Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Presentation - FDA Review of Efficacy and Safety of Moderna COVID-19 Vaccine Emergency Use Authorization Request

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Vaccines and Related Biological Products Advisory Committee Meeting

FDA Review of Efficacy and Safety of Moderna COVID-19 Vaccine Emergency Use Authorization Request

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December 17, 2020

Outline

- Introduction
- Clinical development program
- Efficacy data
- Safety data
- Pharmacovigilance plan/future studies/ongoing study plans
- Benefit/risk assessment in context of proposed use under EUA

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Moderna COVID-19 Vaccine

Vaccine composition	• Based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA • Formulated in lipid nanoparticles (LNP)
Dosing regimen	Intramuscular 2-dose series spaced 28 days apart; 100 µg each dose
Proposed indication and usage under EUA	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

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Clinical Development To Date

DMID 20-0003	Study 201	Study 301
Ongoing Phase 1, open-label, dose-ranging, safety and immunogenicity study in individuals ≥18 years of age	Ongoing Phase 2 randomized, placebo-controlled, observer-blind, dose confirmation study in individuals ≥18 years of age	Ongoing Phase 3, randomized, placebo-controlled, observer-blind, efficacy study in individuals ≥18 years of age

DMID 20-0003

Phase 1 open-label, dose-ranging study to evaluate safety and immunogenicity of mRNA-1273 in healthy adults ≥18 years old

Total of 120 participants in 3 age cohorts: 18-55 yrs (n=60); 56-70 yrs (n=30); ≥71 yrs (n=30)	Dose levels studied: 25 µg, 50 µg, 100 µg, 250 µg

Immunogenicity:

- Two doses induced SARS-CoV-2 binding and neutralizing antibodies
- Th1-biased CD4+ T-cell response elicited

Safety:

- Safety profile supported further clinical development
- No serious adverse events (SAEs) reported in the Phase 1 study at the time of EUA request
- Duration of follow-up: at least 3 months after dose 2

Study 201

Phase 2 safety and dose-confirmation study to evaluate safety and immunogenicity of mRNA-1273 in healthy adults ≥18 years of age	
Total of 600 participants: 18-54 years (n=300), ≥55 years (n=300)	Dose levels studied: 50 µg, 100 µg

Immunogenicity:

- Two doses induced comparable SARS-CoV-2 binding and neutralizing antibodies in both age cohorts

Safety:

- Safety profile supported further clinical development
- Three SAEs (none related) were reported in the vaccine group at time of EUA request
- Duration of follow up: safety data from Day 57 data cut (1 month after dose 2)

Study 301 Design

Phase 3 efficacy and safety study in adults ≥18 years of age

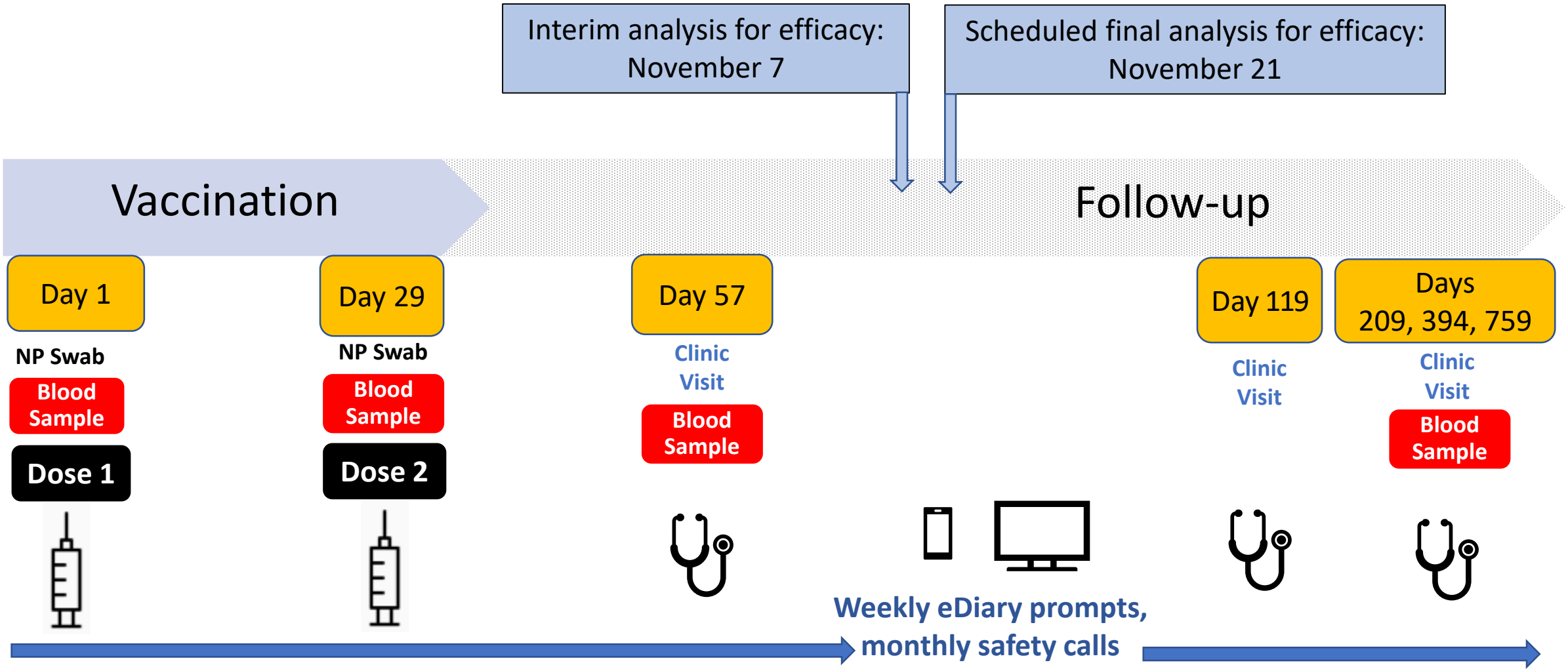
- 30,351 adults ≥18 years of age, randomized 1:1 and vaccinated
- Participants received 2 doses of vaccine (100 µg) or placebo, 28 days apart

