参考資料１３

Vaccines and Related Biological Products Advisory Committee Meeting

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U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Effectiveness and Safety of Novavax COVID-19 Vaccine in Adults ≥ 18 Years of Age *Emergency Use Authorization Request*

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Outline

- Background
- Study 301
  - Design
  - Efficacy
  - Safety
- Additional Safety Data
- Summary of Benefits and Risks
- Question for VRBPAC

Novavax COVID-19 vaccine

Dose	5µg of SARS-CoV-2 recombinant spike (rS) protein with 50 µg Matrix-M adjuvant per dose

Regimen	Two intramuscular doses (0.5 mL) administered 3 weeks apart

Overview of Clinical Studies

Study Number/ Country	Description	NVX recipients in pre-crossover safety population	Study Status
Study 301 USA, Mexico	**Phase 3, randomized, observer-blinded, placebo-controlled efficacy, safety, immunogenicity study**	**19735**	**Ongoing**
	Additional Safety Data		
Study 302 United Kingdom	Phase 3, multicenter, randomized, observer-blinded, placebo-controlled study in adults 18-84 years of age	7569	Ongoing
Study 501 South Africa	Phase 2, randomized, observer-blinded, placebo-controlled study in healthy HIV-negative adults 18-84 years of age and HIV-positive adults 18-64 years of age	2211	Ongoing
Study 101, Part 1 Australia	Phase 1, randomized, observer-blinded, placebo-controlled in adults 18-59 years of age	29	Completed
Study 101, Part 2 Australia/USA	Phase 2, randomized, observer-blinded, placebo-controlled in adults 18-84 years of age	513	Ongoing

301: Study Design

Ongoing randomized, observer-blind, placebo-controlled Phase 3 efficacy, safety, and immunogenicity study in the US and Mexico

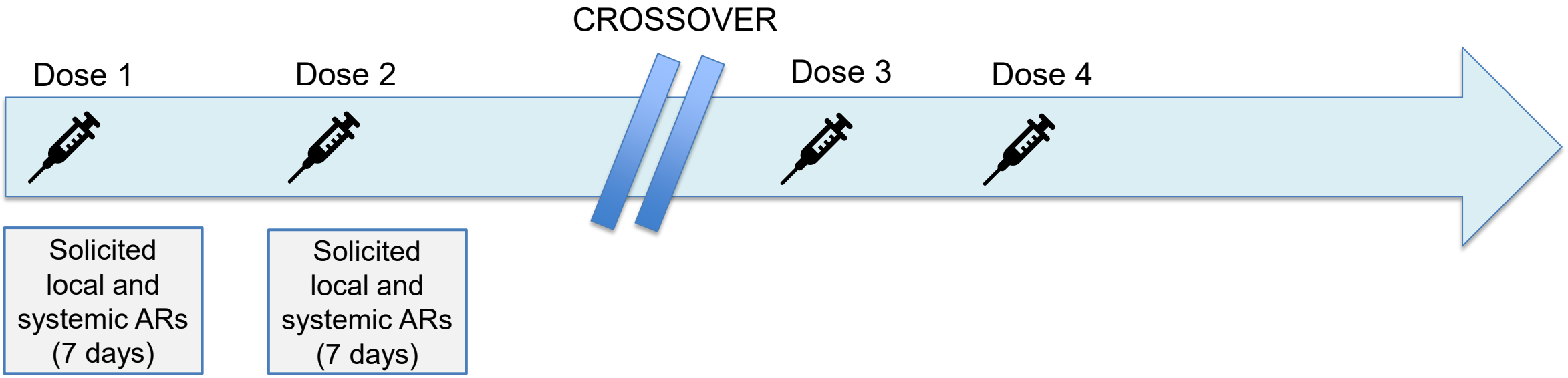
29,945 participants ≥ 18 years of age at substantial risk of exposure to and infection with SARS-CoV-2 (stratified by age: 18-64 years and ≥65 years)

Randomized 2:1

Pre-crossover	Post-crossover
NVX-CoV2373 [NVX] 	Placebo (normal saline) 

Pre-crossover	Post-crossover
Placebo (normal saline) 	NVX-CoV2373 [NVX] 

301: Safety Data Collection



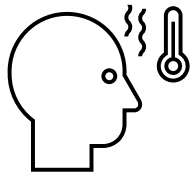
Unsolicited and medically attended AEs (through 28 days post-Dose 2)

Unsolicited and medically attended AEs (through 28 days post-Dose 2)

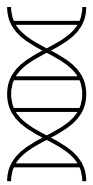
Medically attended AEs attributed to study vaccine, serious AEs, and AEs of special interest (defined as COVID-related AEs and potential immune mediated medical conditions) for the duration of the study in all participants

301: Efficacy Assessments

Efficacy was assessed through daily surveillance of symptoms suggestive of COVID-19 throughout the study follow-up



Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal swab.



Molecular confirmation of SARS-CoV-2 infection (using the Abbott Real Time SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) assay) by the central laboratory was required to meet the primary and secondary efficacy endpoint case definitions.

