Summary of Available Safety/Efficacy Data for COVID-19 Vaccines (Updated 1/8/21)

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The Safety/Efficacy Subcommittee of the Vaccine Advisory Workgroup recommends that vaccination schedules for SARS-CoV-2 vaccines follow CDC ACIP Vaccine Recommendation and Guidelines, available at https://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Considerations for changes in vaccination schedules, including but not limited to changes in dose number per individual vaccinated, dose intervals, and dose amounts, should only be made in accordance to CDC ACIP Recommendations and Guidelines.

BNT162b2 (Pfizer)

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine[1]

Phase 3 Randomized Controlled Trial (Grade 1[S,E])

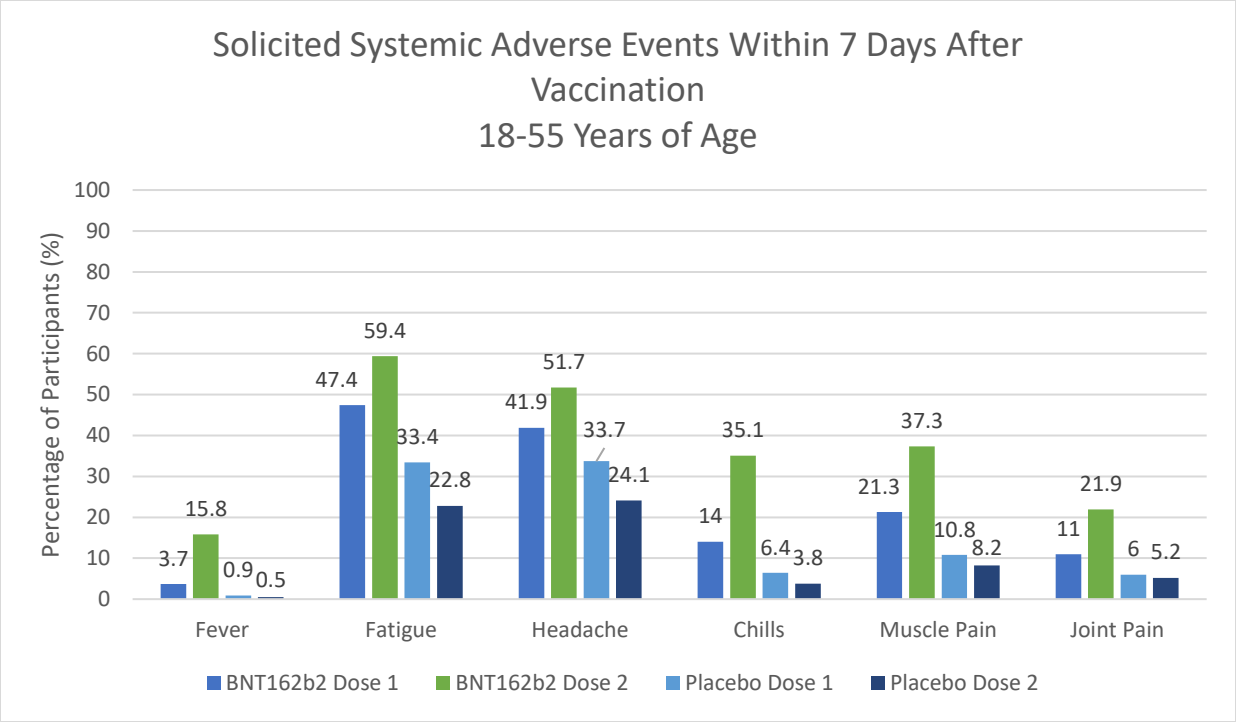
Vaccines and Related Biological Products Advisory Committee December 10, 2020[2]

