COVID-19 vaccine candidates

September 3, 2021

Disclaimer: The information contained in this document is intended for informational purposes only and is in no way intended to be a substitute for or in any manner to be construed as medical or clinical advice for any patient in your care. The authors, editors, reviewers, contributors and publishers cannot be held responsible for the accuracy or continued accuracy of the information or for any errors or omissions in the document or for any consequences in the form of liability, loss, injury, or damage incurred as a result of the use and application of any of the information, either directly or indirectly. All medical and clinical decisions regarding any patient's care are the responsibility of the patient's physician.

Table of contents

Table of contents 3
Summary of changes since last publication (update: September 3, 2021) 4
Late-stage COVID-19 vaccine candidates in United States side-by-side comparison[a] 5
Evidence summary: COVID-19 vaccines 20
Introduction 20
Side-by-side document 21
Efficacy and safety considerations 21
Late-stage vaccine candidates 22
mRNA-1273 22
    Efficacy 23
    Safety 25
BNT 162b2 26
    Efficacy and safety: Phase 1 27
    Phase 2/3 Study 28
mRNA vaccines – Anaphylaxis reactions 30
mRNA vaccines – Myocarditis/pericarditis 31
AZD1222 32
    Efficacy 33
    Safety 34
    Approvals 35
JNJ-78436735 35
    Efficacy and safety: Phase 1/2a 35
    Phase 3 Study 36
Adenovirus-based vaccines - Thrombosis with thrombocytopenia syndrome 39
NVX-CoV2373 39
    Efficacy and safety: Phase 1 39
    Phase 3 40
References 41
Appendix A – mRNA-1273 trials 45
Appendix B – BNT162b2 trials 48
Appendix C – AZD1222 trials 50
Appendix D – JNJ-78436735 trials 58
Appendix E – NVX-CoV2373 trials 62

Summary of changes since last publication (update: September 3, 2021)

- Updated BioNTech/Pfizer vaccine FDA approval and EUA status (table).
- Added information on administration of third dose in immunocompromised individuals (table).
- Added information on administration of a booster dose in non-immunocompromised individuals (table).
- Updated the number of thrombosis with thrombocytopenia and Guillain-Barre syndrome cases reported in association with Janssen COVID-19 vaccine (table).
- Updated the number of myocarditis/pericarditis cases reported to VAERS in association with mRNA vaccination (table).
- Updated information regarding enrollment in BioNTech/Pfizer trial for pediatrics aged 6 mo to <12 y.
- Added 6-month efficacy data for BioNTech/Pfizer vaccine (table).
- Updated information regarding safety of mRNA vaccine during pregnancy (table).
- Updated VE data for Moderna and BioNTech/Pfizer vaccine against Delta variant (Ontario, England, Israel, US, Qatar) (table).
- Removed VE data for all vaccines against Alpha and Beta variants (table).
- Updated J&J expiration dating (table).
- CPT code added for third dose (table).

Note: AstraZeneca information – last update July 16, 2021.

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)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria 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. Submission for EUA ≥ 12 y filed in June.	• FDA approved - Prevention of COVID-19 disease in individuals ≥16 y. • EUA –12-15 y and for third dose in certain immunocompromised individuals ≥ 12 y.	Investigational	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 18 y	Investigational – EUA expected to be submitted in Q4 2021
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	Yes	Yes	No[b]	Yes (EU Ebola)	Yes
Targeted SARS-CoV-2 antigen	Full-length, prefusion stabilized SARS-CoV-2 spike protein				
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 once in the host cell.		• Genetic sequence encoding spike protein is cloned into baculovirus and inserted into Sf9 insect cells, where spike protein is produced and isolated/extracted. • Matrix-M adjuvant boosts immune response; stimulates entry of antigen-presenting cells into the injection site and enhancing B- and T-cell responses.

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
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				
How supplied					
Multidose vial	• 10 to 11 doses/vial[c] • 13 to 15 doses/vial • Vial size: 5 mL (Does not contain latex)	• 6 doses/vial[c] • Vial size: 2 mL (Does not contain latex)	• 10 doses/vial (anticipated U.S. availability) • 8- and 10-doses/vial (UK EUA)	5 doses/vial (Does not contain latex)	10 doses/vial
Anticipated commercial vaccine storage conditions – unopened vial (investigational conditions may differ)					
Frozen or ultra-cold	Store at -50° to -15° C	**Frozen vials prior to use:** • Preferably, transfer vial to an ULT freezer (-90°C to -60°C) immediately upon receipt. • Vials may be stored at -20°C±5°C for up to 2 wks (total cumulative time); the vials may be returned 1 time to storage condition of -90°C to -60°C. • If an ULT freezer is unavailable, the thermal shipper may be used as temporary storage, provided instructions in the re-icing guidelines are followed.	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

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
		Transportation of frozen vials: • If local redistribution is needed and full cartons cannot be transported at -90°C to -60°C, vials may be transported at -20°C±5°C. • Any time spent in transport at -20°C±5°C count against the 2-wk limit for storage at this temperature. • Frozen vials transported at -20°C±5°C may only be returned 1 time to the recommended storage condition of -90°C to -60°C.			
Refrigeration (2-8°C)	Stable for 30 d **Transportation of thawed vials**: • Available data support the transport of ≥ 1 thawed vial(s) at 2-8° C for up to 12 h. • Once thawed and transported at 2-8°C, vial cannot be refrozen. Store at 2-8°C.	Undiluted vial: 30 d **Transportation of thawed vials**: • Available data support the transport of ≥1 thawed vial(s) at 2-8°C for up to 12 h.	Until date printed on packaging (at least 6 mo)	Stable for 6 mo Prior to discarding doses, validate the expiration date through the Expiry Checker i based on lot numbers	Store at 2-8°C
Room temperature	Stable for 24 h	Undiluted vial: 2 h	NR	Stable for 12 h	NR
BU after vial entry	12 h, stored between 2°C - 25°C	6 h, stored between 2°C - 25°C	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
	USP Compounding Expert Committee added operational considerations for preparing conventionally manufactured COVID-19 vaccines after FDA issued EUA.				

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
Dosage and administration					
Dose	100 mcg/0.5 mL	30 mcg/0.3 mL	5×10^{10} vp dose (U.S. phase 3 trial)	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 wk between doses, U.S. phase 3 trial) • 2-dose series (4-12 wk between doses) (UK EUA, EMA EUA) • WHO recommends 8-12 wk between doses based on efficacy and immunogenicity data	• 1 dose • There are insufficient data to support use of an additional mRNA dose after a single-dose of Janssen vaccine in immunocompromised people.	2-dose series (21 d between doses)
	Individuals who receive the second dose up to 4 d before or at any time after the recommended date can be considered fully vaccinated.				
	Third dose: • On August 12, 2021, the EUAs for Pfizer-BioNTech and Moderna vaccines were amended to allow for an additional dose to be given to immunocompromised individuals (solid organ transplant recipients or those who are diagnosed with conditions considered to have an equivalent level of immunocompromise) • The 3rd dose is equivalent to dosing in the original series and to be given at least 28 d following the first 2 doses of the vaccine. • The additional dose should be the same mRNA vaccine as the primary series; the alternate mRNA product can be used if the primary series product is not available.				
	Booster dose: • An additional dose of vaccine administered when the initial sufficient immune response to a primary vaccine series is likely to have waned. • FDA is conducting an evaluation of safety and effectiveness of a booster dose and will host an advisory committee meeting on September 17.				
	• Data for booster at a 50-mcg dose submitted to FDA. • A 50-mcg booster dose evaluated in a phase 2 study (n = 344).	• Data for booster at a 30-mcg dose submitted to FDA. • A 30-mcg booster dose evaluated in a phase 1 study.	NR	A 5×10^{10} vp booster dose evaluated in a phase 1/2a study (n = 64) and in a phase 2 study (n = 73).[d]	A 5-mcg booster dose given 6 mo after the initial dose evaluated in a phase 2 study.