- Randomization stratified by age and risk factor for severe COVID-19:
  - 18 to 64 years without risk factors
  - 18 to 64 years with risk factors
  - ≥65 years regardless of risk factor

  } Goal of 25% to 50% of total study population

- All subjects followed for solicited adverse reactions for 7 days after each dose, unsolicited AEs for 28 days after each dose, and SAEs and medically attended adverse events for entire study duration
- Planned study duration of 2 years

Study 301 Timeline



Active Surveillance for COVID-19 symptoms begins after dose 1

Efficacy: Case Definitions

COVID-19 disease	Severe COVID-19 disease
Positive SARS-CoV-2 PCR* plus : At least TWO of the following systemic symptoms: Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia *Confirmed by central lab using Viracor SAR-CoV-2 RT-PCR (EUA 200124) or local CLIA-certified lab, if no central lab results available.	Confirmed COVID-19 plus at least one of the following symptoms: Severe systemic illness: • RR ≥30 breaths/minute, • HR ≥125 beats/minute, • SPO_2 ≤93% on RA or • PaO2/FiO2 <300mm Hg Respiratory failure or ARDS: • high-flow O2, • noninvasive ventilation, • mechanical ventilation, or ECMO Shock: • SBP <90 mm Hg, • DBP <60 mm Hg or • need vasopressors Significant acute renal, hepatic, or neurologic dysfunction ICU admission Death

Primary Efficacy Endpoint and Analysis

Primary endpoint

Confirmed COVID-19 occurring at least 14 days after dose 2 in participants without evidence of SARS-CoV-2 infection prior to dose 1

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE =1 – hazard ratio from the Cox Model

The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the pre-specified O'Brien-Fleming boundary

Interim analyses (IA) planned after accrual of approximately 53 and 106 cases

First IA conducted upon accrual of 95 cases (data cut Nov 7, 2020)

Primary efficacy analysis planned after accrual of approximately 151 cases

Conducted upon accrual of 196 cases (data cut Nov 21, 2020)

Key Secondary Efficacy Endpoints

Severe COVID-19 ≥14 days after dose 2	Severe COVID-19 cases ≥14 days after dose 2 in participants without evidence of SARS-CoV-2 infection prior to dose 1
CDC-defined COVID-19 ≥14 days after dose 2	Cases confirmed ≥14 days after dose 2 in participants without evidence of SARS-CoV-2 infection prior to dose 1

Additional Considerations

Monitoring for vaccine-enhanced respiratory disease

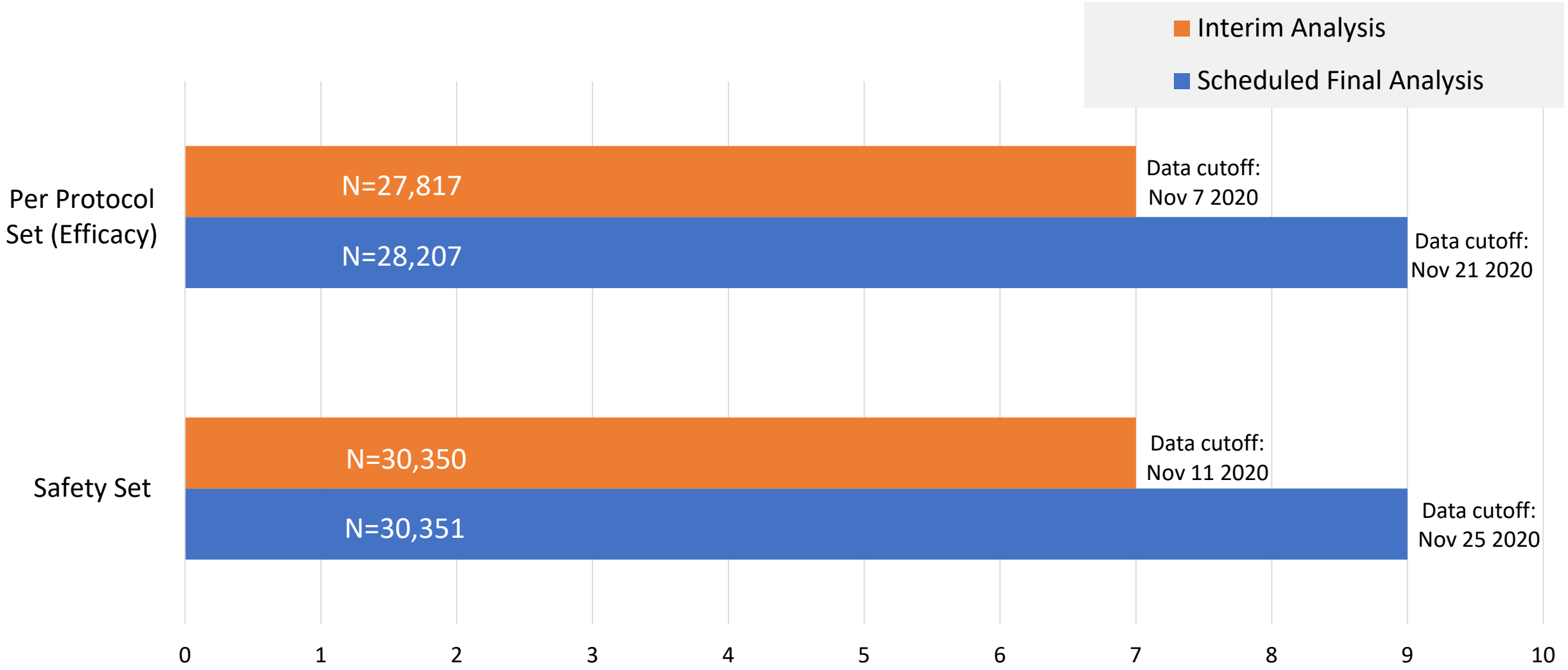
- At least weekly review of severe COVID-19 cases by an unblinded team supporting the Data Safety Monitoring Board
- Study stopping rule would be triggered if the 1-sided probability of observing the same or more extreme case split was ≤5% when the true incidence of severe disease was the same for vaccine and placebo participants