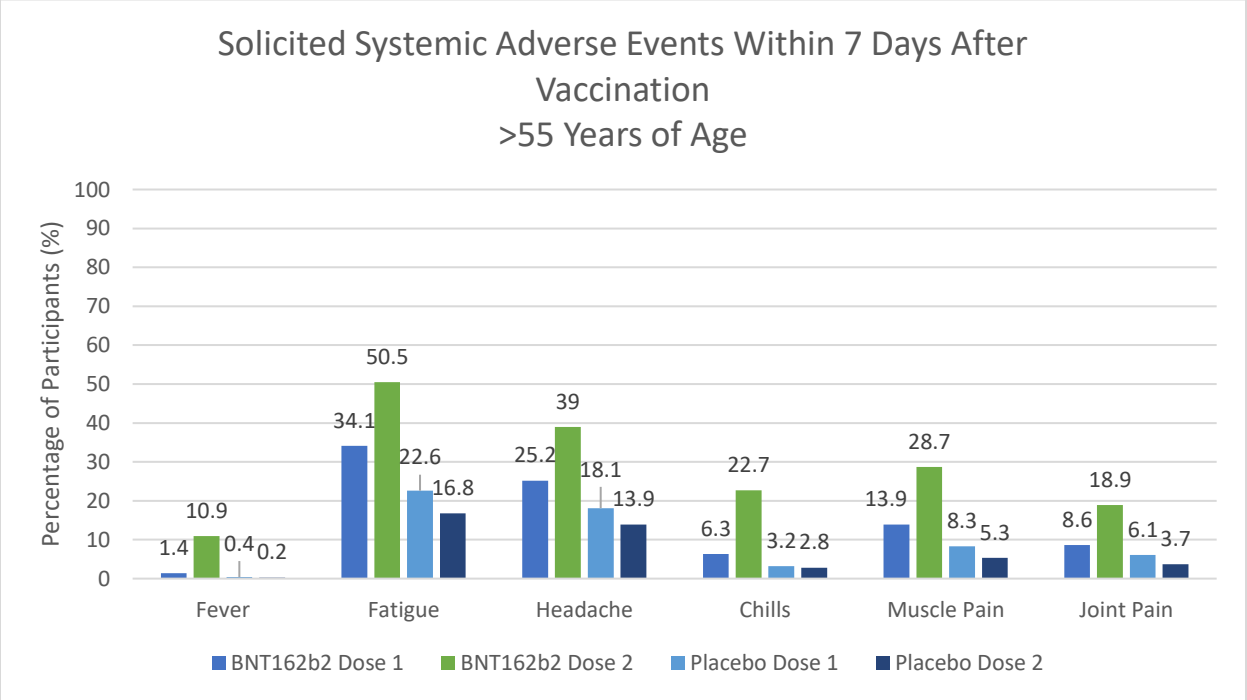
Phase 3 Randomized Controlled Trial, Preprint (Grade 2[S,E])

Safety in Study C4591001 Phase 2/3 (N=8183; cutoff was November 14, 2020)

Dose 1				
	Age 16-55 BNT162b2 (%)	Age 16-55 Placebo (%)	Age >55 BNT162b2 (%)	Age >55 Placebo (%)
Local reactions				
Redness	5	1	5	1
Swelling	6	0	7	1
Pain at injection site	83	14	71	9
Systemic reactions				
Fever	4	1	1	0
Fatigue	47	33	34	23
Headache	42	34	25	18
Chills	14	6	6	3
Vomiting	1	1	0	1
Diarrhea	11	12	8	7
Muscle pain	21	11	14	8
Joint pain	11	6	9	6
Dose 2				
	Age 16-55 BNT162b2 (%)	Age 16-55 Placebo (%)	Age >55 BNT162b2 (%)	Age >55 Placebo (%)
Local reactions				
Redness	6	1	7	1
Swelling	6	0	7	1
Pain at injection site	78	12	66	8
Systemic reactions				
Fever	16	0	11	0
Fatigue	59	23	51	17
Headache	52	24	39	14
Chills	35	4	23	3
Vomiting	2	1	1	0
Diarrhea	10	8	8	6
Muscle pain	37	8	29	5
Joint pain	22	5	19	4

- Frequency of severe local reactions was ≤0.6%
- No grade 4 (life-threatening) reactions were reported
- Median onset for local reactions was Day 1-Day 3 with median duration of 1-2 days
- Median onset for systemic events was Day 2-Day 3 with median duration of 1 day