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
Co-administration with other vaccines	• COVID-19 vaccines may be administered without regard to timing of other vaccines. • Administer each injection in a different site.		NR	Recommendation is the same as for the mRNA vaccines.	NR
Mixing and matching with other COVID-19 vaccines	• WHO lead scientist warns individuals against mixing and matching COVID-19 vaccines. • CDC recommends that both doses of the series should be completed with the same product. • In an exceptional situation in which the mRNA vaccine given for first dose cannot be determined, any available mRNA COVID-19 vaccine may be given at a minimum interval of 28 d after first dose. • In an exceptional situation in which a first dose of an mRNA is given, but the patient is unable to complete the series with an mRNA vaccine, a single dose of Janssen vaccine may be given at a minimum interval of 28 d from the mRNA dose.				A trial was initiated in the UK in June to evaluate a booster dose in patients who have received two doses of another authorized vaccine.[e]
Administration route	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Dilution required	No	Yes	No	No	No
Preparation	• 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.	• 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	• 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
Considerations in specific populations					
Current or prior history of SARS-CoV-2 infection or	• 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		NR	Recommendation is the same as for the mRNA vaccines.	NR

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
history of MIS-C or MIS-A	interval between infection and vaccination. • MIS-C/MIS-A – vaccination can be considered.				
History of passive antibody therapy for COVID-19	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.		NR	Recommendation is the same as for the mRNA vaccines.	NR
History of myocarditis or pericarditis	• Occurrence after first dose of an mRNA – For the majority, defer second dose, but in certain circumstances, a second dose may be considered. • History of myocarditis or pericarditis unrelated to mRNA – May be vaccinated after episode has completely resolved with no evidence of ongoing inflammation or sequelae determined by clinical team.		NR	Recommendation is the same as for the mRNA vaccines.	NR
History of GBS	• May receive any of the authorized or approved COVID-19 vaccines. • Janssen vaccine may be associated with an increased risk of GBS; therefore, an mRNA vaccine may be considered as an alternative.		NR	Recommendation is the same as for the mRNA vaccines.	NR
Persons with immunocompromise	An additional mRNA vaccine (third dose) is recommended for moderately to severely immunocompromised people after an initial 2-dose primary mRNA vaccine series.		NR	Insufficient data to recommend an mRNA dose.	NR
History of thrombosis or risk factors for thrombosis	Should be offered an mRNA vaccine if it has been ≤ 90 d since illness has resolved. After 90 d, patients may be vaccinated with any COVID-19 vaccine.		NR	Recommendation is the same as for the mRNA vaccines.	NR
Pregnancy or lactation	• Experts do not believe that any of the COVID-19 vaccines pose a risk because the vaccines are non-replicating and cannot cause infection in the mother or fetus. However, the safety of COVID-19 vaccines has not been evaluated in clinical trials. There is no recommendation for routine pregnancy testing prior to vaccination. In general, non-live vaccines do not pose a risk to mothers or breast-feeding infants. • V-safe data as of Feb. 28, 2021: 35,691 pregnancies self-reported at time of vaccination (n = 16,439 (Moderna) and n = 19,252 (Pfizer))[f] • V-safe pregnancy registry as of Feb. 28, 2021: 3,958 pregnancies enrolled with 827 completed pregnancies, including 712 live births. No safety signals detected with vaccine (pregnancy outcome, pregnancy complications, neonatal outcomes).[f] No outcomes reported in those vaccinated early in pregnancy; report describes mostly neonatal outcomes from third trimester exposure. • In a V-safe pregnancy cohort of 2,456 participants who received mRNA vaccine at <20 wk of gestation and who were pregnant at ≥6 wk of gestation, there were 165 SABs reported, 253 participants lost to follow-up, and 2,020 known to be pregnant at 20 wks.				

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
	Cumulative risk of SAB from 6-19 wks' gestation was 14.1% (95% CI, 12.1-16.1%) in the vaccine cohort (vs. 12.8% (95% CI, 10.8-14.8% for age-standardized cumulative risk of SAB).[g]				
	--	Phase 2/3 study (NCT04754594) to evaluate safety and immunogenicity of vaccine in pregnancy.	--	Phase 2 study (NCT04765384) to evaluate safety and immunogenicity of vaccine in pregnancy.	--
Safety considerations					
Contraindications	• Severe allergic reaction (e.g. anaphylaxis) after a previous dose of or to a component of the vaccine. • Immediate (within 4 h of exposure) allergic reaction of any severity to a previous dose or known (diagnosed) allergy to a component of the vaccine (CDC).		NR	Recommendation is the same as for the mRNA vaccines.	NR
Precautions	• Appropriate treatment to manage immediate allergic reactions must be available. • Reports suggest increased risks of myocarditis and pericarditis, particularly within 7 d following the second dose. • Syncope may occur in association with administration of injectable vaccines. • Immunocompromised persons may have a diminished response to vaccination. • Vaccine may not protect all vaccine recipients.		NR	• Appropriate treatment to manage immediate allergic reactions must be available. • Reports suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites combined with thrombocytopenia. Most cases occur within 14 d and in females 18-49 y. • Reports suggest an increased risk of GBS during the 42 d following vaccination.	NR
Observation period	• **30 mins** for persons with history of an immediate allergic reaction of any severity to a vaccine or injectable therapy; history of anaphylaxis due to any cause; contraindication to a different CV19 vaccine. • **15 mins**: all others.		NR	Observation period recommendation the same as for mRNA vaccines	NR

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
Adverse events					
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).	• 12-15 y: Pain (90.5%), swelling (10.5%), and redness (8.6%) at injection site. • 16-55 y: Pain (88.6%) and swelling (10.6%) at injection site. • ≥ 56 y: Pain (78.2%), swelling (11.8%), and redness (10.4%) at injection site.	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.	• Most common is injection site pain after first (53.3%) and second dose (76.4%). • Most events grade 1 or 2 severity and of short duration (2.3 d after first dose and 2.8 d after second dose).
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%).	• 12-15 y: Fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%) and joint pain (20.2%). • 16-55 y: Fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), and fever (17.8%). • ≥ 56 y: Fatigue (56.9%), headache (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), and fever (11.5%).	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.	• Most common are headache, muscle pain, and fatigue after both dose 1 (24.5%, 21.4%, and 19.4%) and dose 2 (40%, 40.3%, and 40.3%). • Most events grade 1 or 2 severity with < 2 d duration. • Grade 4 events reported in 3 vaccine recipients.

	Vaccine candidates				
	mRNA vaccines		**Replication-defective vectored vaccines**		**Protein subunit**
	mRNA-1273 (Moderna)	**Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)**	**Vaxzevria AZD1222 (AstraZeneca)**	**JNJ-78436735 (J&J)**	**NVX-CoV2373 (Novavax)**

Post-marketing safety issues (per regulatory agencies & primary literature)	**Anaphylaxis reactions**
	• mRNA-1273: Incident rate (reported 1/22/21): 2.5 cases/million doses
	• mRNA-BNT162b2: Incident rate (reported 1/6/21): 11.1 cases/million doses
	Myocarditis (as of 8/18):
	• Most common in males ≤ 29 y after dose 2.
	• Total of 2,575 reports in VAERS of myopericarditis among all ages.
	  ○ Myopericarditis: 1,903 reports
	  ○ Pericarditis alone: 671 reports
	• 742 cases meeting case definition in persons ≤ 29 y.
	  ○ 701 hospitalized, 667 discharged at time of report
	  ○ 18 hospitalized (5 in ICU)
	• Crude reporting rates (per million doses) of myopericarditis in males ≤ 29 y, after dose 2
	  ○ Age 12-17 y: 42.6 (Pfizer)
	  ○ Age 16-17 y: 71.5 (Pfizer)
	  ○ Age 18-24 y: 37.1 (Pfizer), 37.7 (Moderna)
	  ○ Age 25-29 y: 11.1 (Pfizer), 14.9 (Moderna)
	EMA is evaluating the risk of erythema multiforme, nephrotic syndrome, and glomerulonephritis in association with mRNA vaccines.
			EMA reports as of April 4 (includes UK reports of unknown percentage):
			• 169 cases of CVST
			• 53 cases of SVT
			MHRA (UK) reports as of April 28:
			• 93 cases of CVST
			• 149 other TE
			• Estimated incidence is 10.5/million doses
			• 49 deaths (20% fatality rate)
			• 6 cases following a second dose
				TTS (as of 8/25):
				• 44 cases out of 14.2 million doses
				• Females aged <50 y should be aware of the rare, but increased risk
				GBS (as of 8/25):
				• 176 preliminary reports out of 12.8 million doses
				• Most cases reported 2 wk after vaccination
				• Reported mostly in males, aged > 50 y
					1 case of myocarditis reported in vaccine recipient in phase 3 trial (the safety data board ruled it a viral myocarditis).

Populations of interest					
Pediatrics	**12 to <18 y** • Phase 2/3 trial (NCT04649151) in 12 to < 18 y (TeenCOVE) data published. • EUA filed June 10, 2021.	**12 to 15 y** • FDA approved and recommended for use • Adolescents 12 to 15 y phase 3 trial results (NCT04368728) published.	• Children 5-12 y are enrolled in the UK (COV006). • Trial is paused to examine potential link between AZD1222 and thrombocytopenia &	**12 to <18 y** • Phase 2 trial (NCT04535453) in 12 to < 17 y. **<18 y** • J&J plans to conduct additional trials in pediatrics 2-11 y, <2 y,	**12 to <18 y** • Phase 3 trial (PREVENT-19) in 12 to < 18 y fully enrolled.