301: Efficacy Endpoints

Primary Efficacy Analysis Endpoint	Statistical success criteria
First episode of PCR-confirmed mild, moderate, or severe COVID-19 with onset ≥7 days after Dose 2 (data from up to the blinded crossover period)	Point estimate of vaccine efficacy (VE) ≥50% efficacy AND lower bound of 95% CI >30% (relative risk ≤70%)

Secondary or Exploratory Efficacy Endpoints
First episode of PCR-confirmed COVID-19, as defined in the primary endpoint, by gene sequencing to represent a variant not considered as a "variant of concern / interest" according to the CDC Variants Classification
First episode of PCR-confirmed moderate or severe COVID-19, as defined in the primary endpoint
VE according to race and ethnicity

301: COVID-19 Case Definitions

Mild	Moderate	Severe
• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough OR ≥2 additional COVID-19 symptoms: • New onset or worsening of shortness of breath or difficulty breathing compared to baseline • New onset fatigue • New onset generalized muscle or body aches • New onset headache • New loss of taste or smell • Acute onset of sore throat, congestion, and runny nose • New onset nausea, vomiting, or diarrhea	• High fever (≥38.4°C) for ≥3 days (regardless of use of anti-pyretic medications, need not be contiguous days) • Any evidence of significant LRTI: ○ Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) ○ Tachypnea: 24 to 29 breaths per minute at rest ○ SpO2: 94% to 95% on room air ○ Abnormal chest X-ray or chest computerized tomography consistent with pneumonia or LRTI ○ Adventitious sounds on lung auscultation crackles/rales, wheeze, rhonchi, pleural rub, stridor)	• Tachypnea: ≥30 breaths per minute at rest • Resting heart rate ≥125 beats per minute • Oxygen saturation ≤93% on room air or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen <300 mm Hg • High flow oxygen therapy or non-invasive ventilation/non-invasive positive pressure ventilation (e.g., continuous positive airway pressure or bilevel positive airway pressure) • Mechanical ventilation or extracorporeal membrane oxygenation • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: ○ Acute respiratory distress syndrome, renal failure, hepatic failure, right or left heart failure, septic or cardiogenic shock, stroke, thrombotic event, myocardial infarction, deep vein thrombosis, pulmonary embolism ○ Requirement for: vasopressors, systemic corticosteroids, or hemodialysis. ○ Admission to an intensive care unit ○ Death

301: Datasets to Support EUA

FDA conducted independent analyses of datasets with different cut-off/extraction dates:

- Cleaned efficacy and safety data with cutoff of September 27, 2021
- Safety data (by FDA request for review of clinically important safety events) with extraction date of February 17, 2022, not fully cleaned

301: Disposition

Disposition*	NVX-CoV2373 N=19963	Placebo N=9882	Total N=29945
Randomized, n (%)	19963	9982	**29945**
Treated, n (%)	19714 (100)	9868 (100)	**29582 (100)**
Blinded, placebo-controlled follow-up period, n (%)	--	--	**--**
Completed 2 doses	19087 (96.8)	9440 (95.7)	**28527 (96.4)**
Discontinued	2407 (12.2)	2192 (22.2)	**4599 (15.5)**
Blinded crossover period, n (%)	--	--	**--**
Did not receive NVX-CoV2373 or placebo	4395 (22.3)	3473 (35.2)	**7868 (26.6)**
Crossed over to receive NVX-CoV2373 or placebo	15319 (77.7)	6395 (64.8)	**21714 (73.4)**
Completed dose 4	15103 (76.6)	6327 (64.1)	**21431 (72.4)**
Discontinued	666 (3.4)	194 (2.0)	**860 (2.9)**

*Full analysis set population

301: Efficacy Analysis Populations

Population	NVX-CoV2373 n (%)	Placebo n (%)	Total n (%)
ITT	19963	9982	29945
PP-EFF	17272 (87.6)	8385 (85.0)	25657 (86.7)
Excluded from PP-EFF	2442 (12.4)	1483 (15.0)	3925 (13.3)
Baseline positive anti-NP result	1100 (5.6)	622 (6.3)	1722 (5.8)
PP-EFF-2	18438 (93.5)	9035 (91.6)	27473 (92.9)
Excluded from PP-EFF-2	1276 (6.5)	833 (8.4)	2109 (7.1)

Intention to Treat (ITT) Set: All participants randomized into the study

Per-protocol efficacy (PP-EFF): All participants who received the full prescribed regimen of study vaccine/ placebo, had no major protocol deviations prior to first COVID-19 positive episode or administrative censoring, with no confirmed infection or prior infection due to SARS-CoV-2 at baseline and not censored prior to the start of the observation period

PP-EFF-2: includes participants in the PP-EFF regardless of baseline SARS-CoV-2 status as determined by PCR

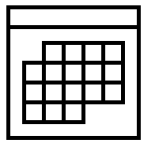
301: Efficacy Analysis Population: Demographics

	NVX-CoV2373 N=17272	Placebo N=8385	Total N=25657
Sex	48% female	50% female	49%
Median age	47.0 years	47.0 years	47.0 years
≥65 years	12%	12%	12%
Race/Ethnicity	76% White, 11% African American, 6% American Indian or Alaska Native, 4% Asian; 22% Hispanic	76% White, 11% African American, 6% American Indian or Alaska Native, 5% Asian; 22% Hispanic	76% White, 11% African American, 6% American Indian or Alaska Native, 4% Asian; 22% Hispanic
Countries	US (94%), Mexico (6%)	US (94%), Mexico (6%)	US (94%), Mexico (6%)
Co-morbidities	Obesity: 37% Chronic kidney disease: 1% Chronic lung disease: 14% Cardiovascular disease: 1% DM Type 2: 8%	Obesity: 40% Chronic kidney disease: 1% Chronic lung disease: 15% Cardiovascular disease: 1% DM Type 2: 8%	Obesity: 37% Chronic kidney disease: 1% Chronic lung disease: 15% Cardiovascular disease: 1% DM Type 2: 8%
High-risk*	95%	95%	95%

DM= Diabetes mellitus; Obesity= Body mass index >30 kg/m^3

* High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances

301: Efficacy Analyses



The primary efficacy endpoint was assessed until a participant received the first blinded, crossover vaccination or until the data cutoff of September 27, 2021, whichever came first.

In the Per-Protocol Efficacy Set, during the pre-crossover period, 21.7% of the participants who received placebo were additionally unblinded with the intention to receive a COVID-19 vaccine under EUA as compared to 13.2% of the participants who received NVX-CoV2373. Participants who were unblinded to receive a COVID-19 vaccine under EUA were censored from the efficacy analyses at the time of unblinding.