Solicited Systemic Adverse Events Within 7 Days After Vaccination
18-55 Years of Age
Percentage of Participants (%)
100
90
80
70
60
50
40
30
20
10
0
3.7
15.8
0.9
0.5
47.4
59.4
33.4
22.8
41.9
51.7
33.7
24.1
14
35.1
6.4
3.8
21.3
37.3
10.8
8.2
11
21.9
6
5.2
Fever
Fatigue
Headache
Chills
Muscle Pain
Joint Pain
BNT162b2 Dose 1
BNT162b2 Dose 2
Placebo Dose 1
Placebo Dose 2


Solicited Systemic Adverse Events Within 7 Days After Vaccination
>55 Years of Age
Percentage of Participants (%)
100
90
80
70
60
50
40
30
20
10
0
1.4
10.9
0.4
0.2
34.1
50.5
22.6
16.8
25.2
39
18.1
13.9
6.3
22.7
3.2
2.8
13.9
28.7
8.3
5.3
8.6
18.9
6.1
3.7
Fever
Fatigue
Headache
Chills
Muscle Pain
Joint Pain
BNT162b2 Dose 1
BNT162b2 Dose 2
Placebo Dose 1
Placebo Dose 2

Adolescents Ages 12-15, N=100 (NOT INCLUDED IN EUA)

Dose 1		
	BNT162b2, N=49 (%)	Placebo, N=51 (%)
Local reactions		
Redness	2	0
Swelling	4	2
Pain at injection site	71.4	17.6
Systemic reactions		
Fever	14.3	0
Fatigue	49	25.5
Headache	42.9	35.3
Chills	30.6	7.8
Vomiting	Similar for vaccine and placebo for both doses	
Diarrhea	Similar for vaccine and placebo for both doses	
Muscle pain	22.4	13.7
Joint pain	12.2	9.8
Dose 2		
	BNT162b2, N=49 (%)	Placebo, N=51 (%)
Local reactions		
Redness	4	0
Swelling	6	0
Pain at injection site	58.7	8.7
Systemic reactions		
Fever	19.6	0
Fatigue	49	6.5
Headache	45.7	21.7
Chills	28.3	8.7
Vomiting	Similar for vaccine and placebo for both doses	
Diarrhea	Similar for vaccine and placebo for both doses	
Muscle pain	30.4	4.3
Joint pain	17.4	6.5

- Two severe local reactions were reported in the vaccine group (redness and pain at injection site)
- Most systemic events were mild to moderate in severity

Adverse Events in Participants with Median 2 Months Follow-Up After Dose 2

Subjects Reporting at Least 1 Adverse Event from Dose 1 to 1 Month After Dose 2 (N=37,586)		
	BNT162b2, N=18801 (%)	Placebo, N=18785 (%)
Any event	27	12.5
Related to vaccine	20.8	5.1
Severe	1.2	0.6
Any serious adverse event	0.5	0.4
Any event leading to withdrawal	0.2	0.1
Death	0	0

- There were 6 total deaths in the study; 2 in the vaccine group and 4 in the placebo group

- One participant in the vaccine group died from arteriosclerosis and the other died of cardiac arrest

Efficacy in Study C4591001 Phase 2/3 (N=36,621); cutoff was November 14, 2020)

First Primary Outcome: Vaccine Efficacy in Patients Without Evidence of Prior Infection With SARS-CoV-2 from 7 Days After Dose 2 (N=36621)				
	BNT162b2, N=18242	Placebo, N=18379	Efficacy (95% CI)	Pr (Efficacy>30%)
Confirmed COVID cases	8	162	95% (90.3-97.5%)	>0.9999
Severe cases	1	3	66.4% (-124.8-96.3%)	0.7429

- Results were similar when using CDC-defined symptoms

Second Primary Outcome: Vaccine Efficacy in Patients with and Without Evidence of Prior Infection with SARS-CoV-2 from 7 Days After Dose 2 (N=40137)				
	BNT162b2, N=19965	Placebo, N=20172	Efficacy (95% CI)	Pr (Efficacy>30%)
Confirmed COVID cases	9	169	94.6% (89.9-97.3%)	>0.9999
Severe cases	1	3	66.3% (-125.5-96.3%)	0.7419