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
	6 mo to <12 y • Phase 2/3 trial (NCT04796896) in 6 mo to <12 y (KidCOVE) enrolled. • Dose, 2-12 y: 50 or 100 mcg • Dose, <2 y: 25, 50, or 100 mcg	**6 mo to <12 y** • Phase 1/2/3 trial in 6 mo to <12 y began March 2021. • Plan to enroll approx. 4,500 children • EUA submission planned in Sept-Oct 2021 for 5-11 y, followed by 6 mo-5 y thereafter. • Dose, 5-11 y: 10 mcg • Dose, 6 mo-5 y: 3 mcg	thrombosis in adults.	and in immunocompromised pediatrics 1-17 y.	
Immunocompromised patients[h]	Condition	Solid Organ Transplant	Autoimmune/Rheumatic Disease	Cancer	Hemodialysis
	% with anti-spike antibody response	14% - 58%	74% - 100%	51% - 95%	96%
	Risk factors for diminished antibody response	• Antimetabolites • Shorter time after transplant • Older age	• Antimetabolites • B-cell depletion • Corticosteroids	• B-cell chronic lymphocytic leukemia • Older age • On therapy • Poor disease response	• Older age • Lower lymphocyte counts

	• On August 12, 2021, the EUAs for the Pfizer-BioNTech and Moderna vaccines were amended to allow for an additional (3rd) dose to be administered to immunocompromised individuals—specifically, solid organ transplant recipients or those who are diagnosed with conditions considered to have an equivalent level of immunocompromise.
	• The Advisory Committee on Immunization Practices met on August 13 to discuss clinical considerations for additional doses in immunocompromised individuals; the panel unanimously voted to recommend a 3rd dose of the vaccine for these individuals. Oher countries administering additional doses to immunocompromised individuals include France, Israel, and Germany; the UK plans to implement in September.
	• Suggested best practices for timing of vaccination with concomitant immunosuppression[h]
	  ○ When possible, vaccinate at a time of reduced immunosuppression (e.g., between chemo cycles, prior to solid-organ transplant)
	  ○ Rituximab may be problematic due to its potent effect on B cells. If possible, time vaccination near end of cycle.				

	Vaccine candidates				
	mRNA vaccines		**Replication-defective vectored vaccines**		**Protein subunit**
	mRNA-1273 (Moderna)	**Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)**	**Vaxzevria AZD1222 (AstraZeneca)**	**JNJ-78436735 (J&J)**	**NVX-CoV2373 (Novavax)**
	○ In most cases, reducing immunosuppression to increase vaccine response is not recommended, esp. transplant patients. The ACR recommends holding immunomodulatory therapy (mycophenolate, methotrexate) in those with stable disease for 1-2 wk after vaccination.				
	COVE Transplant study (NCT04860297) enrolling kidney or liver adult transplant patients.	--	--	--	--
Phase 3 trials efficacy results					
Symptomatic COVID-19 (without previous SARS-CoV-2 infection)	**COVE study** • 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) (New topline results through 6 mo after dose 2 show VE remains high at 90%) **TeenCOVE study** • Secondary endpoint • 4 cases in placebo group vs. 0 cases in vaccine group • VE: 100% (VE 93% per CDC definition for COVID-19)	**≥ 12 y cohort (6-mo data)** • Primary endpoint, measured from 7 d to 6 mo after dose 2 • 850 cases in placebo group vs. 77 cases in vaccine group • VE: 91.3% (95% CI, 89.0-93.2) **12-15 y cohort** • Descriptive, measured ≥ 7 d after dose 2 • 16 cases in placebo group vs. 0 cases in vaccine group • VE: 100% (95% CI, 75.3-100.0)	• Primary endpoint, measured ≥ 15 d after dose 2 • VE: 76% (95% CI, 68-82)	• 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 **UK trial** • 96 cases in placebo group vs.10 cases in vaccine group • Overall VE: 89.7% (95% CI, 80.2-94.6) • VE against original strain: 96.4% (95% CI, 73.8-99.4) • VE alpha variant: 86.3% (95% CI, 71.3-93.5) **U.S./Mexico trial** • 63 cases in placebo group vs. 14 cases in vaccine group • Overall VE: 90.4% (95% CI, 82.9-94.6) • VE, variants not considered VoC/VoI: 100% (95% CI, 80.8-100) • VE, VoC/VoI: 93.2% (95% CI, 83.9-97.1)

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
Moderate or severe COVID-19	**COVE study** • 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 • Severe disease, **as defined by FDA**: 30 cases in placebo group vs. 1 case in vaccine group, VE: 96.7% (95% CI, 80.3-99.9) • No severe cases in 12-15 y old cohort	• Secondary endpoint, prevention of **severe or critical disease and hospitalization** • 8 cases in placebo group vs. 0 cases in vaccine group • VE: 100%	• 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)	**UK trial** • 5 **severe cases** in placebo group vs. 0 cases in vaccine group (4 of 5 severe cases were caused by alpha variant) • VE: 100% **U.S./Mexico trial** • 14 moderate/severe cases (10 moderate, 4 severe) in placebo group vs. 0 cases in vaccine group • VE: 100% (95% CI, 87-100)
COVID-19-related deaths	• 1 in placebo group • 0 in vaccine group	• 2 in placebo group • 1 in vaccine group	NR	• 7 in placebo group • 0 in vaccine group	0 in vaccine group in UK and US/Mexico trials
Variants of Concern – clinical effectiveness					
Definition	Evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.				

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
B.1.617.2 (Delta)	**Front-line workers in US (Delta prominent weeks)**[i] • Adjusted VE against symptomatic disease: 66% (95% CI, 26-84%).		England[j,k] • VE for symptomatic disease after second dose: 59.8% (95% CI, 28.9-77.3) • VE for hospitalization after second dose: 92% (95% CI, 75-97) Scotland[o] • VE for RT-PCR confirmed infection 14 d after second dose: 60% (95% CI, 53-66) vs. 73% for alpha	In a subset (n = 8) of participants from the ENSEMBLE study, activity was noted with a duration of 8 months.[l]	NR
	Mayo Clinic (1/21-7/21)[m] • VE against symptomatic infection in July: 76% (95% CI, 58-87%). • VE against hospitalization in July: 81% (95% CI, 33-96.3%). **Ontario (12/20-5/21)**[n] • VE against symptomatic infection ≥ 14 d after dose 1: 72%; 95% CI, 57-82% (vs. 83% for alpha). • VE against hospitalization or death ≥ 14 d after dose 1: 96% (95% CI, 72-99%). **Qatar (12/20-7/21)**[p] VE against asymptomatic or symptomatic infection: • ≥ 14 d after dose 1: 79% (95% CI, 58.9-90.1%). • ≥ 14 d after dose 2: 84.8% (95% CI, 75.9-90.8%). VE against severe, critical or fatal COVID-19 disease ≥ 14 d after dose 2: 100% (95% CI, 41.2-100%).	**England**[j,k] Adjusted VE against symptomatic infection: • ≥21 d after dose 1: 35.6% (95% CI, 22.7-46.4) • ≥14 d after dose 2: 88.0% (95% CI, 85.3-90.1) • VE for hospitalization after second dose[q]: 96% (95% CI, 86-99) vs. 96% for alpha. **Mayo Clinic (1/21-7/21)**[m] • VE against symptomatic infection in July: 42% (95% CI, 13-32%). • VE against hospitalization in July:75% (95% CI, 24-93.9%). **Ontario (12/20-5/21)**[n] VE against symptomatic disease: • ≥ 14 d after dose 1: 56%; 95% CI, 45-64% (vs. 66% for alpha). • ≥ 7 d after dose 2: 87%; 95% CI, 64-95% (vs. 89% for alpha).			

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
		VE against hospitalization or death ≥ 14 d after dose 1: 78%; 95% CI, 65-86%. **Qatar (12/20-7/21)**[p] VE against asymptomatic or symptomatic infection: • ≥ 14 d after dose 1: 64.2% (95% CI, 38.1-80.1%). • ≥ 14 d after dose 2: 53.5% (95% CI, 43.9-61.4%). VE against severe, critical or fatal COVID-19 disease ≥ 14 d after dose 2: 89.7% (95% CI, 61-98.1%). **Scotland**[r] VE for RT-PCR confirmed infection 14 d after second dose: 79% (95% CI, 75-82) vs. 92% for alpha **Israel (6/21-7/21)**[q] VE and lower/upper confidence intervals: • SARS-CoV-2 cases: 39.0% (9.0-59.0) • Symptomatic COVID-19: 40.5% (8.7-61.2) • COVID-19 hospitalization: 88.0% (78.9-93.2) • Severe-COVID-19: 91.4% (82.5-95.7)			
CPT codes (Payment allowance)	91301 ($0.010) 0011A – first dose ($40.00) 0012A – second dose	91300 ($0.010) 0001A – first dose ($40.00) 0002A – second dose	91302 ($0.010) 0021A – first dose ($40.00)	91303 ($0.010) 0031A – vaccine administration ($40.00)	NR

	Vaccine candidates				
	mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
	mRNA-1273 (Moderna)	Comirnaty mRNA-BNT162b2 (BioNTech/Pfizer)	Vaxzevria AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
	($40.00) 0013A – third dose ($40.00)	($40.00) 0003A – third dose ($40.00)	0022A – second dose ($40.00)		
Clinical summary	Please view the evidence summary for an expanded discussion of data.				