Study 301 Analysis Populations

Population (N)	Description
Full Analysis Set (FAS) (N=30,351: 15,181 vaccine; 15,170 placebo)	All randomized participants who received at least one dose. Participants analyzed according to the group to which they were randomized.
Modified Intent to Treat (mITT) Set (N=29,148: 14,550 vaccine; 14,598 placebo)	All participants in the FAS who had no immunologic or virologic evidence of prior SARS-CoV-2 infection (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid) at Day 1 before the first dose.
Per Protocol Set (PPS) (N=28,207: 14,134 vaccine; 14,073 placebo)	All participants in the mITT Set who received planned doses per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to database lock and unblinding, that impact critical or key study data.
Safety Set (N=30,351: 15,185 vaccine; 15,166 placebo)	All randomized participants who received at least one dose. Participants analyzed according to the group to which they were randomized.

*Numbers based on final scheduled analysis

Median Follow-Up Duration (Weeks)



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Study 301: Demographics, Efficacy Population

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Study 301: Subject Disposition, Efficacy Population

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Subjects excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the subject was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Subject	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Primary Efficacy Endpoint (Scheduled Final Analysis)—PPS

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)	Met Predefined Success Criterion
All subjects	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6% (90.6%, 97.9%)	NA
65 years and older	4/3583 (0.1) 4.595	29/3552 (0.8) 33.728	86.4% (61.4%, 95.5%)	NA

Subgroup Analyses of Primary Efficacy Endpoint (Interim Analysis)–PPS

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)
Age (years)			
18 to <65	5/10407 (<0.1) 2.504	75/10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3/676 (0.4) 21.726	100%
Age and risk for severe COVID-19			
18 and <65 and not at risk	4/8309 (<0.1) 2.524	57/8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1/2098 (<0.1) 2.428	18/2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15/3499 (0.4) 21.046	100%
Sex			
Female	3/6661 (<0.1) 2.271	45/6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2/7273 (<0.1) 1.433	45/7369 (0.6) 31.883	95.5% (81.5%, 98.9%)

Subgroup Analyses of Primary Efficacy Endpoint (Interim Analysis)–PPS

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)
Race and Ethnicity			
Non-Hispanic white	5/8858 (<0.1) 2.657	70/8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20/5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0/2783	12/2769 (0.4) 26.346	100%
Not Hispanic or Latino	5/11019 (<0.1) 2.243	77/10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0/107	0/110	
Asian	0/616	3/684 (0.4) 26.549	100%
Black or African American	0/1369	4/1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0/33	0/30	
White	5/11078 (<0.1) 2.215	80/11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0/293	1/304 (0.3)	100%
Other	0/298	2/293 (0.7) 45.645	100%

Subgroup Analyses of Primary Efficacy Endpoint by Comorbidity (Interim Analysis)–PPS

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24/3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4/10818 (<0.1) 1.911	66/10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

** Post hoc analysis

Subgroup analyses of Primary Efficacy Endpoint by Baseline SARS-CoV-2 Status (Interim Analysis)–FAS

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

[a]Baseline SARS-CoV-2 status based on RT-PCR and serology against SARS-CoV-2 nucleocapsid pre-dose-1

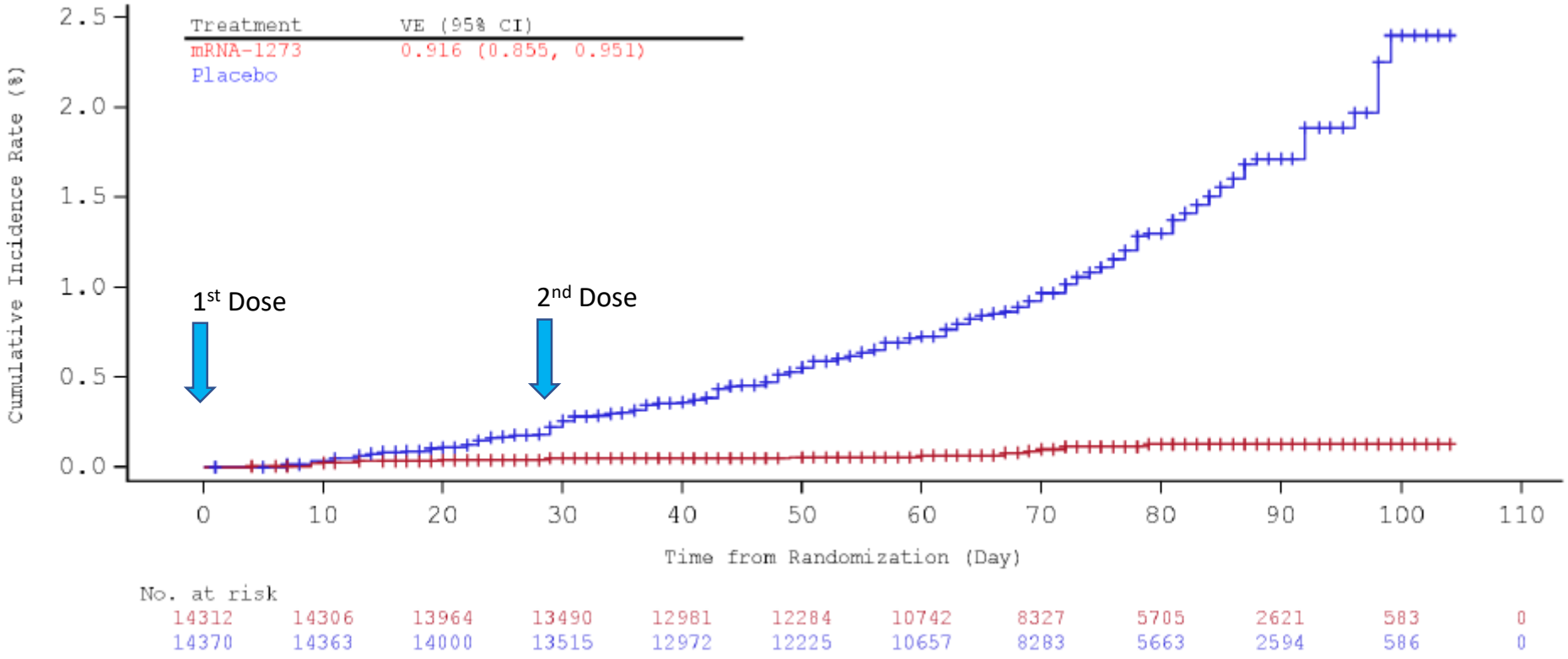
Secondary Efficacy Analysis of Severe COVID-19 (Scheduled Final Analysis)—PPS