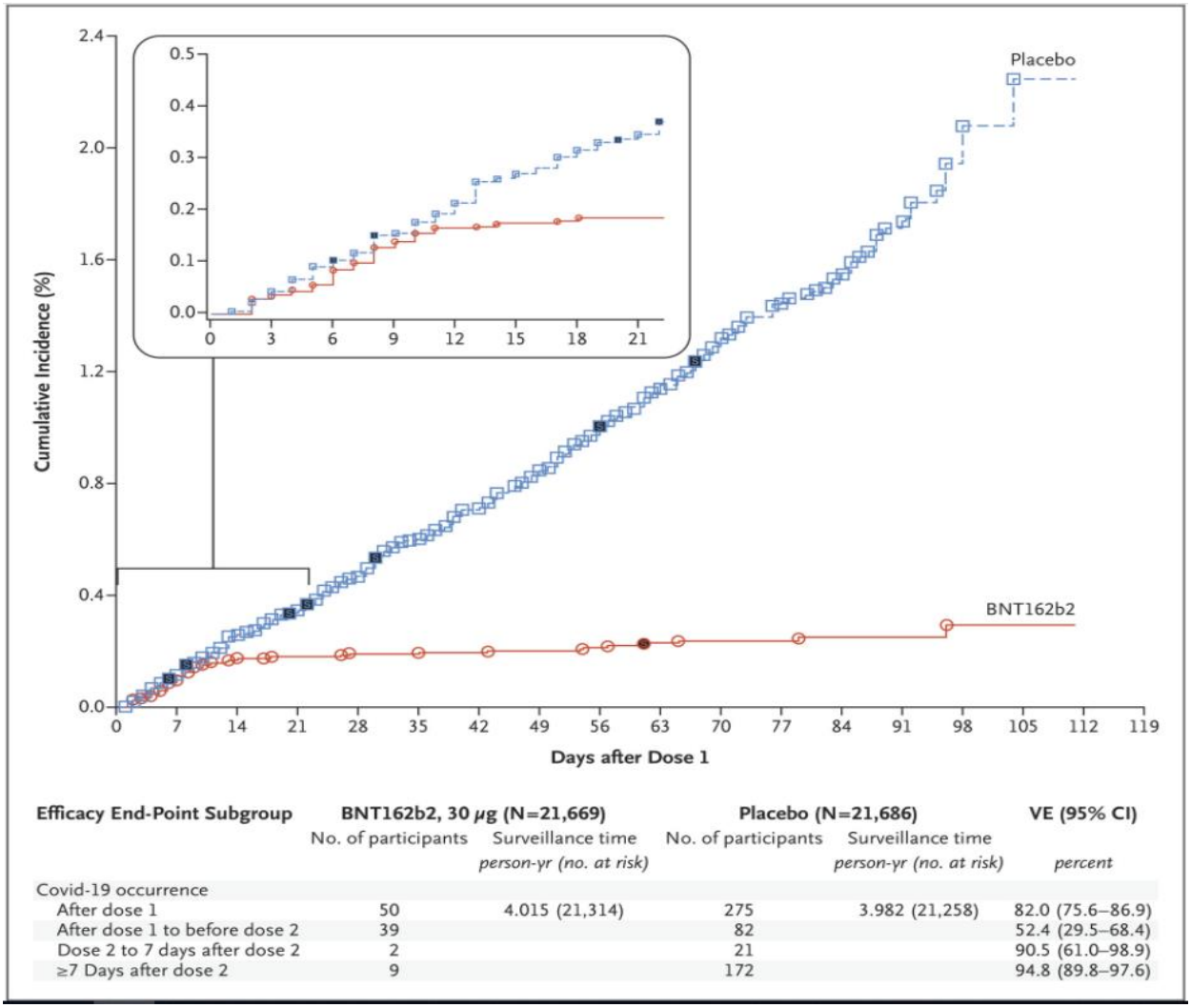
- Results were similar when using CDC-defined symptoms