Abbreviations: ADE = adverse drug event; BU = beyond use; aTE: arterial thromboembolic event; CPT = current procedural terminology; CVST = cerebral venous sinus thrombosis; EMA = European Medicines Agency; EUA = emergency use authorization; GBS = Buillain-Barre syndrome; GMT = geometric mean titer; HIV = human immunodeficiency virus; ITP = immune thrombocytopenia purpura; LD = low dose; LNP = lipid nanoparticle; MIS-A = multisystem inflammatory syndrome – adults; MIS-C = multisystem inflammatory syndrome – children; mRNA = messenger ribonucleic acid; NR = not reported; PPE = personal protective equipment; RT = room temperature; SAB = spontaneous abortion; SD = standard dose; SVT = splanchnic vein thrombosis; TE = thromboembolic event; TTS = thrombotic thrombocytopenia syndrome; ULT = ultra-low temperature; VE = vaccine efficacy; VTE = venous thromboembolism; 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. 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] Sadoff J, Le Gars M, Cardenas V, et al. Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late bosting. medRxiv. Posted August 26,2021. doi: https://doi.org/10.1101/2021.08.25.21262569.

[e] Novavax. Novavax statement on participation in mix-and-match COVID-19 vaccine booster trial in the United Kingdom. Novavax website. **https://ir.novavax.com/2021-05-21-Novavax-Statement-on-Participation-in-Mix-and-Match-COVID-19-Vaccine-Booster-Trial-in-the-United-Kingdom**. Accessed July 15, 2021.

[f] Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *N Engl J Med*. Published online on April 21, 2021. Available at: doi:10.1056/NEJMoa2104983.

[g] Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 vaccine pregnancy registry 2020-21. Research Square. Posted August 9, 2021. doi: 10.21203/rs.3.rs-798175/v1.

[h] Kaul D. How should we advise our immunocompromised patients after COVID-19 vaccination? NEJM Journal Watch website. **https://www.jwatch.org/na53599/2021/06/14/how-should-we-advise-our-immunocompromised-patients-after**. Published June 14, 2021. Accessed July 16, 2021.

i Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection among frontline workers before and during B.1.617.2 (Delta) variant predominance – Eight U.S. locations, December 2020-August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1167-1169.

[j] Bernal JL, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. *New Engl J Med*. 2021;385(7):585-594.

[k] Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Global Health Network website. **https://media.tghn.org/articles/Effectiveness_of_COVID-19_vaccines_against_hospital_admission_with_the_Delta_B._G6gnnqJ.pdf.** Accessed June 29, 2021.

[l] Positive new data for Johnson & Johnson single-shot COVID-19 vaccine on activity against delta variant and long-lasting durability of response. J&J website. **https://www.janssen.com/positive-new-data-johnson-johnson-single-shot-covid-19-vaccine-activity-against-delta-variant-and**. Published July 1, 2021. Accessed July 14, 2021.

[m] Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv. Posted August 21, 2021. doi: **https://doi.org/10.1101/2021.08.06.21261707**.

[n] Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. medRxiv. Posted July 16, 2021. doi: https://doi.org/10.1101/2021.06.28.21259420.

[o] Sheikh A, McMenamin J, Taylor B, Robertson C for Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*. 2021;397(10293):2461-2462.

[p] Tang P, Hasa MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. medRxiv. Posted August 11, 2021. doi: **https://doi.org/10.1101/2021.08.11.21261885**.

[q] Israel Ministry of Health. Unpublished preliminary data collected June 20,2021 – July 17, 2021 (delta variant). As cited in **https://www.nature.com/articles/d41586-021-02054-z**. Available at **https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf**.

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 2020 and enrolled 600 healthy participants with no known history or risk of SARS-CoV-2 infection who were aged 18 years and older. Participants were stratified into two age-based cohorts (≥18 to <55 and ≥55) andrandomized 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] A preliminary report of the findings from the study were published in ***Vaccine*** and are briefly summarized in Appendix A.

The phase 3 trial was initiated in July and results were 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	57	93% (80.8,97.5)

	(8309)	(8323)	
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]

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.[28] 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.[29] 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.[30] 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.[31] 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 are considered a contraindication to vaccination with an mRNA COVID-19 vaccine. Because of potential cross-reactive hypersensitivity between polyethylene glycol and polysorbate, a known polysorbate allergy is considered a precaution to vaccination with a mRNA vaccine.[31] 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.[31,32] As information is rapidly changing, the CDC and ACAAI will update guidance.

Table 3: Ingredients in mRNA COVID-19 vaccines[31]

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

mRNA vaccines – Myocarditis/pericarditis

The first reports of myocarditis/pericarditis after vaccination with BNT162b2 came from Israel at the end of April.[33] On June 23, the CDC's ACIP met to discuss the association between mRNA vaccines (Pfizer and Moderna) and the occurrence of myocarditis/pericarditis. Based on data reported to the Vaccine Adverse Event Reporting System (VAERS) through June 11, the ACIP panel concluded that there is a higher than expected number of myocarditis/pericarditis reports after vaccination with mRNA and there is likely a causal association between heart inflammation and vaccination. Preliminary data indicate cases are clustered within 4 days of the second dose and predominantly occur in young males. The observed number of cases of myocarditis/pericarditis after dose 2 using a 7-day risk window are greater than the

expected background rate in males aged 12-17 years, 18-24 years, 25-29 years, 30-39 years, and 40-49 years; however, the strongest signal thus far has been observed in those aged 12 to 17 years. The myocarditis/pericarditis reporting rate per million doses decreases with increasing age from a high of 66.7 cases per 1 million doses in males aged 12 to 17 years to a low of 1.4 cases per 1 million doses in males aged 65 years and older.[34] Continued surveillance in males aged 12-17 years is strongly encouraged since the vaccine was authorized for use in this age group on May 11 and administration of the second dose was ongoing at the time of preliminary data collection. While the greatest risk for post-vaccination myocarditis appears to be for young males, observed cases were higher than expected for females aged 12 to 29 years and 12 to 24 years after dose 2, depending on whether a risk window of 7 days or 21 days post dose 2, respectively is used.[34] Several case reports and case series of post-vaccination myocarditis have been published.[35-39] Based on the CDC review of 323 cases that met the agency's definition of myocarditis or pericarditis (or both), 309 cases were hospitalized, but 218 (79%) cases had recovered from symptoms at the time of ACIP meeting.[34] Many of the published case reports/series also suggest a limited course, but uncertainty remains about long-term course because of short follow-up.

Though no formal vote occurred after the meeting, ACIP members delivered a strong endorsement that the benefits of vaccination continue to outweigh risks and all persons aged 12 years and older should be vaccinated against COVID-19.[40] Fact sheets for mRNA vaccines have been updated to include information on the risk of myocarditis and pericarditis. For information on clinical considerations, please consult the CDC's **Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines among Adolescents and Young Adults**. As other countries review data, several are taking a more cautious approach to pediatric vaccination. Advisory committees in the UK, Germany, and Sweden have opted against recommending the vaccine for all adolescents and instead recommend that vaccination efforts should target those with pre-existing conditions.