301: Primary Efficacy Analysis

Vaccine Efficacy in Protecting Against PCR-Confirmed Mild, Moderate, or Severe COVID-19 With Onset From 7 Days After Second Injection, Per-Protocol Efficacy Set

Age Group	NVX-CoV2373 n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Placebo n/N (%) (Mean Incidence Rate/ 1000 Person-Years)	Vaccine Efficacy (95% CI)
All participants	17/17272 (0.098) (4.34)	79/8385 (0.942) (45.25)	90.41 (83.81, 94.32)
18 to <65 years	15/15228 (0.099) (5.70)	75/7417 (1.011) (63.69)	91.06 (84.44, 94.87)
≥65 years	2/2044 (0.098) (5.76)	4/968 (0.413) (26.52)	78.63 (-16.64, 96.08)

VE(%) =100 × (1-RR); RR is ratio of incidence rates of active group relative to the placebo arm (NVX-CoV2373/placebo) with first occurrence of event with onset during a surveillance period from 7 days after second injection up to censor date.

	NVX-CoV2373 cases	Placebo cases
Mild	17	66
Moderate	0	9
Severe	0	4

301: Efficacy Analysis: ≥65 years of age

The limited number of cases (n=6) in participants ≥65 years of age precluded a conclusive assessment of efficacy in this subgroup. A post-hoc supportive analysis of vaccine efficacy among participants 50-64 years of age was conducted at FDA's request, and neutralizing antibody titers in participants 50-64 years of age were compared descriptively to those in participants ≥65 years of age.

SARS-CoV-2 Neutralizing GMTs at Baseline (Day 0) and 14 Days After Second Vaccination in Participants 50-64 Years of Age, Per Protocol Immunogenicity Analysis Set

Timepoint	NVX-CoV2373 Participants 50-64 Years N=144	NVX-CoV2373 Participants ≥65 Years N=358	GMR
Day 0 (baseline)	--	--	--
GMT	10.2	10.4	--
95% CI	9.8, 10.7	10.0, 10.9	--
Day 35	--	--	--
GMT	978.6	899.8	--
95% CI	770.5, 1243.0	762.9, 1061.3	--
GMR ($GMT_{\geq 65\ Years}/GMT_{50\text{-}64\ Years}$)	--	--	**0.91**
95% CI	--	--	**0.68, 1.2**

Abbreviations: CI=confidence interval; GMR=geometric mean ratio; GMT=geometric mean titer; MN=microneutralization assay, SARS-CoV-2 strain: Wuhan-Hu-1.
N=number of SARS-CoV2 baseline seronegative 50-64 and ≥65-year-olds. Baseline defined as the last non-missing assessment prior to the study vaccine administration.

VE estimate for 50-64 years of age: 90.7% [95% CI 72.9, 96.8])

301: Secondary Efficacy Analyses

Secondary Efficacy Analysis	Results
Efficacy Against COVID-19 Among Variants	Of the 96 cases in the primary efficacy analysis, 75 had sequence data available, the majority of which were Alpha (53%), Iota (11%), or Epsilon (7%). **Currently, none of the variants identified in the primary efficacy analysis are considered variants of concern (VOC)/variants of interest (VOI).**
Vaccine Efficacy in Protecting Against PCR-Confirmed Moderate to Severe COVID-19	A total of 13 moderate to severe COVID-19 cases were reported in the placebo arm, and none were reported in the NVX arm, resulting in VE of 100% (95% CI 85.4, 100.0).
Subgroup Analyses of Vaccine Efficacy	The point estimate of VE across the subgroups was comparable to the overall study population; however, lower efficacy rates were observed for participants of Hispanic or Latino ethnicity (VE= 77.0% [95% CI 48.7, 90.0]).

301: Safety Analysis Population

The safety analysis population included participants who received at least 1 dose of NVX-CoV2373 (data cutoff September 27, 2021)

Population	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29582	Blinded Crossover NVX to Placebo N=15298	Blinded Crossover Placebo to NVX N=6371	Blinded Crossover Total N=21669
First vaccination series	--	--	--	--	--	--
Completed 2 doses, n	19111	9416	28527	NA	NA	NA
Median follow up post-Dose 2, months	**2.5**	**2.5**	**2.5**	NA	NA	NA
Completed at least 2 months follow up post-Dose 2[1], n (%)	**14825 (77.8)**	**6852 (72.8)**	**21677 (76.0)**	NA	NA	NA
Crossover vaccination series	--	--	--	--	--	--
Completed 4 doses, n	NA	NA	NA	15084	6303	21387
Median follow up post-Dose 4, months	NA	NA	NA	**4.4**	**4.4**	**4.4**
Completed at least 2 months follow up post-Dose 4[2], n (%)	NA	NA	NA	**14934 (99.0)**	**6244 (99.1)**	**21178 (99.0)**

*At FDA's request, the Sponsor provided additional safety data through an extraction date of **February 17, 2022**, for evaluation of clinically important adverse events (**median post-crossover follow-up duration of 8.4 months** after the completion of the 2-dose crossover series)*