Vaccine Efficacy in Patients Without Evidence of Prior Infection With SARS-CoV-2 from 14 Days After Dose 2 (N=36436)				
	BNT162b2, N=18175	Placebo, N=18261	Efficacy (95% CI)	Pr (Efficacy>30%)
Confirmed COVID cases	8	139	94.2% (88.7-97.2%)	>0.9999
Severe cases	1	3	66.4% (-124.7-96.3%)	0.7432

Vaccine Efficacy in Patients with and Without Evidence of Prior Infection with SARS-CoV-2 from 14 Days After Dose 2 (N=40136)				
	BNT162b2, N=19965	Placebo, N=20171	Efficacy (95% CI)	Pr (Efficacy>30%)
Confirmed COVID cases	8	144	94.4% (89.1-97.3%)	>0.9999
Severe cases	1	3	66.3% (-125.5-96.3%)	0.7418

Primary Efficacy Outcome by Age (N=36523)			
	BNT162b2, N=18198	Placebo, N=18325	Efficacy (95% CI)
All Participants	8	162	95 (90.3-97.6%
16-55 Years	5	114	95.6% (89.4-98.6%)
>55 Years	3	48	93.7% (80.6-98.8%)

All Confirmed Cases of COVID-19 After Dose 1 (N=43355)			
	BNT162b2, N=21669	Placebo, N=21686	Efficacy (95% CI)
First COVID-19 occurrence after dose 1	50	275	82% (75.6-86.9%)
After dose 1 to before dose 2	39	82	52.4% (29.5-68.4%)
Dose 2 to 7 days after dose 2	2	21	90.5% (61-98.9%)
≥ 7 days after dose 2	9	172	94.8% (89.8-97.6%)
First severe COVID-19 occurrence after dose 1	1	9	88.9% (20.1-99.7%)
After dose 1 to before dose 2	0	4	100% (-51.5-100%)
Dose 2 to 7 days after dose 2	0	1	100% (-3800-100%)
≥ 7 days after dose 2	1	4	75% (-152.6-99.5%)



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

COVID-19 Occurrence from 7 Days After Dose 2 in Participants Without Evidence of Prior Infection (N=36523)			
	BNT162b2, N=18198	Placebo, N=18325	Efficacy (95% CI)
Age			
16-55	5	114	95.6% (89.4-98.6%)
>55	3	48	93.7% (80.6-98.8%)
≥65	1	19	94.7% (66.7-99.9%)
Sex			
Male	3	81	96.4% (88.9-99.3%)
Female	5	81	93.7% (84.7-98%)
Race			
White	7	146	95.2% (89.8-98.1%)
Black/African American	0	7	100% (31.2-100%)
All others	1	9	89.3 (22.6-99.8%
Ethnicity			
Hispanic/Latino	3	53	94.4 (82.7-98.9%)
Non-Hispanic/Latino	5	109	95.4% (88.9-98.5%)
Country			
Argentina	1	35	97.2% (83.3-99.9%)
Brazil	1	8	88.7% (8.1-99.7%)
USA	6	119	94.9% (88.6-98.2)

Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints[3]

Press Release 11/18/20 (Grade 4[S,E])

- Final efficacy analysis for the Phase 3 trial has been completed
  - The vaccine met all primary efficacy endpoints
- Efficacy

	Placebo	BNT162b2	P-value
Confirmed COVID Cases	162	8	<0.0001
Severe Cases	9	1	-

  - Pfizer reported a vaccine efficacy rate of 95% in patients without prior COVID-19 infection (first primary endpoint) and in participants with and without prior COVID-19 infection (second primary endpoint)
  - Analysis was based on cases measured 7 days after the second dose was given
  - Efficacy was consistent across race, age, gender, and ethnicity
  - Efficacy in adults over 65 was reported to be >94%
- Safety
  - No serious safety concerns related to the vaccine have been reported by the DSMB

Grade 3 (severe) events (>2% frequency)	Occurrence (%)
Fatigue (1st and 2nd dose)	3.8
Headache (2nd dose)	2.0

  - Older adults tended to report fewer and milder adverse events following vaccination
- Next steps
  - The safety milestone required by the FDA for an EUA has been achieved