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.[41] The tPA component has been demonstrated to enhance immunogenicity in another ChAdOx1 vectored CoV vaccine (ChAdOx1 MERS).[41] 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.[41] 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.[42]

In a **press release** published on November 23, 2020, 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%.[43] 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.[44] 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).[44] On March 23, 2021, AstraZeneca released top line data on the results from the U.S. phase 3 trial. Vaccine efficacy against symptomatic COVID-19 was reported to be 79% and the VE against severe disease and hospitalization was reported to be 100%.[45] Following the top line data release the National Institute of Allergy and Infectious Diseases (NIAID) published a response statement indicating the Data and Safety Monitoring Board (DSMB) was concerned about the timeliness and completeness of the information and urged the company to work with the DSMB to review the efficacy data to ensure it is accurate and up to date.[46] Shortly after, AstraZeneca issued a response indicating the data were based on a pre-specified interim analysis cut-off date of February 17 and that they would “immediately engage” with the DSMB to share the primary analysis and up to date efficacy data with an issuance of results within 48 hours.[47] A subsequent top line data release on March 25 adding 49 cases to the previously announced interim analysis reported a VE of 76% (95% CI, 68-82) against symptomatic infection in the overall cohort and a VE of 85% (95% CI, 58-95) against symptomatic infection in patients 65 years of age or older.[48]

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.[41]

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.[42]

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.[44] In response to reports of possible clotting complications in patients receiving AZD1222, the European Medicines Agency (EMA) published a release stating the benefits of the vaccine outweigh the risk despite the potential link to thrombosis with thrombocytopenia on March 18.[49] Seven cases of disseminated intravascular coagulation and 18 cases of cerebral venous sinus thrombosis were reported and occurred mostly within 14 days. Nine of these patients died. Most of the reports occurred in patients under 55 years of age and were women. On March 23, AstraZeneca released top line data on the results the U.S. phase 3 trial.[48] It was reported that the vaccine was well tolerated. Refer to the efficacy section for relevant follow up. On April 7, the EMA provided updated information regarding reports of thrombocytopenia and clots following administration of AZD1222. [50] Most cases occurred in women under 60 years of age and within 2 weeks of receipt of the vaccine. Reports reviewed included 62 cases of cerebral venous sinus thrombosis (CVST) and 24 cases of splanchnic vein thrombosis of which 18 were fatal. These reports were mostly submitted through spontaneous reporting systems at a time when ~25 million people had received vaccine in the United Kingdom (UK) and European Economic Area (EEA). EMA continues to affirm the overall benefit-risk profile of AZD1222 remains positive. Updated report numbers (April 4, 2021) include 169 CVST cases and 53 cases of splanchnic vein thrombosis at a time when ~34 million people had been vaccinated in the EEA and UK. Patients 18-29 years of age in the UK will be offered an alternative COVID-19 (i.e. Moderna or Pfizer-BioNTech) vaccine as the data may suggest a trend towards increased incidence of these adverse events with decreasing age.[51] In an April 28 update, UK indicated 242 thromboembolic events (TE) had been reported (93 CVSTs, 149 other). Events occurred in 141 women and 100 men ranging in age from 18 to 93 years of age. Forty-nine patients died resulting in a case fatality rate of 20%. The overall incidence of cases is stated as 10.5 per million doses administered. Prior to this report, there was no indication TEs occurred following second doses; however, the new dataset describes 6 patients who

experienced a TE following the second dose.[52] Other countries have been reported to have implemented a lower age limit for AZD1222 eligibility including Spain (>60 years of age), Belgium (>55 years of age) and Australia (≥50 years of age). Denmark announced it will not use AZD1222. A population-based cohort trial of 18 to 65-year-old patients receiving the vaccine in Denmark and Norway evaluated the rates of cardiovascular and hemostatic events in the first 28 days after administration by searching national patient registries. Out of 281,264 patients receiving the vaccine, the baseline expected venous TE rate of 30 was eclipsed by the actual reported rate of 59 events (standardized morbidity ratio: 1.97 [1.5-2.54]) with an excess event rate of 11 (5.6-17) per 100,000 vaccinations. A higher rate of CVST was observed compared to expected (standardized morbidity ratio: 20.25 (8.14-41.73) with an excess of 2.5 (0.9-5.2) events per 100,000 vaccinations.[53] On May 7, The UK's Joint Committee on Vaccination and Immunisation published a press release advising that patients 30-39 years of age without underlying health conditions be offered an alternative vaccine to AZD1222 (as long as this does not cause significant delay in vaccination) due to low risk of infection and extremely rare cases of thrombosis and thrombocytopenia reported following the vaccine. This was an expansion of age from the previous recommendation in adults less than 30 years of age.[54]

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.[55] Clinical trials consists of a phase 1 trial **(NCT04509947**; active, not recruiting), a phase 1/2a trial (**NCT04436276**; active, not recruiting), a phase 2 trial (**NCT04535453**; active, recruiting) and 2 phase 3 trials (**NCT04505722** [ENSEMBLE]**;** active, not recruiting and **NCT04614948** [ENSEMBLE 2]**;** active, recruiting). Summaries of the published manuscript of the phase 1/2a trial and the descriptions of the phase 2 and 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.[55] The phase 2 trial was initiated in September 2020 with no interim results published to date. The ENSEMBLE phase 3 trial was initiated in September 2020 and enrollment of participants (n = 44,325) was completed in mid-December 2020. Results from the ENSEMBLE trial were published in the ***New England Journal of Medicine*** in April 2021.[56] The ENSEMBLE 2 phase 3 trial began in November 2020 and will enroll approximately 30,000 participants.

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.[55] 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.[55]

Phase 3 Study

The phase 3 ENSEMBLE trial evaluated a single dose approach using 5 X 10^{10} virus particles in adult patients (n = 43,783). 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.[56,57]

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.[56]

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.[56,57]

Cumulative incidence curves for the first COVID-19 occurrence started to diverge between vaccine and placebo recipients around 14 days after vaccination.[56,57]

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.[56,57]

Among all adverse events collected, numerical imbalances were observed between vaccine and placebo recipients for thromboembolic events (11 versus 3), seizures (4 versus 1), 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.[56,57]

Out of an abundance of caution, the FDA and CDC released a joint statement on April 13, 2021 recommending a pause in the use of the J&J vaccine because of 6 reported cases of CVST with thrombocytopenia occurring in women 18 to 48 years of age.[58,59] The ACIP convened 2 emergency meetings - on April 14 and April 23 - to evaluate the potential safety signal. On April 23, 2021, after careful review of 15 cases of thrombosis with thrombocytopenia – coined thrombosis with thrombocytopenia syndrome (TTS) – ACIP voted 10 to 4 in favor of lifting the pause and resuming vaccination with the J&J vaccine provided that the label includes a warning about the serious, but rare adverse event of TTS.[60]The decision to remove the pause was supported by a risk-benefit analysis, which suggested that the potential benefits of the vaccine (prevention of deaths, ICU admissions, and hospitalizations) outweighed the potential risk of TTS occurrence. Identification and treatment for TTS has been added to the vaccine providers' and the recipients/caregivers' fact sheets.

As of May 7, there are 28 confirmed cases of TTS out of 8.7 million vaccine doses administered. Of the 28 cases, 22 occurred in females and 6 in males, ages 18 to 59 years with a median age of onset of 40 years. The median time to symptom onset in these cases was 9 days (range 3-15 days) after vaccination and 19 of the 28 cases had documented thromboses in cerebral venous sinus locations. While risk factors for development of TTS are unknown, traditional risk factors for thrombosis were noted in some, but not all cases. These included: oral contraceptive use (n = 3); obesity (n = 12); hypothyroidism (n = 3); hypertension (n = 7); diabetes (n = 3); current cigarette smoking (n = 2); malignancy (n = 1); fertility treatment (n=1) and coagulation disorders (n = 0). Of the 28 cases, 3 died, 4 remain hospitalized, 2 have been discharged to a post-acute care facility and 19 have been discharged home.[61] These cases are similar to the thrombotic events noted after receipt of AZD1222; however, a broader demographic appears to be risk after AZD1222 vaccination.

While TTS is very rare, the risk appears to be highest in women aged 30 to 49 years. Reporting rates of TTS cases per 1 million J&J vaccine doses administered are as follows: 4.7 cases per million in 18-29 year old females; 12.4 cases per million in 30-39 year old females; 9.4 cases per million in 40-49 year old females; and 2.7 cases per million in 50-64 year old females. Reporting rates of TTS cases in males per 1 million J&J vaccine doses administered is: 2.8 cases per million in 18-29 year old males; 1.4 cases per million in 30-39 year old males; 1.3 cases per million in 40-49 year old males and 1.3 cases per million in 50-64 year old males. While the mRNA vaccines have been associated with cases of thrombosis or cases of thrombocytopenia, no cases of TTS have been reported in the almost 200 million doses administered in the U.S.[61]

Adenovirus-based vaccines - Thrombosis with thrombocytopenia syndrome

Reports of rare, but serious and potentially fatal adverse events following receipt of the adenovirus-based vaccines (i.e. JNJ-78436735, AZD1222) including CVST with thrombocytopenia started to emerge in early April. Specific case reports, patient characteristics and dispositions are discussed in the individual vaccine sections. A University of Oxford pre-published, non-peer reviewed study reported a higher incidence of CVST in patients with confirmed COVID-19 infection as compared to patients administered COVID-19 vaccines; however, only one case of CVST in patients with confirmed COVID-19 was associated with thrombocytopenia. The presence of thrombocytopenia in only one patient with confirmed COVID-19 infection suggests a different mechanism than that of case reports of CVST with thrombocytopenia associated with COVID-19 vaccines.[62]

As of late April, multiple countries have discontinued use of one or both adenovirus-based vaccines in some or all patient populations. The pathogenesis of these adverse events may be associated with platelet-activating antibodies against platelet factor 4 and resembles a heparin-induced thrombocytopenia-like immune mediated syndrome.[63,64] A recommendation to avoid the use of heparin in lieu of alternative treatments for these patients was shared in the joint FDA/CDC statement specific to the JNJ reports; however, this approach may also be prudent regarding this patient presentation following AZD1222 administration.[58] The American Society of Hematology has published **information** regarding the diagnosis and treatment of TTS related to vaccine administration.[65]

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.[66] 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.[66]

Efficacy and safety: Phase 1

Phase 1 clinical trial data[66] (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 (UK). The trial enrolled 15,000 patients between the ages of 18 and 84 years, both "with and without relevant comorbidities." Participants were 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 also received a licensed seasonal influenza vaccine as part of a co-administration sub-study. The primary efficacy analysis is 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 are 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.[67] The protocol for this phase 3 study was published October 27, 2020.