301: Safety Analysis Population: Demographics

	NVX-CoV2373 N=19735	Placebo N=9847	Total N=29945
Sex	48% female	49% female	48% female
Median age	47.0 years	47.0 years	47.0 years
≥65 years	13%	13%	13%
Race/Ethnicity	75% White, 12% African American, 7% American Indian or Alaska Native, 4% Asian; 22% Hispanic	75% White, 12% African American, 7% American Indian or Alaska Native, 4% Asian; 22% Hispanic	75% White, 12% African American, 7% American Indian or Alaska Native, 4% Asian; 22% Hispanic
Countries	US (94%), Mexico (6%)	US (94%), Mexico (6%)	US (94%), Mexico (6%)
Co-morbidities	Obesity: 37% Chronic kidney disease: 1% Chronic lung disease: 14% Cardiovascular disease: 1% DM Type 2: 8%	Obesity: 40% Chronic kidney disease: 1% Chronic lung disease: 15% Cardiovascular disease: 1% DM Type 2: 8%	Obesity: 37% Chronic kidney disease: 1% Chronic lung disease: 14% Cardiovascular disease: 1% DM Type 2: 8%
High-risk	94%	93%	93%

DM= Diabetes mellitus; Obesity= Body mass index >30 kg/m^3

* High-risk adults were defined as 1) age ≥65 years with or without comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances; 2) age <65 years with comorbidities and/or living or working conditions involving known frequent exposure to SARS-CoV-2 or to densely populated circumstances

301: Safety- Solicited reactogenicity

Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set

	NVX-CoV2373 Dose 1 N=18135	Placebo Dose 1 N=8982	NVX-CoV2373 Dose 2 N=17196	Placebo Dose 2 N=8339
Any solicited local reaction, n (%)	--	--	--	--
Any (Grade ≥1)	10494 (57.9)	1900 (21.2)	13524 (78.7)	1802 (21.6)
Grade 3	196 (1.1)	22 (0.2)	1141 (6.6)	24 (0.3)
Grade 4	0	0	5 (<0.1)	1 (<0.1)
Any solicited systemic reaction, n (%)	--	--	--	--
Any (Grade ≥1)	8614 (47.5)	3593 (40.0)	11920 (69.3)	2990 (35.9)
Grade 3	419 (2.3)	187 (2.1)	2058 (12.0)	170 (2.0)
Grade 4	15 (0.1)	4 (<0.1)	18 (0.1)	5 (0.1)

301: Safety- Solicited local reactogenicity

Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants 18 to <65 Years of Age

Event	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Pain/tenderness, (%)	--	--	--	--
Any (Grade ≥1)	60.5	21.7	80.8	22.1
Grade 3	1.1	0.2	6.3	0.3
Grade 4	0	0	<0.1	<0.1
Erythema, (%)	--	--	--	--
Any (Grade ≥1)	1.0	0.3	6.9	0.4
Grade 3	<0.1	0	0.9	<0.1
Grade 4	0	0	0	0
Swelling, (%)	--	--	--	--
Any (Grade ≥1)	0.9	0.3	6.2	0.3
Grade 3	<0.1	<0.1	0.5	<0.1
Grade 4	0	0	0	0

Frequency of Solicited Local Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants ≥65 Years of Age

Event	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Pain/tenderness, (%)	--	--	--	--
Any (Grade ≥1)	37.9	15.7	61.4	16.5
Grade 3	0.6	0.3	2.1	0.1
Grade 4	0	0	0	0
Erythema, (%)	--	--	--	--
Any (Grade ≥1)	0.7	0.5	4.8	0.4
Grade 3	0	0	0.3	0
Grade 4	0	0	0	0
Swelling, (%)	--	--	--	--
Any (Grade ≥1)	0.8	0.1	5.4	0.4
Grade 3	<0.1	0	0.4	0.1
Grade 4	0	0	0	0

- Pain: Grade 1: Does not interfere with activity; Grade 3: Any use of narcotic pain reliever or prevents daily activity; and Grade 4: Emergency room visit or hospitalization.
- Tenderness: Grade 1: Mild discomfort to touch; Grade 3: Significant discomfort at rest; and Grade 4: ER visit or hospitalization.
- Erythema: Grade 1: 2.5 to 5 cm; Grade 3: >10 cm; and Grade 4: Necrosis or exfoliative dermatitis.
- Swelling/induration: Grade 1: 2.5 to 5 cm and does not interfere with activity; Grade 3: >10 cm or prevents daily activity; and Grade 4: Necrosis.

301: Safety- Solicited systemic reactogenicity

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants 18 to <65 Years of Age

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Any solicited systemic reaction, (%)	--	--	--	--
Any (Grade ≥1)	49.7	41.2	72.1	36.9
Grade 3	2.4	2.2	13.0	2.1
Grade 4	0.1	0.1	0.1	0.1
Fatigue/malaise, (%)	--	--	--	--
Any (Grade ≥1)	30.8	26.6	58.3	25.7
Grade 1	15.1	13.1	16.9	12.1
Grade 2	14.1	12.1	30.8	12.0
Grade 3	1.6	1.4	10.5	1.6
Grade 4	0.1	<0.1	0.1	<0.1
Headache, (%)	--	--	--	--
Any (Grade ≥1)	26.2	23.7	47.1	20.3
Grade 1	19.9	18.3	24.9	15.0
Grade 2	5.5	4.7	18.8	4.8
Grade 3	0.8	0.7	3.3	0.5
Grade 4	<0.1	<0.1	<0.1	<0.1
Muscle pain (myalgia), (%)	--	--	--	--
Any (Grade ≥1)	24.1	13.6	50.7	12.2
Grade 1	17.8	9.6	22.9	8.3
Grade 2	5.8	3.6	22.5	3.5
Grade 3	0.5	0.4	5.3	0.4
Grade 4	<0.1	<0.1	<0.1	0.1