Pfizer and BioNTech plan to submit a request to the FDA for an EUA within days

Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study[4]

Press Release 11/9/20 (Grade 4[S,E])

- Enrollment
  - 43,538 participants
  - 42% of global and 30% of US participants have racially and ethnically diverse backgrounds
  - Ages 12-85
- Endpoints
  - Primary efficacy endpoint: confirmed COVID-19 cases accruing from 7 days after second dose
  - Secondary efficacy endpoint: confirmed COVID-19 cases accruing 14 days after second dose
  - Study will evaluate the potential to provide protection against COVID-19 in those who have had prior exposure and prevention against severe COVID-19
- Preliminary analysis (11/8/20)
  - 94 confirmed cases
  - Data Monitoring Committee reported >90% efficacy at 7 days after second dose
  - No serious safety concerns have been observed
- Looking forward
  - Final analysis will be done once a total of 164 confirmed COVID-19 cases have accrued
  - A median of two months of safety data following the second dose will be available by the third week of November
  - Participants will be monitored for long-term protection and safety for 2 years after their second dose
  - Pfizer expects to produce 50 million vaccine doses globally in 2020 and up to 1.3 billion doses in 2021

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates[5]

Phase 1 Clinical Trial (Grade 2^S)

	Age 18-55 (n=12), %	Age 18-55 Placebo (n=9), %	Age 65-85 (n=12), %	Age 65-85 Placebo (n=9), %
First Dose				
Pain at injection site	92	0	65	0
Redness	8	0	0	0
Swelling	0	0	0	0
Fever	17	0	0	0
Fatigue	42	33	25	22
Chills	33	0	0	0
Headache	50	33	0	11
Vomiting	8	0	0	0
Diarrhea	8	0	0	11
Muscle pain	25	0	0	22
Joint pain	17	0	0	11
Second Dose				
Pain at injection site	83	22	75	0
Redness	0	0	0	0
Swelling	0	0	0	0
Fever	17	0	8	0
Fatigue	75	56	42	0
Chills	58	11	17	0
Headache	67	11	25	0
Vomiting	0	11	0	0
Diarrhea	0	0	0	11
Muscle pain	58	0	25	0
Joint pain	17	0	8	0

- Adverse events were solicited for 7 days following vaccination
- No grade 4 adverse events reported in any group
- The only local AEs reported were pain at injection site
- A small number of recipients from younger group reported severe systemic AEs, but no recipients from older group reported severe systemic AEs
- Largest change in laboratory values was transient decreases in lymphocyte counts that resolved within a week

mRNA-1273 (Moderna)