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All subjects	0	30* (0.2) 9.138	100%

*9 of the 30 cases resulted in hospitalization

Note: There was one severe case in a vaccine recipient which occurred 2 months after dose 2, requiring hospitalization, that was not adjudicated by the data cut off date

Cumulative Incidence Curve of COVID-19 Starting After Randomization—mITT Set



Post Hoc Analysis of COVID-19 Cases from Randomization by Time Period (Interim Analysis)—FAS

	Vaccine Group N=15180 Cases/No. at Risk Incidence Rate per 1000 person-yrs	Placebo Group N=15170 Cases/No. at Risk Incidence Rate per 1000 person-yrs	VE (%) (95% CI)
First COVID-19 occurrence after dose 1	21 7.1 (2947.5)	173 59.0 (2932.2)	87.9% (81.0%, 92.7%)
Any time after dose 1 to before dose 2	14 11.3 (1237.6)	46 37.0 (1242.1)	69.5% (43.5%, 84.5%)
Any time after dose 2**	7/13857 2.5 (2823.9)	127/13792 (2801.8)	94.5% (88.4%, 97.8%)

**Subjects who were not at risk (cases or censored at prior time period) are excluded from this analysis

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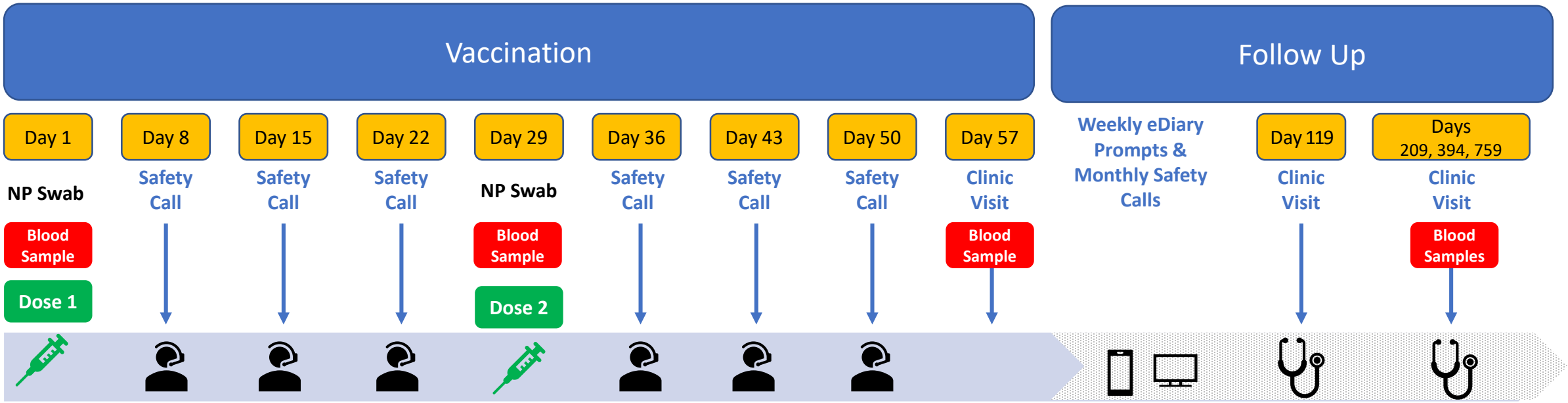
Study 301 Scheduled Visits & Safety Calls



COVID-19 active surveillance throughout the study
Daily telemedicine visits for participants with COVID-19
eDiary captures solicited local and systemic adverse reactions in all participants for 7 days after each dose
SAEs and MAAEs captured through the study

Subject Disposition, Safety Population

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15166	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Subject	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)