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants ≥65 Years of Age

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Any solicited systemic reaction, (%)	--	--	--	--
Any (Grade ≥1)	32.2	31.5	48.7	28.2
Grade 3	1.6	1.1	4.4	1.5
Grade 4	<0.1	0	0.1	0
Fatigue/malaise, (%)	--	--	--	--
Any (Grade ≥1)	19.7	18.1	34.9	18.6
Grade 1	10.9	9.4	14.4	9.8
Grade 2	7.8	8.3	17.1	7.5
Grade 3	1.0	0.5	3.3	1.3
Grade 4	0	0	0	0
Headache, (%)	--	--	--	--
Any (Grade ≥1)	15.3	16.5	24.5	14.7
Grade 1	13.0	13.7	18.5	12.0
Grade 2	1..7	2.4	5.1	2.6
Grade 3	0.5	0.4	0.9	0.2
Grade 4	<0.1	0	0.1	0
Muscle pain (myalgia), (%)	--	--	--	--
Any (Grade ≥1)	12.6	11.2	27.4	10.4
Grade 1	9.9	7.9	16.8	7.0
Grade 2	2.6	3.0	9.0	3.3
Grade 3	0.1	0.4	1.6	0.2
Grade 4	0	0	0	0

301: Safety- Solicited systemic reactogenicity

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants 18 to <65 Years of Age

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=15884	Placebo Dose 1 N=7868	NVX-CoV2373 Dose 2 N=15148	Placebo Dose 2 N=7361
Joint pain (arthralgia), (%)	--	--	--	--
Any (Grade ≥1)	7.9	6.6	23.4	6.9
Grade 1	4.9	4.1	9.8	4.3
Grade 2	2.7	2.2	10.9	2.2
Grade 3	0.3	0.3	2.6	0.3
Grade 4	<0.1	0	<0.1	<0.1
Nausea/vomiting, (%)	--	--	--	--
Any (Grade ≥1)	6.7	5.9	12.0	5.7
Grade 1	5.4	4.6	8.6	4.3
Grade 2	1.2	1.2	3.2	1.2
Grade 3	0.1	0.1	0.2	0.1
Grade 4	<0.1	<0.1	0.1	<0.1
Fever, (%)	--	--	--	--
Any (Grade ≥1)	0.4	0.4	6.2	0.2
Grade 1	0.2	0.2	4.1	0.2
Grade 2	0.1	0.1	1.7	<0.1
Grade 3	<0.1	0.1	0.4	<0.1
Grade 4	<0.1	<0.1	<0.1	0

Frequency of Solicited Systemic Reactions Within 7 Days After Each Dose, Safety Analysis Set Participants ≥65 Years of Age

Solicited Systemic Reaction	NVX-CoV2373 Dose 1 N=2251	Placebo Dose 1 N=1114	NVX-CoV2373 Dose 2 N=2048	Placebo Dose 2 N=978
Joint pain (arthralgia), (%)	--	--	--	--
Any (Grade ≥1)	6.2	6.4	13.2	6.4
Grade 1	3.8	3.5	6.9	3.5
Grade 2	2.2	2.5	5.5	2.8
Grade 3	0.2	0.4	0.8	0.2
Grade 4	0	0	0.1	0
Nausea/vomiting, (%)	--	--	--	--
Any (Grade ≥1)	3.6	2.9	5.3	3.6
Grade 1	3.1	2.3	4.1	2.9
Grade 2	0.5	0.5	1.0	0.7
Grade 3	0	0	0.2	0
Grade 4	0	0	0	0
Fever, (%)	--	--	--	--
Any (Grade ≥1)	0.4	0.3	2.0	0.7
Grade 1	0.2	0.2	1.5	0.5
Grade 2	0.1	0.1	0.4	0.1
Grade 3	<0.1	0	0.1	0.1
Grade 4	0	0	0	0

Fever: Grade 1: 38.0 to 38.4°C/100.4 to 101.1°F; Grade 2: 38.5 to 38.9°C/101.2 to 102.0°F; Grade 3: 39.0 to 40°C/102.1 to 104°F; and Grade 4: >40°C/>104°F.
Headache: Grade 1: No interference with activity; Grade 2: Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity; Grade 3: Significant; any use of narcotic pain reliever or prevents daily activity; and Grade 4: ER visit or hospitalization.
Fatigue/malaise: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Myalgia/arthralgia: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Significant; prevents daily activity; and Grade 4: ER visit or hospitalization.
Nausea/vomiting: Grade 1: No interference with activity or 1 to 2 episodes/24 hours; Grade 2: Some interference with activity or >2 episodes/24 hours; Grade 3: Prevents daily activity, requires outpatient IV hydration; and Grade 4: ER visit or hospitalization for hypotensive shock.

301: Safety- Unsolicited Events

Frequency of Unsolicited Events Through 28 Days after Dose 2

Subjects Reporting at Least One	NVX-CoV2373	Placebo
Unsolicited adverse event, n/N (%)	--	--
Non-serious unsolicited AE	--	--
Pre-crossover period	2285/19735 (11.6)	1101/9847 (11.2)
Post-crossover period	522/6416 (8.1)	850/15298 (5.6)
Related non-serious unsolicited AE		
Pre-crossover period	481/19735 (2.4)	148/9847 (1.5)
Post-crossover period	131/6416 (2.0)	54/15298 (0.4)
Grade 3 non-serious unsolicited AE	--	--
Pre-crossover period	88/19735 (0.4)	37/9847 (0.4)
Post-crossover period	18/6416 (0.3)	20/15298 (0.1)
Related Grade 3 non-serious unsolicited AE		
Pre-crossover period	18/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	3/6416 (<0.1)	1/15298 (<0.1)

Through September 27, 2021 data cutoff

301: Safety- Unsolicited Events

Key Findings in Pre-crossover Period

- No adverse event preferred term (PT) reported by more than 1% of participants in either group.
- Imbalances in the SOC of General disorders and administration site conditions and Blood and lymphatic system disorders were noted, largely due to AEs associated with reactogenicity (including chills, injection site pruritis, and influenza-like illness) and lymphadenopathy.
- Lymphadenopathy were reported by a higher proportion of participants in the NVX arm for Dose 1 and Dose 2 (0.06% and 0.2%, respectively) than in the placebo arm (0.03% and 0.02%, respectively).
- The most commonly reported (≥0.1% of participants) severe unsolicited event in the NVX arm was fatigue (n=10, 0.1%).

