Humoral response by Spike-specific ELISA against SARS-CoV-2 *Cohort 1a (18-55 yo; 1 or 2 doses)* • Day 29: Incidence of seroconversion of 99% or more in all groups: low dose/placebo; high dose/placebo; low dose/low dose; high dose/high dose • After the first dose, the incidence of seroconversion was 100% in all but the high dose/placebo group (97%) • 14 days after second dose, 100% seroconversion in all groups. *Cohort 3 (≥ 65yo; 1 dose)* • Day 15: Incidence of seroconversion of 75% (low dose) and 77% (high dose) • Day 29: Incidence of seroconversion was 96% (low and high dose)	Solicited Local AE • Cohort 1: 64% (low dose), 78% (high dose), 9% (placebo) • Cohort 3: 41% (low dose), 42% (high dose), 14% (placebo) • Most frequent local AE was injection site pain Solicited Systemic AE • Cohort 1: ○ Total: 65% (low dose), 84% (high dose), 21% (placebo) ○ Fever: 15% (low dose), 39% (high dose); Grade 3 fever: 5% (low dose), 9% (high dose) ○ Grade 3: 9% (low dose), 20% (high dose) • Cohort 3: ○ Total:46% (low dose), 55% (high dose), 23% (placebo) ○ Fever: 4% (low dose), 1% (high dose) ○ Grade 3: 1% (low dose), 2% (high dose) • Most frequent SAEs were headache, fatigue, and myalgia Unsolicited AE • Cohort 1: 21% (low dose), 35% (high dose), 17% (placebo) • Cohort 3: 17% (low dose), 24% (high dose), 16% (placebo)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 3 trial Ad26.COV2.S (JNJ-78436735) ENSEMBLE	40,000	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

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