Solicited Local Reactions Within 7 Days After Dose 1

	Age 18 to 64		Age ≥65	
Reaction Type	**Vaccine N=11401 n (%)**	**Placebo N=11404 n (%)**	**Vaccine N=3761 n (%)**	**Placebo N=3746 n (%)**
Any Local Reaction	9960 (87.4)	2432 (21.3)	2805 (74.6)	566 (15.1)
Grade 3	452 (4.0)	39 (0.3)	77 (2.0)	39 (1.0)
Pain	9908 (86.9)	2179 (19.1)	2782 (74.0)	481 (12.8)
Grade 3*	367 (3.2)	23 (0.2)	50 (1.3)	32 (0.9)
Erythema (Redness) ≥25mm	345 (3.0)	46 (0.4)	86 (2.3)	19 (0.5)
Grade 3 >100mm	34 (0.3)	11 (<0.1)	8 (0.2)	2 (<0.1)
Swelling (Hardness) ≥25mm	768 (6.7)	33 (0.3)	166 (4.4)	19 (0.5)
Grade 3 >100mm	62 (0.5)	3 (<0.1)	20 (0.5)	3 (<0.1)
Axillary swelling/tenderness (vaccination arm)	1322 (11.6)	567 (5.0)	231 (6.1)	155 (4.1)
Grade 3**	36 (0.3)	13 (0.1)	12 (0.3)	14 (0.4)

*Pain, grade 3: any use of Rx pain reliever/prevents daily activity

**Axillary swelling/tenderness, grade 3: any use of Rx pain reliever/prevents daily activity

Note: No grade 4 solicited local adverse reactions were reported.

Solicited Local Reactions Within 7 Days After Dose 2

Reaction Type	Age 18 to 64		Age ≥65	
	Vaccine N=10357 n (%)	Placebo N=10317 n (%)	Vaccine N=3587 n (%)	Placebo N=3549 n (%)
Any Local Reaction	9371 (90.5)	2134 (20.7)	3010 (83.9)	473 (13.3)
Grade 3	766 (7.4)	41 (0.4)	212 (5.9)	29 (0.8)
Pain	9335 (90.1)	1942 (18.8)	2990 (83.4)	421 (11.9)
Grade 3*	479 (4.6)	21 (0.2)	96 (2.7)	17 (0.5)
Erythema (Redness) ≥25mm	928 (9.0)	42 (0.4)	265 (7.4)	13 (0.4)
Grade 3 >100mm	206 (2.0)	12 (0.1)	75 (2.1)	3 (<0.1)
Swelling (Hardness) ≥25mm	1309 (12.6)	35 (0.3)	386 (10.8)	13/ (0.4)
Grade 3 >100mm	176 (1.7)	4 (<0.1)	69 (1.9)	7/ (0.2)
Axillary swelling/tenderness (vaccination arm)	1654 (16.0)	444 (4.3)	302 (8.4)	90 (2.5)
Grade 3**	45 (0.4)	10 (<0.1)	21 (0.6)	8 (0.2)

*Pain, grade 3: any use of Rx pain reliever/prevents daily activity

**Axillary swelling/tenderness, grade 3: any use of Rx pain reliever/prevents daily activity

Note: No grade 4 solicited local adverse reactions were reported

Solicited Systemic Reactions Within 7 Days After Dose 1

Reaction Type	Age 18 to 64		Age ≥65	
	Vaccine N=11401 n (%)	Placebo N=11404 n (%)	Vaccine N=3761 n (%)	Placebo N=3745 n (%)
Any Systemic Reaction	6503 (57.0)	5063 (44.4)	1818 (48.3)	1335 (35.6)
Grade 3	363 (3.2)	248 (2.2)	84 (2.2)	63 (1.7)
Grade 4	5 (<0.1)	4 (<0.1)	0	0
Fever	105 (0.9)	39 (0.3)	10 (0.3)	7 (0.2)
Grade 3	10 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Grade 4	4 (<0.1)	4 (<0.1)	0	2 (<0.1)
Headache	4031 (35.4)	3303 (29.0)	921 (24.5)	724 (19.3)
Grade 3	219 (1.9)	162 (1.4)	52 (1.4)	34 (0.9)
Fatigue	4384 (38.5)	3282 (28.8)	1251 (33.3)	851 (22.7)
Grade 3	120 (1.1)	83 (0.7)	30 (0.8)	23 (0.6)
Grade 4	1 (<0.1)	0	0	0
Myalgia	2698 (23.7)	1626 (14.3)	743 (19.8)	443 (11.8)
Grade 3	73 (0.6)	38 (0.3)	17 (0.5)	9 (0.2)
Arthralgia	1892 (16.6)	1327 (11.6)	618 (16.4)	456 (12.2)
Grade 3	47 (0.4)	29 (0.3)	13 (0.3)	8 (0.2)
Grade 4	1 (<0.1)	0	0	0
Nausea/Vomiting	1069 (9.4)	908 (8.0)	194 (5.2)	166 (4.4)
Grade 3	6 (<0.1)	8 (<0.1)	4 (0.1)	4 (0.1)
Chills	1051 (9.2)	730 (6.4)	202 (5.4)	148 (4.0)
Grade 3	17 (0.1)	8 (<0.1)	7 (0.2)	6 (0.2)

Fever, grade 3: ≥39.0C (≥102.1F)
Fever, grade 4: >40.0°C (>104.0°F)
Headache, grade 3: significant; any use of prescription pain reliever or prevents daily activity
Fatigue, myalgia, arthralgia, grade 3: significant; prevents daily activity; Grade 4: ER visit/hospitalization
Nausea/Vomiting, grade 3: prevents daily activity, outpatient IVF
Chills, grade 3: Prevents daily activity and requires medical intervention