Through September 27, 2021 data cutoff

301: Safety- Serious Adverse Events

Subjects Reporting at Least One	NVX-CoV2373	Placebo
SAE, n/N (%)	--	--
Pre-crossover period	199/19735 (1.0)	108/9847 (1.1)
Post-crossover period	88/6416 (1.4)	178/15298 (1.2)
Related SAE	--	--
Pre-crossover period	5/19735 (<0.1)	3/9847 (<0.1)
Post-crossover period	2/6416 (<0.1)	3/15298 (<0.1)
Deaths, n/N (%)	--	--
Pre-crossover period	11/19735 (<0.1)	5/9847 (<0.1)
Post-crossover period	6/6416 (<0.1)	10/15298 (<0.1)

301: Safety- Fatal Serious Adverse Events

	Pre-Crossover (through September 27, 2021)	Post-Crossover (through September 27, 2021)
Novavax	N= 11 (<0.1%) Cardiac arrest (n=5) Myocardial infarction, cerebrovascular accident (CVA), gunshot wound, septic shock, drug toxicity, drug overdose (n=1 each)	N= 6 (<0.1%) Cardiac arrest, traumatic rupture of vertebral artery aneurysm, septic shock, drug toxicity (n=1 each) Motor vehicle accident (n=2)
Placebo	N= 5 (<0.1%) Cardiac arrest (n=3) Myocardial infarction, COVID-19 pneumonia (n=1 each)	N= 10 (<0.1%) Myocardial infarction, ischemic stroke, suicide, opiate toxicity, alcoholic liver disease, alcoholic cardiomyopathy (n=1 each) End stage chronic obstructive pulmonary disease (n= 2) Death of unknown cause (n= 2)

Additional data through February 17, 2022: All deaths had a time to onset of 140 days or more following Dose 4 in the crossover period.

301: Safety- Serious Adverse Events

Pre-crossover (through September 27, 2021)

Most common SAEs occurring at higher rates in the NVX arm than the placebo arm:

- Cerebrovascular accident (0.04% NVX and 0% placebo)
- Cholecystitis acute (0.03% NVX and 0% placebo)
- Atrial fibrillation (0.04% NVX and 0.02% placebo)
- Pneumonia aspiration (0.02% NVX and 0% placebo)
- Spontaneous abortion (0.02% NVX and 0% placebo)

301: Safety- Serious Adverse Events

Post-crossover (through September 27, 2021)

The most common SAEs occurring at higher rates following crossover to NVX versus placebo:

- Ischemic cardiac events: Myocardial infarction (0.08% NVX and 0.01% placebo), coronary artery disease (0.05% NVX and 0.01% placebo)
- All cholecystitis (chronic and acute) (0.1% NVX and 0.02% placebo)
- Pneumonia (0.06% NVX and 0.02% placebo)

301: Safety- Events of Clinical Interest

Numerical Imbalances Observed in the Following Categories:

- Cardiac
- Neurovascular
- Embolic/Thrombotic
- Biliary

301: Safety- Events of Clinical Interest

Cardiac

Pre-crossover

- Imbalance in cardiac failure and cardiomyopathy (0.05% in NVX arm and 0.02% in placebo arm)
  - Almost all in participants with risk factors; time to onset comparable between groups

Post-crossover

- Imbalance in events consistent with myocardial infarction (0.1% after crossover NVX and 0.05% after crossover placebo)
- Time to onset comparable between groups

Through September 27, 2021 data cutoff unless otherwise indicated.

301: Safety- Events of Clinical Interest

Neurovascular

Pre-crossover

- Imbalance in events consistent with stroke in (0.06% in NVX arm and 0.02% in placebo arm), including 3 of 11 events occurring within 15 days of the most recent dose of NVX
- Both events in the placebo arm occurred within 15 days of the most recent dose of placebo

Cumulatively through February 17, 2022

- A total of 19 neurovascular events consistent with stroke were reported following NVX in the pre- and post-crossover periods (N=26,106)
- Time to onset from last NVX dose: <30 days (N=3), 31-60 days (N=5), >61 days (N=11)

Through September 27, 2021 data cutoff unless otherwise indicated.

301: Safety- Events of Clinical Interest

Embolic/Thrombotic

Pre- and post-crossover

- Non-cardiac, non-neurovascular embolic and thrombotic events were balanced in the pre- and post- crossover periods.
- However, 8 participants in the NVX arm experienced thrombotic/embolic events within 21 days of the most recent NVX dose, without plausible alternative etiologies.

Cumulatively through February 17, 2022

- An imbalance in events of pulmonary embolism was noted for the post-crossover period (0.1% of participants who crossed over to receive NVX compared to 0.05% of participants who crossed over to receive placebo).
- However, most events in both treatment arms had onset >90 days following the most recent dose, and the proportion of events with onset <2 weeks was comparable.

Through September 27, 2021 data cutoff unless otherwise indicated.

301: Safety- Events of Clinical Interest

Biliary

Pre- and post-crossover

- Imbalance in cholecystitis (pre-crossover: 0.05% NVX and 0.01% placebo; post-crossover: 0.1% after crossover NVX and 0.02% after crossover placebo)
- Of 18 events in NVX recipients in both periods, 6 (33%) had onset within 30 days of NVX

Through September 27, 2021 data cutoff unless otherwise indicated.

301: Safety- Events of Clinical Interest

Specific events of clinical interest/adverse events of special interest

Bell's palsy

- In the pre-crossover period, Bell's palsy within 30 days of vaccination was reported by one participant each in the placebo and NVX arms.