On March 11, 2021, Novavax **announced** the final analysis of phase 3 trial data from the UK.[68] This analysis is based on 106 cases, of which 96 cases were observed in the placebo group and 10 cases were observed in the NVX-CoV2373 group. Efficacy by strain was calculated to be 96.4% (95% CI, 73.8 to 99.5%) against the original COVID-19 strain and 86.3% (95% CI, 71.3 to 93.5%) against the B.1.1.7 (alpha) UK variant (post-hoc analysis). The overall efficacy of the vaccine was shown to be 89.7% (95% CI, 80.2 to 94.6%) against mild, moderate, or severe COVID-19. NVX-CoV2373 demonstrated 100% efficacy against severe disease, including hospitalization and death. In this same press release, Novavax also announced 55.4% efficacy against the South African variant (B.1.351/501Y.V2) in HIV-negative patients in the phase 2b trial conducted in South Africa. In the South African trial, the vaccine also demonstrated 100% efficacy against severe disease, including all hospitalization and death.

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.[69]

On June 14, 2021, Novavax **announced** the preliminary results of the PREVENT-19 trial. The study enrolled 29,960 participants aged 18 years and older. Efficacy endpoints were assessed from January 25 to April 30, 2021. For the primary endpoint, prevention of PCR-confirmed symptomatic COVID-19, 63 cases of COVID-19 were observed in the placebo-treated group vs. 14 cases in the NVX-CoV2373 vaccine-treated group (vaccine efficacy 90.4%; 95% CI, 82.9-94.6). Sequence data is available for 54 of the 77 cases. Of the sequenced cases, Variants of Interest accounted for 9

cases. Variants of concern accounted for 35 cases, and other variants accounted for 10 cases as defined by the CDC definition of variants. For the secondary endpoint, prevention of PCR-confirmed symptomatic moderate or severe COVID-19, 10 moderate cases and 4 severe cases were observed, all in the placebo-treated group (vaccine efficacy: 100%; 95% CI, 87.0-100). Preliminary safety data showed fatigue, headache, and muscle pain, lasting less than 2 days, were the most common systemic symptoms. The pediatric and adolescent arms recently completed enrollment with 2,248 participants.[70]

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. Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. Published online on February 9, 2021. doi: 10.1016/j.vaccine.2021.02.007.
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. 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.
29. 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.
30. 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.
31. Centers for Disease Control and Prevention. Clinical considerations for use of 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 March 5, 2021. Accessed March 26, 2021.
32. 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.
33. Wise J. Covid-19: Should we be worried about reports of myocarditis and pericarditis after mRNA vaccines? *BMJ*. 2021;373:n1635.
34. Shimabukuro T. COVID-19 Vaccine safety update. CDC website. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf. Published June 23, 2021. Accessed June 28, 2021.
35. Mansour J, Short RG, Bhalla S, et al. Acute myocarditis after a second dose of the mRNA COVID-19 vaccine: a report of two cases. *Clin Imaging*. 2021;78:247-249.

36. Larson KF, Ammirati E, Adler E, et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. *Circulation*. Published online June 16, 2021. doi: 10.1161/CIRCULATIONAHA.121.055913.
37. Snapiri O, Danziger CR, Shirman N, et al. Transient cardiac injury in adolescents receiving the BNT162b2 mRNA COVID-19 vaccine. *Pediatr Infect Dis J*. Published online June 2, 2021. doi: 10.1097/INF.0000000000003235.
38. Mouch SA, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. *Vaccine*. 2021;39(29):3790-3793.
39. Park J, Brekke DR, Bratincsak A. Self-limited myocarditis presenting with chest pain and ST segment elevation in adolescents after vaccination with the BNT162b2 mRNA vaccine. *Cardiol Young*. Published June 28, 2021. doi:10.1017/S1047951121002547.
40. Statement following CDC ACIP meeting from nation's leading doctors, nurses and public health leaders on benefits of vaccination. HHS.gov website. https://www.hhs.gov/about/news/2021/06/23/statement-following-cdc-acip-meeting-nations-leading-doctors-nurses-public-health-leaders-benefits-vaccination.html. Published June 23, 2021. Accessed June 29, 2021.
41. 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.
42. 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.
43. 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.
44. 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.
45. AstraZeneca. AZD1222 US phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AstraZeneca website. https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html. Published March 22, 2021. Accessed March 23, 2021.
46. National Institutes of Health. NIAID statement on AstraZeneca vaccine. NIH website. https://www.nih.gov/news-events/news-releases/niaid-statement-astrazeneca-vaccine. Published March 23, 2021. Accessed March 23, 2021.
47. AstraZeneca. Update following statement by NIAID on AZD1222 US phase III trial data. AstraZeneca website. https://www.astrazeneca.com/media-centre/press-releases/2021/update-following-statement-by-niaid-on-azd1222-us-phase-iii-trial-data.html. Published March 23, 2021. Accessed March 23, 2021.
48. AstraZeneca. AZD1222 US phase III primary analysis confirms safety and efficacy. AstraZeneca website. https://www.astrazeneca.com/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html**.** Published March 25, 2021. Accessed March 25, 2021.
49. European Medicines Agency. COVID-19 vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. European Medicines Agency website. https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots. Published March 18, 2021. Accessed March 23, 2021.
50. European Medicines Agency. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. European Medicines Agency website. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood**.** Published April 7, 2021. Accessed April 8, 2021.
51. UK Medicines and Healthcare Products Regulatory Agency. JCVI statement on the use of the AstraZeneca COVID-19 vaccine. UK Medicines and Healthcare Products Regulatory Agency website. https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement/jcvi-statement-on-use-of-the-astrazeneca-covid-19-vaccine-7-april-2021. Published April 7, 2021. Accessed April 8, 2021.
52. UK Medicines & Healthcare Products Regulatory Agency. Coronavirus vaccine-weekly summary of Yellow Card reporting. Medicine & Healthcare products Regulatory Agency website.

https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Published April 28, 2021. Accessed May 12, 2021.
53. Pottegard A, Lund LC, Karlstad O, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ.* 2021;373:n1114. doi: https://doi.org/10.1136/bmj.n1114.
54. JCVI advises on COVID-19 vaccine for people aged under 40. Public Health England website. https://www.gov.uk/government/news/jcvi-advises-on-covid-19-vaccine-for-people-aged-under-40. Published May 7, 2021. Accessed June 10, 2021.
55. 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.
56. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.CoV2.S vaccine against COVID-19. *N Engl J Med*. Published online ahead of print April 21, 2021. doi: 10.1056/NEJMoa2101544.
57. 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.
58. Joint CDC and FDA statement on Johnson & Johnson COVID-19 vaccine. Food and Drug Administration website. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine**.** Published April 13, 2021. Accessed April 20, 2021.
59. Reports of cerebral venous sinus thrombosis with thrombocytopenia after Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices website. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04/03-COVID-Shimabukuro-508.pdf**.** Published April 14, 2021. Accessed April 20, 2021.
60. FDA and CDC lift recommended pause on Johnson & Johnson (Janssen) COVID-19 vaccine use following thorough safety review. Food and Drug Administration website. https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough/**.** Published April 23, 2021. Accessed April 26, 2021.
61. Shimabukuro T. Updated: Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination. CDC website. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf.Published May 12, 2021. Accessed May 12, 2021.
62. Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis: a retrospective cohort study of 513,284 confirmed COVID-19 cases and a comparison with 489,871 people receiving a COVID-19 mRNA vaccine. *Open Science Framework*. https://osf.io/a9jdq**.**
63. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med*. Published online ahead of print April 9, 2021. doi: 10.1056/NEJMoa2104840.
64. Schultz NH, Sorvoll IH, Michelsen AE et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med*. Published online ahead of print April 9, 2021. doi: 10.1056/NEJMoa2104882.
65. Thrombosis with thrombocytopenia syndrome (also termed vaccine-induced thrombotic thrombocytopenia). American Society of Hematology website. https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Published April 23, 2021. Accessed April 26, 2021.
66. 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.
67. 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.
68. Novavax. Novavax confirms high levels of efficacy against original and variant COVID-19 strains in United Kingdom and South Africa trials. Novavax website. 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-confirms-high-levels-efficacy-against-original-and-0. Published March 11, 2021. Accessed March 24, 2021.
69. 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.
70. Novavax. Novavax COVID-19 Vaccine Demonstrates 90% Overall Efficacy and 100% Protection Against Moderate and Severe Disease in PREVENT-19 Phase 3 Trial. Novavax website. https://ir.novavax.com/2021-06-14-Novavax-COVID-19-Vaccine-Demonstrates-90-Overall-Efficacy-and-100-Protection-Against-Moderate-and-Severe-Disease-in-PREVENT-19-Phase-3-Trial**.** Published June 14, 2021. Accessed June 25, 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 2 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