Solicited Systemic Reactions Within 7 Days After Dose 2

Reaction Type	Age 18 to 64		Age ≥65	
	Vaccine N=10357 n (%)	Placebo N=10315 n (%)	Vaccine N=3587 n (%)	Placebo N=3549 n (%)
Any Systemic Reaction	8484 (81.9)	3967 (38.4)	2580 (71.9)	1102 (31.1)
Grade 3	1801 (17.4)	215 (2.1)	387 (10.8)	58 (1.6)
Grade 4	10 (<0.1)	2 (<0.1)	2 (<0.1)	1 (<0.1)
Fever	1806 (17.4)	38 (0.4)	366 (10.2)	5 (0.1)
Grade 3	168 (1.6)	1 (<0.1)	18 (0.5)	0
Grade 4	10 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Headache	6500 (62.8)	2617 (25.4)	1665 (46.4)	635 (17.9)
Grade 3	515 (5.0)	124 (1.2)	107 (3.0)	32 (0.9)
Fatigue	7002 (67.6)	2530 (24.5)	2094 (58.4)	695 (19.6)
Grade 3	1099 (10.6)	81 (0.8)	248 (6.9)	20 (0.6)
Myalgia	6353 (61.3)	1312 (12.7)	1683 (46.9)	385 (10.8)
Grade 3	1032 (10.0)	39 (0.4)	201 (5.6)	10 (0.3)
Arthralgia	4685 (45.2)	1087 (10.5)	1252 (34.9)	381 (10.7)
Grade 3	603 (5.8)	36 (0.3)	122 (3.4)	7 (0.2)
Nausea/Vomiting	2209 (21.3)	754 (7.3)	425 (11.8)	129 (3.6)
Grade 3	8 (<0.1)	8 (<0.1)	10 (0.3)	3 (<0.1)
Grade 4	0	0	1 (<0.1)	0
Chills	5001 (48.3)	611 (5.9)	1099 (30.6)	144 (4.1)
Grade 3	151 (1.5)	14 (0.1)	27 (0.8)	2 (<0.1)

Fever, grade 3: ≥39.0C (≥102.1F)
Fever, grade 4: >40.0°C (>104.0°F)
Headache, grade 3: significant; any use of prescription pain reliever or prevents daily activity
Fatigue, myalgia, arthralgia-Grade 3: significant; prevents daily activity; Grade 4: ER visit/hospitalization
Nausea/Vomiting, grade 3 activity, outpatient IVF
Chills, grade 3: Prevents daily activity and requires medical intervention

Solicited Safety, by Baseline SARS-CoV-2 Status

Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)

[a]There were no reports of grade 4 injection site reaction

Baseline SARS-CoV-2 status based on RT-PCR and serology against SARS-CoV-2 nucleocapsid pre-dose-1

Unsolicited Safety, by Baseline SARS-CoV-2 Status

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

**Related as assessed by Investigator

Unsolicited AEs (non-serious)

Higher frequency in vaccine group vs. placebo

- Hypersensitivity-related events
  - Vaccine: 1.5% (n=233), placebo: 1.1% (n=166)
  - Plausible relationship to vaccination
  - No anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine
- Lymphadenopathy-related events (outside of solicited period)
  - Vaccine: 1.1% (n=173), placebo: 0.63% (n=95)
  - Plausible relationship to vaccination
- Delayed localized reactions with onset after 7 days seen mostly after dose 1 (1.4% in vaccine group vs 0.4% placebo group)
- Bell's palsy
  - Vaccine n=3, placebo n=1
  - Occurred 17 after dose 1 (placebo recipient); 22, 28, and 32 days after dose 2 (vaccine recipients)
  - Observed rate consistent with background rate in general population
  - No clear basis upon which to conclude a causal relationship at this time

Serious Adverse Events

Deaths: 13 total (6 vaccine, 7 placebo) As of December 3, 2020	Vaccine group deaths: • 78 yo: Cardiac arrest 21 days after dose 1 • 77 yo: Myocardial infarction 45 days after dose 2 • 70 yo: Found deceased at home 57 days after dose 2 • 56 yo: Found deceased at home 37 days after dose 1 • 72 yo: Multiorgan failure 59 days after dose 2 • 62 yo: Suicide 21 days after dose 1
Related SAEs (FDA conclusion)	• 65 yo: Intractable nausea/vomiting – 1 day post dose 2 • 2 subjects (46 yo, 51 yo) with facial swelling – 1 day and 2 days post dose 2, respectively – Both subjects had prior dermal filler

Pregnancies

Women were screened for pregnancy prior to each vaccination; a positive test resulted in exclusion or discontinuation from vaccination

13 pregnancies (as of December 2, 2020)

- Totals reported: 6 vaccine, 7 placebo
- Vaccination prior to last menstrual period (LMP): 2 vaccine, 3 placebo
- Vaccination within 30 days after LMP: 2 vaccine, 3 placebo
- Vaccination >30 days after LMP: 1 vaccine, 1 placebo
- LMP not known: 1 vaccine, 0 placebo
- Pregnancy outcomes:
  - Placebo group: Spontaneous abortion, elective abortion
  - Otherwise not known, to date

Summary - Efficacy

- The totality of the clinical data submitted with the EUA request meets the expectations for duration of follow-up
- In the scheduled final analysis, vaccine efficacy ≥14 days post dose 2 was 94.1%, (95% CI: 89.3; 96.8) in participants without prior evidence of SARS-CoV-2 infection
- Efficacy outcomes were consistent (>93%) across demographic subgroups
- In the scheduled final analysis, there were 30 severe COVID-19 cases in the placebo group and 1 (still unadjudicated case) in the vaccine group
- Data suggests potential efficacy following a single dose; interpretation is limited because almost all participants received a second dose

Summary - Safety

- The totality of the clinical data submitted with the EUA request meets the expectations for duration of follow-up in >30,000 participants
- Reactogenicity was generally more frequent after dose 2 (all ages), mostly mild to moderate, and less frequent and severe in adults ≥65 years than in younger adults
  - There were no safety concerns identified in subgroup analyses by age, sex, race, ethnicity, health risks for severe COVID-19, and prior SARS-CoV-2 infection
- Lymphadenopathy reported as solicited and unsolicited adverse events were more frequent in the vaccine group compared with placebo
- Delayed localized injection site reaction with onset after 7 days was more frequent in the vaccine group compared to the placebo, and mostly seen after dose 1
- Hypersensitivity-related events were more frequent in the vaccine group compared with placebo
  - No anaphylactic or severe hypersensitivity reactions with temporal relation to vaccination
- As of the scheduled final analysis, 3 cases of Bell's palsy were reported in vaccine recipients, and one in placebo recipients. Although there is no clear basis upon which to conclude a causal relationship at this time, FDA recommends further surveillance if vaccine is authorized for widespread use.