Uveitis

- Three participants in the NVX arm had new-onset uveitis events within 3 weeks of vaccination, one of which recurred with re-challenge. Two events of uveitis were reported in the placebo arm, one of which had onset within one week of placebo, in a participant with a history of uveitis.

Hypersensitivity

- One event of angioedema and urticaria 2 days post-Dose 2 of NVX is potentially related but also started concomitant antibiotic.

Through September 27, 2021 data cutoff unless otherwise indicated.

Safety- Events of Clinical Interest from Other Studies

Additional safety data from Studies 101 (Part 1/2), 302, and 501 (pre-crossover only) was reviewed, including serious adverse events and adverse events of special interest.

- One event of Guillain-Barré syndrome was reported by a 65-year-old female NVX recipient who experienced progressive neuropathy starting 9 days following Dose 1.
- There were no other new SAEs, AESIs or PIMMCs in studies 101, 302, or 501 that were considered at least possibly related by FDA that were not previously identified in study 301.

All studies: Safety- Myocarditis/Pericarditis

In a total clinical safety database of ~ 40,000 vaccine recipients, to date, 6 NVX recipients have reported myocarditis and/or pericarditis, including 5 events within 20-days post-NVX.

Safety- Myocarditis/Pericarditis

Study	Age/ Sex	Preferred Term	NVX Dose Number, Days to Onset	Comments	Seriousness/Outcome
301	16/M	Myocarditis	Crossover Dose 2, 2 days	Preceding nonspecific viral illness and concomitant methylphenidate use. (Peak troponin ~32,000 ng/L)	Serious event. Hospitalized 5 days and treated with IVIG. Event recovered/resolved.
302	19/M	Myocarditis	Dose 2, 2 days	MRI consistent with myocarditis (peak troponin ~7,800 ng/L). Pharyngitis and lymphadenopathy 11 days later	Serious event. Hospitalized 5 days. Event resolved after approximately 1 month.
301	28/M	Non-ST elevation MI	Booster, 3 days	Adverse event described as acute MI but myocarditis in differential, with chest pain and elevated troponin (~300 ng/L). Unclear rationale for diagnosis of non-ST-elevation myocardial infarction versus myocarditis. Cardiac MRI scheduled.	Serious event. Hospitalized 2 days. Event not recovered/not resolved at time of this report.
302	60/F	Pericarditis	Crossover Dose 1, 8 days	With fever, elevated white blood cell count and neutrophils, ECG consistent with pericarditis. Troponin normal.	Serious event. Hospitalized 2 days. Event recovered/ resolved.
301	20/M	Pericarditis and myocarditis	Crossover Dose 1, 10 days	History of sore throat and fever 8 days prior to events, with exposure to streptococcal pharyngitis, and elevated anti streptolysin O titers. Troponin normal.	Non-serious event. Participant was not hospitalized. Second CO dose not administered. Participant lost to follow-up.

One case of myocarditis/pericarditis occurred at 28-days post-Dose 1 of NVX and was confounded by concomitant COVID-19.
One case of myocarditis 72 days post-Dose 2 placebo (Study 301).

Foreign Postmarketing Safety Data

The sponsor submitted postmarketing safety data as of April 30, 2022
(744,235 doses administered in Australia, Canada, European Union, New Zealand, and South Korea)

Sponsor reported a "potential safety signal" for myocarditis and pericarditis

- 37 reports identified, 2 duplicates (n=35 valid reports representing 36 AEs)
  - Pericarditis (n=29)*
  - Myocarditis (n=4)
  - Myopericarditis (n=2)
  - Carditis (n=1)

- Observed-to-expected (O/E) rate ratios† elevated:

Dose	O/E Rate Ratio (95% CI)	Assuming Sensitivity of 50%	Assuming Sensitivity of 25%
All doses	4.95 (3.50 - 6.79)	9.90 (7.00 – 13.58)	19.79 (14.01 – 27.17)

*Includes 5 reports of pericarditis in individuals with a history of pericarditis after mRNA COVID-19 vaccine.
†Does not include adjudication of individual cases by sponsor. Includes 2 duplicate reports.