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
Chu L, et al Phase 2 trial (NCT04405076)	600	Inclusion criteria • Healthy adults aged ≥ 18 y old • BMI, 18-30 kg/m^2 • No previous history of SARS-CoV-2 infection **Baseline characteristics** ≥18-<55 y old cohort • Female, n = 117 (59%) • Age, mean: 37.4 y • White, n = 277 (92%) • BMI, mean (SD): 25.2(3) ≥55 y old cohort • Female, n = 213 (71%) • Age, mean: 64.3 y • White, n = 292 (97%) • BMI, mean (SD): 25.4(3)	**Intervention group** 2 injections of mRNA-1273 given 28 d apart at 2 different dose levels ≥18-<55 y old cohort • 50 mcg (n = 100) • 100 mcg (n = 100) • Placebo (n = 100) ≥55 y old cohort • 50 mcg (n = 100) • 100 mcg (n = 100) • Placebo (n =100)	Anti-SARS-CoV-2-spike binding antibody levels **Day 43 (14 d after dose 2)** ≥18-<55 y old cohort, GM mean (95% CI) peak levels • 50 mcg: 189 (173-207) • 100 mcg: 239 (221-259) • Convalescent plasma: 48 (38-60) ≥55 y old cohort, GM mean (95% CI) peak levels • 50 mcg: 153 (135-175) • 100 mcg: 162 (142-185) • Convalescent plasma: 48 (38-60) In both cohorts, binding antibody levels exceed that of convalescent plasma through day 57 (28 d after dose 2) Seroconversion rates, based on SARS-CoV-2 specific neutralizing antibody response **Day 43 (14 d after dose 2)** ≥18-<55 y old cohort • 50 mcg: 100% • 100 mcg: 100% ≥55 y old cohort • 50 mcg: 100% • 100 mcg: 100%	Pain at injection site, dose 1 • 50 mcg, young cohort (73%); older cohort (58%) • 100 mcg, young cohort (86%); older cohort (81%) Pain at injection site, dose 2 • 50 mcg, young cohort (80%); older cohort (79%) • 100 mcg, young cohort (90%); older cohort (81%) Most common systemic AE after dose 1 was headache (29% and 25% for 50 mcg and 100 mg in young cohort vs. 29% and 18%, respectively in older cohort). Fatigue was also commonly reported after dose 1 (24% and 30% for 50 mcg and 100 mcg in young cohort vs. 24% and 20%, respectively in older cohort). Incidence of headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills were higher after dose 2 vs. dose 1. Most common grade 3 AEs after dose 2: Fatigue (9.1%), myalgia (7.6%)
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)
				
				Note: There were no confirmed cases of COVID-19 in adolescents aged 12-15 years who received the BNT162b2 vaccine (VE = 100%; 95% CI: 75.3 to 100 for adolescents without prior evidence of infection and 95% CI: 78.1 to 100 for adolescents with or without evidence of prior SARS-CoV-2 infection).
				
				Secondary efficacy endpoint
				
				Severe COVID-19 disease: 10 cases observed after the first dose (1 vaccine; 9 placebo)
				
				Safety 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]	**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**

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	**Discontinuation and Safety**
				○ ChAdOx1 Prime-Boost (n = 10): 137 [IQR: 46.4, 206.8] ○ MenACWY (n = 44): 1 [1, 1] • Day 28: ○ ChAdOx1 Prime (n = 127): 157.1 [IQR: 96.2, 316.9] ○ ChAdOx1 Prime-Boost (n = 10): 210.7 [IQR: 149.4. 321.6 9] ○ MenACWY (n = 130): 1 [1, 1] • Day 56: ○ ChAdOx1 Prime (n = 43): 119 [IQR: 70.3, 203.4] ○ ChAdOx1 Prime-Boost (n = 10): 639.2 [IQR: 360, 792.2] ○ MenACWY (n = 44): 1 [1, 2.6] ***Note:*** EU values were obtained from CP and were not reported in text. However, ChAdOx1 Prime & ChAdOx1 Prime-Boost responses at 14-56 d were visually within the range of values obtained from CP. **Anti-SARS-CoV-2 neutralizing antibodies: PHE MNA_{80}** • Day 28: ○ ChAdOx1 Prime (n = 35): 51 [IQR:32, 103]; **Note:** Neutralizing antibodies were detected in 32/35 (91%) with the PHE MNA_{80} assay ○ ChAdOx1 Prime-Boost (n = 10): 70 [IQR: 32.8, 168] ○ MenACWY (n = 2): 10 [10, 10]	• ChAdOx1 + paracetamol: n = 27 (48%) • ChAdOx1: n = 294 (60%) • MenACWY+ paracetamol: n = 15 (26%) • MenACWY: n = 118 (25%) **Malaise** • ChAdOx1 + paracetamol: n = 27 (48%) • ChAdOx1: n = 296 (61%) • MenACWY+ paracetamol: n = 6 (11%) • MenACWY: n = 83 (17%)

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
				Anti-SARS-CoV-2 neutralizing antibodies: PHE $PRNT_{50}$ • Day 28: o ChAdOx1 Prime (n = 35): 218 [IQR: 122, 395]; **Note:** Neutralizing antibodies were detected in 35/35 (100%) with the PHE $PRNT_{50}$ assay o 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-19 • Currently working in an occupation with a high risk to SARS-CoV-2 exposure (cohorts 1&3 only)	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 2 trial	1,210	For full inclusion and exclusion criteria, see **NCT04535453** Inclusion criteria, adults • 18-55 y and healthy or ≥65 y with good/stable health • BMI <30 kg/m^2 • Participants of child bearing potential must have negative pregnancy test prior to study vaccine administration. • Will not donate bone marrow, blood/blood products until 3 mo after last dose of study vaccine Adolescents • 12-17 yo and healthy • Must not have comorbidities related to an increase risk of severe COVID-19	16 groups • 2-dose regimen at different dose levels or single-dose regimen at different dose levels or placebo on 1 and 57 d • 2-dose regimen at fixed-dose level or placebo on 1 and 29 day • 1-dose or 2-dose regimen at fixed dose level or placebo on 1 and 57 d. Plus a booster or placebo at 12 mo post first vaccine. • 1-dose or 2-dose regimen at fixed dose level or placebo on 1 and 57 d. Plus a booster or placebo at 12 mo post first vaccine.	**Primary outcomes** • Multiple outcomes listed. Refer to **NCT04535453** **Secondary outcomes** • Multiple outcomes listed. Refer to **NCT04535453**	

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 3 trial Ad26.COV2.S (JNJ-78436735) ENSEMBLE	44,325	For full inclusion and exclusion criteria, see **NCT04505722** Inclusion criteria • ≥ 18 y • Contraceptive use consistent with regulations on acceptable methods for those participating in clinical trials • Those of child bearing potential must have negative pregnancy test prior to study vaccine administration • Will not donate bone marrow, blood/blood products until 3 mo after last dose of study vaccine Exclusion criteria • Clinically significant acute illness • Live attenuated vaccines 28 d before/after study vaccine or non-live vaccine 14 d before/after study vaccine • Previously received a Coronavirus vaccine • Receive other investigational medications/devices within defined timeframes	Treatment • $5X10^{10}$ vp administered intramuscularly X 1 Placebo • Placebo administered intramuscularly X 1	**Primary efficacy endpoints** Efficacy of JNJ-78436735 against moderate to severe/critical COVID-19, 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 results: VE of 72% (95% CI, 58.2-81.7) **Secondary efficacy endpoints** Efficacy of JNJ-78436735 against symptomatic (mild to severe) COVID-19 without previous SARS-CoV-2 infection, 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) Planned analysis: Efficacy of JNJ-78436735 against severe/critical COVID-19 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) COVID-19-related deaths: 7 in placebo group vs. 0 in vaccine group **Safety endpoints** • Reactogenicity subset (n = 6,736): Most common solicited adverse drug events: injection site pain (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). • Local adverse events: mostly grade 1 or 2 severity; <0.5% incidence of grade 3 events. • There were numeric imbalances with more events in vaccine vs. placebo group for: thromboembolic events; seizures; and tinnitus.	