Outline

- Introduction
- Clinical development program
- Efficacy data
- Safety data
- **Pharmacovigilance plan/future studies/ongoing study plans**
- Benefit/risk assessment in context of proposed use under EUA

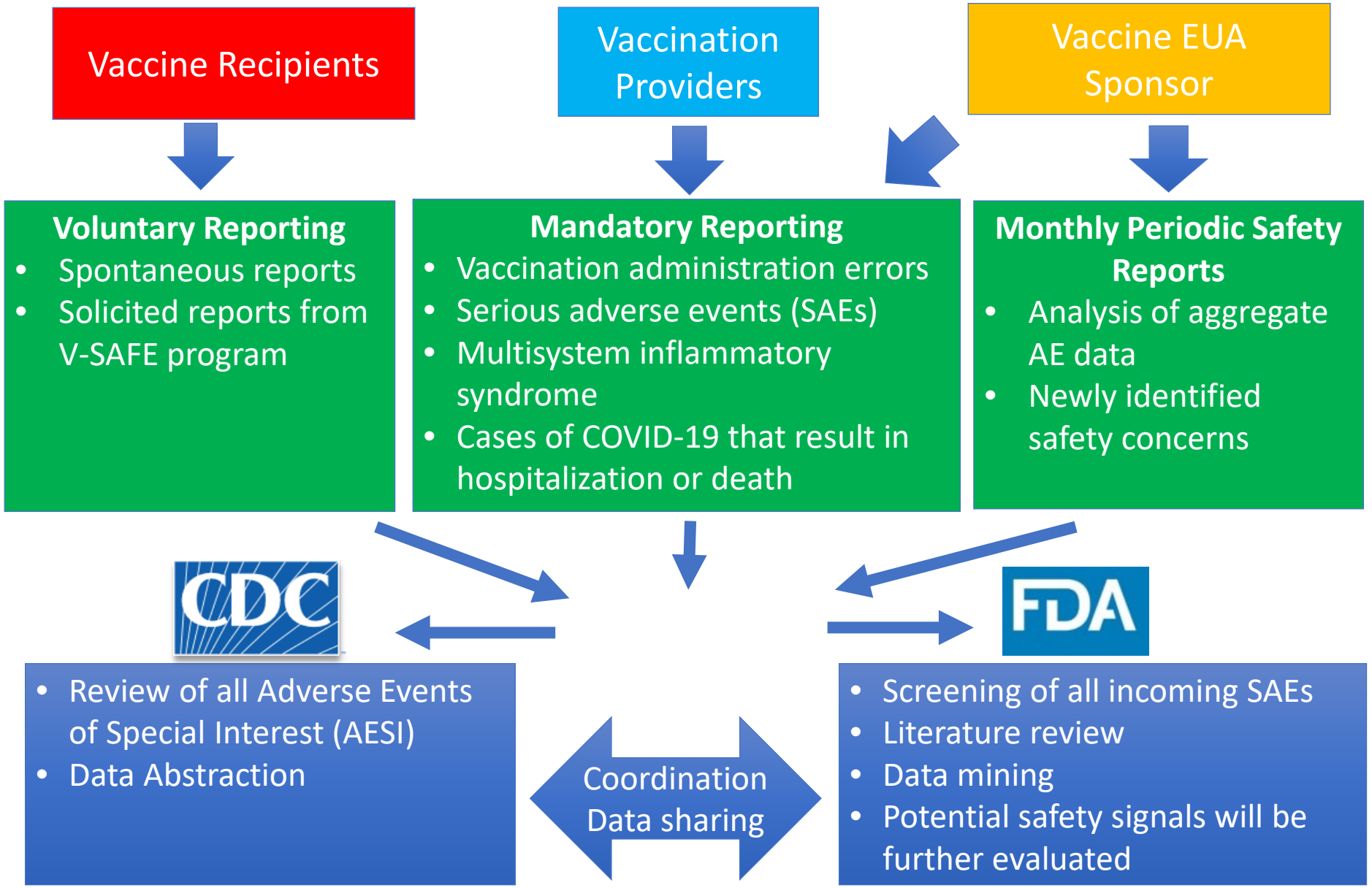
Pharmacovigilance Plan

Safety specifications of the pharmacovigilance plan:

- Important potential risks
  - Vaccine-associated enhanced disease
  - Anaphylactic reactions (including anaphylaxis)

- Important missing information
  - Use in pregnant and breast-feeding women
  - Use in the pediatric population
  - Long-term safety and effectiveness
  - Immunogenicity in subjects with immunosuppression
  - Concomitant administration with non-COVID vaccines

Adverse Event Reporting under EUA



Safety Surveillance Studies

Pregnancy Cohort:

- Passive pregnancy registry to monitor vaccination during pregnancy within populations expected to receive vaccine under EUA.