Summary of Benefits/Risks

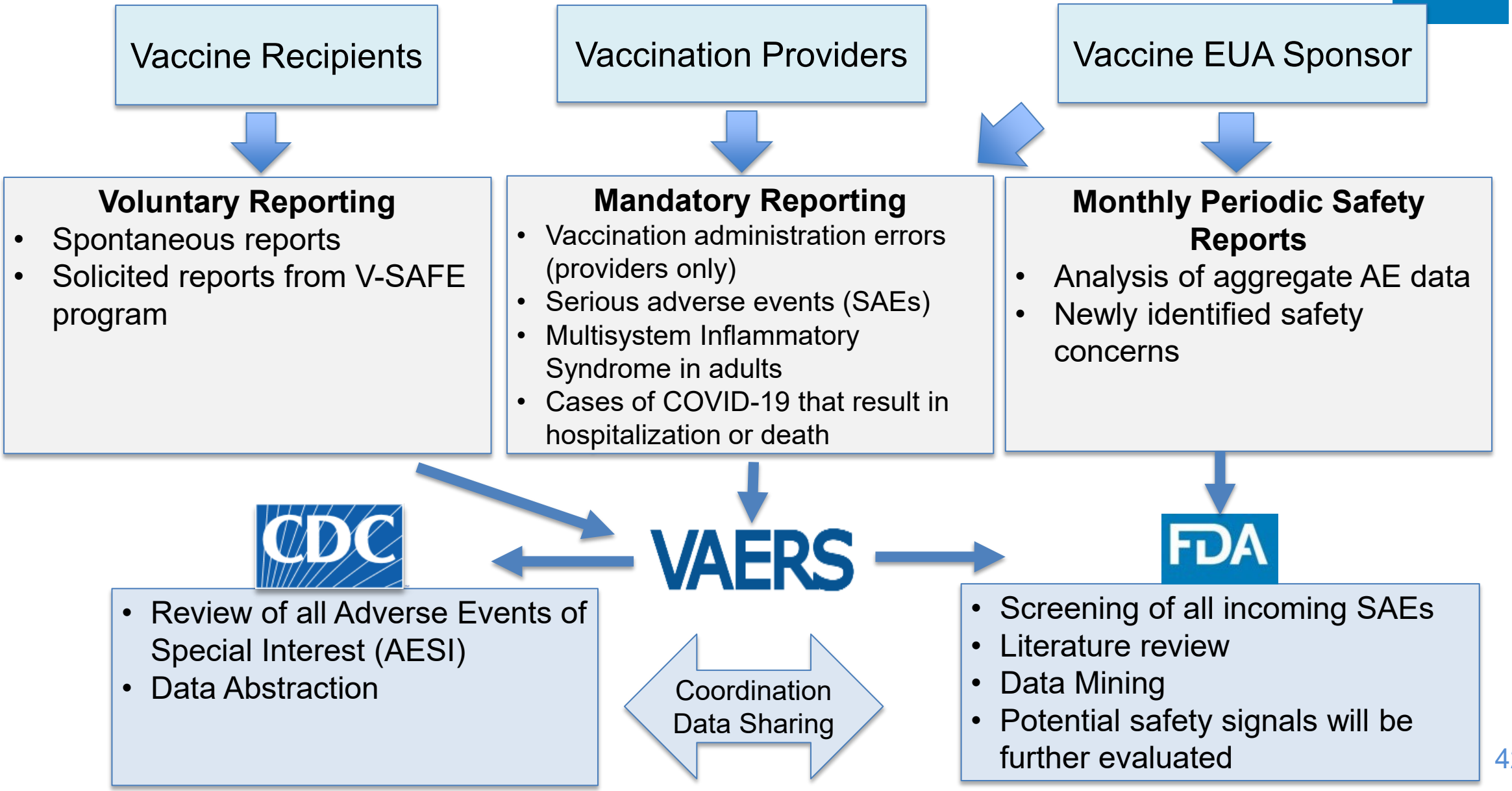
Known and Potential Benefits	Uncertainties in Benefits	Known and Potential Risks	Uncertainties in Risks
• Vaccine efficacy: 90.41% (95% CI 83.81, 94.32) • Vaccine efficacy estimates from study 301 are generally consistent across subgroups stratified by demographic variables (including age, race, and ethnicity) and risk for severe COVID-19.	• Effectiveness against: currently circulating SARS-CoV-2 variants, long term effects of COVID-19 disease • Effectiveness in: certain populations at higher risk of severe COVID-19, individuals previously infected with SARS-CoV-2 • Duration of protection	• Local and systemic reactogenicity • Myocarditis/pericarditis • Guillain-Barré syndrome	• Safety in certain subpopulations • Adverse reactions that are uncommon or that require longer follow-up to be detected, including imbalances observed in study 301: biliary events, neurovascular events, cardiac events, uveitis

Pharmacovigilance Plan

Important identified risks	*FDA recommends adding myocarditis and pericarditis*
Important potential risks	Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease, myocarditis and pericarditis, and anaphylaxis
Missing information	Use in pregnancy and while breast feeding, use in immunocompromised patients, use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders), use in patients with autoimmune or inflammatory disorders, interaction with other vaccines, and long-term safety

Surveillance activities	• Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days: Serious adverse events (irrespective of attribution to vaccination); Cases of Multisystem Inflammatory Syndrome in adults; Cases of COVID-19 that result in hospitalization or death
	• The Sponsor will conduct:
	  • Passive and active surveillance activities for continued vaccine safety monitoring.
	  • Periodic aggregate review of safety data and submit periodic safety reports
	  • Five planned surveillance studies, including active follow-up studies for safety in the US and UK

Adverse Event (AE) Reporting Under the EUA



FDA Vaccine Surveillance Programs: Post-Authorization

Passive Surveillance of Vaccines	Vaccine Adverse Event Reporting System (VAERS) • Management shared by CDC and FDA
Active Surveillance of Vaccines	• FDA Biologics Effectiveness and Safety System (BEST) • FDA-CMS partnership

Sponsor Surveillance Studies

The sponsor has proposed five post-authorization surveillance studies:

Pregnancy Exposure Registry	To evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with the Novavax COVID-19 vaccine.
US Active Follow-Up for Safety Study	To evaluate the risk of select Adverse Events of Special Interest (AESIs) in association with administration of the Novavax COVID-19 vaccine in adults aged 18 years and older in the real-world setting in the United States (US).
UK Active Follow-Up for Safety Study	To evaluate the risk of select AESIs in association with administration of the Novavax COVID-19 vaccine in adults aged 18 years and older in the real-world setting in the United Kingdom (UK).
US Real World Effectiveness Study	To assess the effectiveness of the Novavax COVID-19 vaccine in preventing symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults aged 18 years and older in the US.
European Real World Effectiveness Study	To assess the effectiveness of the Novavax COVID-19 vaccine against hospitalization due to laboratory confirmed SARS-CoV-2 in adults aged 18 years and older in multiple European countries.

Additional Monitoring Activities for Events of Interest

Additional post-authorization safety monitoring will be performed for the previously described adverse events of clinical interest

Active Surveillance	• U.S. and U.K. active surveillance safety studies will include assessment for cardiac, neurovascular, embolic/thrombotic, and biliary events
Enhanced Pharmacovigilance	• Sponsor to provide updated assessment of interval and aggregate data in monthly periodic safety reports • Targeted questionnaire for follow up of spontaneous reports of GBS

Question for VRBPAC