Study Design	N	Patient Selection	Treatment Interventions	Main results	
				Immunogenicity	Discontinuation and Safety
Phase 3 trial Ad26.COV2.S (JNJ-78436735) ENSEMBLE 2	30,000	For full inclusion and exclusion criteria, see **NCT04614948** Inclusion criteria • ≥ 18 y • Contraceptive use consistent with regulations on acceptable methods for those participating in clinical trials • Those of child bearing potential must have negative pregnancy test prior to study vaccine administration • Will not donate bone marrow, blood/blood products until 3 mo after last dose of study vaccine Exclusion criteria • Clinically significant illness • Known/suspected allergy or other serious AE to vaccines or their excipients • Live attenuated vaccines 28 d before/after study vaccine or non-live vaccine 14 d before/after study vaccine • Previously received a Coronavirus vaccine • Receive other investigational medications/devices within defined timeframes	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 (14 d after second dose) Secondary outcomes to be measured • First occurrence of molecularly confirmed moderate to severe/critical COVID-19 regardless of serostatus • First occurrence of molecularly confirmed moderate to severe/critical COVID-19 regardless of serostatus after 2nd vaccination (71 d) • First occurrence of molecularly confirmed moderate to severe/critical COVID-19 after 1st vaccination who were seronegative at baseline • First occurrence of molecularly confirmed moderate to severe/critical COVID-19 who were seronegative at baseline after 2nd vaccination (71 d) • First occurrence of COVID-19 requiring medical intervention • SARS-COV-2 viral/load in participant with molecularly confirmed, moderate to severe/critical COVID-19 • First occurrence of molecularly confirmed mild COVID-19 • First occurrence of molecularly confirmed COVID-19 defined by the US FDA harmonized case definition • Burden of disease based on first occurrence of molecularly confirmed symptomatic COVID-19 • Serologic conversion between baseline and 14 d, 6 mo and 1 yr after the 2nd vaccine using ELISA • First occurrence of SARS-CoV-2 infection • SAE • Medically-attended AE • Medically-attended AEs leading to study discontinuations • Solicited local AEs during 7 d following each vaccination • Solicited systemic AEs during 7 d following each vaccination • Unsolicited local AEs during 28 d following each vaccination • SARs-CoV-2 binding antibodies assessed by ELISA	

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

Study Design	N	Patient Selection	Treatment Interventions	Main results

Retrospective cohort study , BNT162b2 vaccine
 	
Israel
 	
Dec 2020 – Jan 2021
	9,109	• All HCWs at Sheba Medical Centre—Israel's largest hospital—not having previously been infected with SARS-CoV-2 were deemed eligible to receive the BNT162b2 vaccine	• Comparison of vaccinated vs. unvaccinated HCWs
			  ○ 9,109 eligible staff
			  ○ 7,214 (79%) received dose 1
			  ○ 6,037 (84% of staff who received dose 1) received dose 2
			  ○ Almost all (n=5,505, 91%) of fully vaccinated HCWs received second dose on days 21 or 22 after first dose
			• Active daily symptom reporting and immediate same-day testing allowed for investigation of exposed or symptomatic HCWs
			• HCWs testing positive for SARS-CoV-2 on PCR but remaining asymptomatic were defined as cases of "SARS-CoV-2 infection"
			• Symptomatic HCWs were defined as cases of "COVID-19"
				• n=170 SARS-CoV-2 infections
				  ○ n=99 (58%) of which were symptomatic
				  ○ n=81 (48%) were vaccinated
				  ○ n=78 (46%) tested positive after first dose
				  ○ n=3 (2%) tested positive after second dose
				• n=125 infections could be traced
				  ○ n=87 (70%) community acquired
				• Adjusted* rate reductions of SARS-CoV-2 infection (all cases, symptomatic and not):
				  ○ 30% (95% CI, 2-50) within the first 14 days of receiving first dose
				  ○ 75% (95% CI, 72-84), 15 to 28 days after first dose
				• Adjusted* rate reductions of symptomatic SARS-CoV-2 infection:
				  ○ 47% (95% CI, 17-66) within the first 14 days of receiving first dose
				  ○ 85% (95% CI, 71-92), 15 to 28 days after first dose
				
				*rate ratios adjusted for community exposure rates using Poisson regression

Study Design	N	Patient Selection	Treatment Interventions	Main results
Observational study, BNT162b2 vaccine Israel Dec 2020 – Feb 2021	1,193,236	• n=596,618 newly vaccinated persons aged 16 and older (median age 45, IQR 55-62) matched in a 1:1 ratio to an unvaccinated control, using data repositories of Clalit Health Services—Israel's largest Health Care organization • Patients matched based on variables associated with the probability of both vaccination and infection or severity of COVID-19 (e.g. age, sex, neighborhood of residence) • Population groups for which there was a high variability in the probability of exposure or outcomes (i.e. those at extreme ends of the spectrum) and for which controlling for these was not feasible (e.g. nursing home residents, persons medically confined to the home, health care workers) were excluded	• The following outcomes were compared between vaccinated and unvaccinated cohorts ○ Documented SARS-CoV-2 infection (PCR confirmed) ○ Symptomatic COVID-19 ○ Hospitalization for COVID-19 ○ Severe COVID-19 (NIH criteria) ○ Death from COVID-19 • Investigators also performed a supplementary analysis, in which SARS-CoV-2 infection without documented symptoms was used as "an imperfect proxy for asymptomatic infection."	• At days 14 through 20 after the first dose of BNT162b2, estimated VE (95% CI) for the study outcomes was as follows: ○ documented infection, 46% (40 to 51) ○ symptomatic COVID-19, 57% (50 to 63) ○ hospitalization, 74% (56 to 86) ○ severe illness, 62% (39 to 80) ○ death, 72% (19 to 100) • In the follow-up period starting 7 days after the second dose, the estimated VE (95% CI) for the study outcomes was as follows: ○ documented infection, 92% (88 to 95) ○ symptomatic COVID-19, 94% (87 to 98) ○ hospitalization, 87% (55 to 100) ○ severe disease, 92% (75 to 100) • For the asymptomatic infection proxy, estimated vaccine effectiveness was 29% (95% CI, 17 to 39) at days 14 through 20 after the first dose and 90% (95% CI, 83 to 94) at 7 or more days after the second dose.

Study Design	N	Patient Selection	Treatment Interventions	Main results
Observational study, BNT162b2 Israel MoH Jan 2021 – Mar 2021	Unspecified	Analysis by the Israel MoH of individuals fully vaccinated with the Pfizer-BioNTech vaccine	• De-identified aggregate Israel MoH public health surveillance data used to compare lab-confirmed SARS-CoV-2 outcomes between vaccinated and unvaccinated persons • VE estimates, adjusted for age, gender, and week specimens collected, determined for: ○ SARS-CoV-2 infection (symptomatic and asymptomatic) ○ Asymptomatic SARS-CoV-2 ○ COVID-19 cases (symptomatic only) ○ COVID-19 hospitalizations ○ Severe and critical COVID-19 hospitalizations (see Pfizer/BioNTech announcement for definitions) • COVID-19 deaths	Limited information available through Pfizer website; claims include: • VE two weeks after second dose of vaccine at least 97% in preventing symptomatic disease, severe/critical disease, and death • Analysis conducted when more than 80% of tested specimens in Israel were variant B.1.1.7(alpha), providing real-world evidence of efficacy against this variant • Data suggest Pfizer-BioNTech vaccine prevents asymptomatic SARS-CoV-2 infection • "Latest data analysis finds unvaccinated individuals were 44 times more likely to develop symptomatic COVID-19 and 29 times more likely to die from COVID-19"
Observational study, BNT162b2, mRNA-1273 U.S. CDC Dec. 2020-Mar 2021	3,950	• Essential workers without previous documented illness • Self-collection of nasal swabs weekly Baseline Demographics • Female: 62.1% • 18-49 y: 71.9% • Caucasian: 86.3% • Non-Hispanic: 82.9% • No chronic conditions: 68.9%	• 2,479 (62.8%) received both recommended mRNA vaccines • 477 (12.1%) received only 1 dose by study end Vaccine • BNT162b2: 62.7% • mRNA-1273:29.6% • Unknown: 7.7%	• SARS-CoV-2 infection was diagnosed in 205 (5.2%) participants • Majority (87.3%) were associated with symptoms consistent with COVID-19-associated illness; 10.7% were asymptomatic • 22.9% of infections were medically attended; including 2 hospitalizations; 0 deaths Infection rates • During unvaccinated period, the incidence rate for infection was 1.38/1,000 person-days • For the period ≥ 14 d after first dose and before second dose, the incidence rate for infection was 0.19/1,000 person-days. Estimated adjusted VE: 80% (95% CI, 59-90) • For the period ≥ 14 d after second dose, the incidence rate for infection was 0.04/1,000 person-days. Estimated adjusted VE: 90% (95% CI, 68-97)

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