Active Follow-up for Safety:

- Retrospective analyses of medical and pharmacy claims data
- Objectives; estimation of background rates of 23 prespecified AESI, descriptive analyses of observed vs expected rates
- Self-controlled risk interval analyses if certain criteria are met from descriptive analyses

Proposed Revisions to Study 301, if an EUA is Issued

- Still in discussion
- Revised protocol has not yet been submitted for FDA review
- General plans
  - No change for participants who choose to remain blinded
  - For participants who choose to be unblinded, proactively re-consent and offer vaccine for those in placebo group
  - All participants will continue to be followed for 2 years

Outline

- Introduction
- Clinical development program
- Efficacy data
- Safety data
- Pharmacovigilance Plan/Future Studies/Ongoing Study Plans
- **Benefit/risk assessment in context of proposed use under EUA**

Benefit/Risk Assessment in Context of Proposed EUA

Benefits
• Reduced risk of confirmed COVID-19 at least 14 days after completing a 2-dose vaccination regimen in individuals without prior history of SARS-CoV-2 infection • Reduced risk of confirmed severe COVID-19 at least 14 days after completing a 2-dose vaccination regimen in individuals without prior history of SARS-CoV-2 infection • Subgroups - Efficacy findings consistent across subgroups (age ≥65 years, race, ethnicity, comorbidities)

Benefit/Risk Assessment in Context of Proposed EUA

Risks

- Reactogenicity: Local and systemic adverse reactions
- SAEs possibly related to vaccination
  - Intractable nausea/vomiting (n=1): temporally associated and biologically plausible
  - Facial swelling (n=2): temporally associated and biologically plausible
    - Potential contribution of dermal filler
- Serious hypersensitivity reactions have not been reported in this study but have been reported in clinical experience with Pfizer mRNA vaccine
- No specific safety concerns were identified in analyses of subgroups, including prior SARS-CoV-2 infection.
- Limitations of the risk assessment:
  - Follow up duration
  - Pregnant women were excluded

Item for VRBPAC Discussion (no vote)

In considering Moderna's plans for unblinding and crossover of placebo recipients, please discuss the most critical data to further inform vaccine safety and effectiveness to support licensure that should be accrued in:

- Ongoing clinical trials with the Moderna COVID-19 vaccine
- Other studies (e.g., additional clinical trials or observational studies) with the Moderna COVID-19 vaccine

Question for VRBPAC Vote (yes/no)

Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older?

Extra Slides

Post Hoc Analysis of Asymptomatic Infection Between Dose 1 and Dose 2—Per Protocol Set

RT-PCR NP Swab Results and Symptoms at Different Time Points	**Vaccine Group N=13,934 n (%)**	**Placebo Group N=13,883 n (%)**
Subjects with negative RT-PCR pre-dose 1 and positive RT-PCR pre-dose 2	13 (0.09)	39 (0.28)
Subjects with documented COVID-19 symptoms between dose 1 and 2	1 (<0.01)	2 (0.01)
Subjects with no documented COVID-19 symptoms between dose 1 and 2	12 (0.09)	37 (0.27)

Interim Analysis Dataset (Nov 11, 2020)

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No

Unadjudicated and CDC-defined COVID-19

Interim Analysis (PPS)

	Vaccine Group N=13934	**Placebo Group N=13883**	**VE (95% CI)**
COVID-19 starting 14 days after dose 2	6	107	94.5% (87.4, 97.6)
Secondary definition of COVID-19 starting 14 days after dose 2	6	121	95.1% (88.9, 97.8)

Scheduled Final Analysis (PPS)

	Vaccine Group N=14134	**Placebo Group N=14073**	**VE (95% CI)**
COVID-19 starting 14 days after dose 2	11	202	94.7% (90.2, 97.1)
Secondary definition of COVID-19 starting 14 days after dose 2	11	221	95.1% (91.1, 97.3)

Summary of Number of Participants With a Potential COVID-19 Illness or Eligible Symptom(s) Not Meeting Per-Protocol Case Criteria, Starting From Randomization, Per-Protocol Set

	Vaccine Group N=515 n (%)	Placebo Group N=542 n (%)	Total N=1057 n (%)
Only having a positive RT-PCR at Day 29 visit (not symptom-prompted) [a]	3 (0.6)	1 (0.2)	4 (0.4)
Only having a positive RT-PCR test (local, unscheduled) [b]	0	1 (0.2)	1 (0.1)
Without a positive RT-PCR	512 (99.4)	540 (99.6)	1052 (99.5)
RT-PCR negative (other than Day 29)	492 (95.5)	501 (92.4)	993 (93.9)
Only RT-PCR negative at Day 29	19 (3.7)	37 (6.8%)	56 (5.3)
No RT-PCR result post Baseline [c]	1 (0.2)	2 (0.4)	3 (0.3)

Post Hoc Efficacy Analyses—mITT Participants Who Received Only One Dose at the Time of Interim Analysis

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Cases n/N (person-years)	Placebo Group N=1079 Cases n/N (person-years)	VE (%) (95% CI)
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

**Subjects who were not at risk (cases or censored at prior time period) are excluded from this analysis

Post Hoc Efficacy Analyses—mITT Participants Who Received Only One Dose at the Time of Interim Analysis

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of subjects with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

Primary Efficacy Endpoint (Interim Analysis)—PPS

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)	Met Predefined Success Criterion
All subjects	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5/10407 (<0.1) 2.504	75/10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0/3527	15/3499 (0.4) 21.046	100%	NA

Secondary Efficacy Analysis of Severe COVID-19 (Interim Analysis)—PPS

Severe Case 14 Days After Dose 2 Based on Adjudication Committeee Assessments	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)
All subjects	0	11* (<0.1); 4.072	100%

*3 of the 11 cases resulted in hospitalization

Note: There was one severe case in a vaccine recipient which occurred 2 months after dose 2, requiring hospitalization, that was not adjudicated by the data cut off date