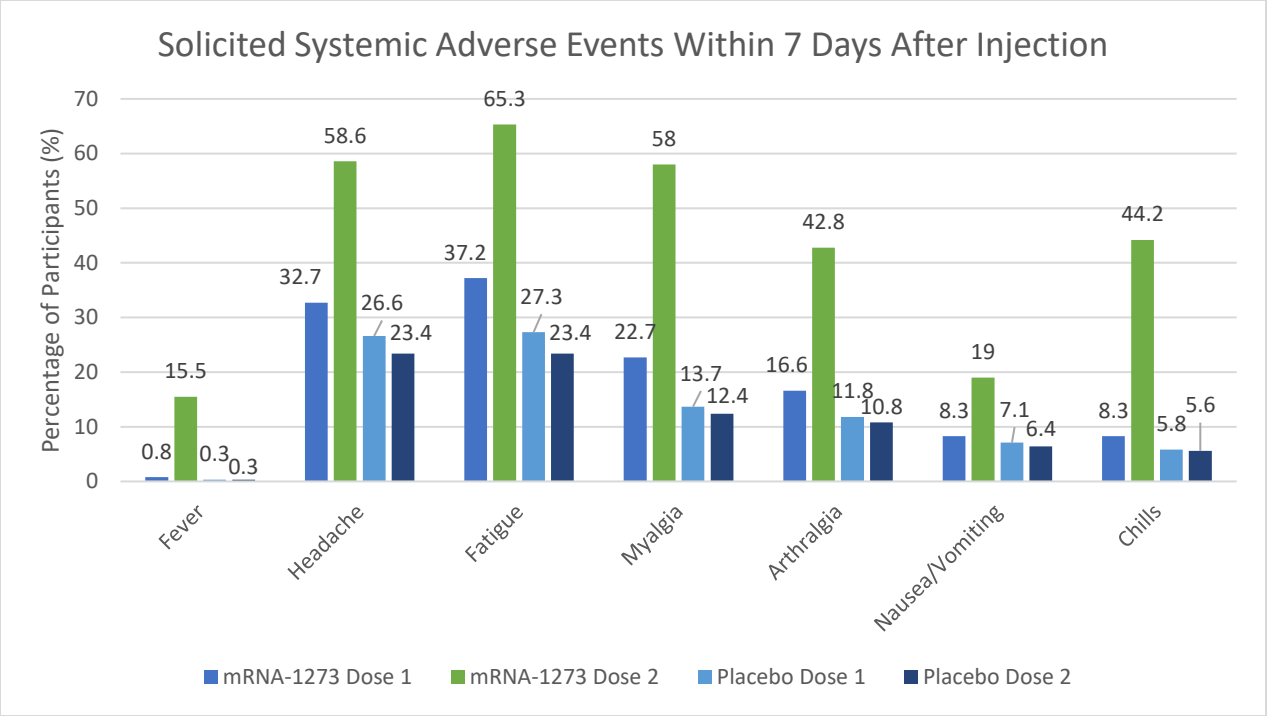
Vaccines and Related Biological Products Advisory Committee December 17, 2020[6]

Phase 3 Randomized Controlled Trial, Preprint (Grade 2[S,E])

Safety of Study 301 (November 25 Dataset)

Solicited Adverse Reactions Within 7 Days After 1st and 2nd Injection		
Dose 1		
	mRNA-1273 (N=15168), % (Grade 3)	Placebo (N=15155), % (Grade 3)
Local reactions	84.2 (3.5)	19.8 (0.5)
Pain	83.7 (2.7)	17.5 (0.4)
Erythema	2.8 (0.3)	0.4 (<0.1)
Swelling	6.1 (0.5)	0.3 (<0.1)
Lymphadenopathy	10.2 (0.3)	4.8 (0.2)
Systemic reactions	54.9 (3)	42.2 (2.1)
Fever	0.8 (<0.1)	0.3 (<0.1)
Headache	32.7 (1.8)	26.6 (1.3)
Fatigue	37.2 (1)	27.3 (0.7)
Myalgia	22.7 (0.6)	13.7 (0.3)
Arthralgia	16.6 (0.4)	11.8 (0.2)
Nausea/Vomiting	8.3 (<0.1)	7.1 (<0.1)
Chills	8.3 (0.2)	5.8 (<0.1)
Dose 2		
	mRNA-1273 (N=14677), % (Grade ≥3)	Placebo (N=14566), % (Grade ≥3)
Local reactions	88.6 (7)	18.8 (0.5)
Pain	88.2 (4.1)	17 (0.3)
Erythema	8.6 (2)	0.4 (0.1)
Swelling	12.2 (1.7)	0.3 (<0.1)
Lymphadenopathy	14.2 (0.5)	3.9 (0.1)
Systemic reactions	79.4 (15.9)	36.5 (2)
Fever	15.5 (1.5)	0.3 (<0.1)
Headache	58.6 (4.5)	23.4 (1.1)
Fatigue	65.3 (9.7)	23.4 (0.7)
Myalgia	58 (9)	12.4 (0.4)
Arthralgia	42.8 (5.2)	10.8 (0.3)
Nausea/Vomiting	19 (0.1)	6.4 (<0.1)
Chills	44.2 (1.3)	5.6 (0.1)

- Local and systemic adverse reactions were more commonly reported by younger adults (ages 18-64) than older adults (age ≥65)
- The majority of solicited adverse reactions occurred within 1-2 days after injected and persisted for a median of 1-2 days
- There were no grade 4 solicited local adverse reactions
- There were 11 grade 4 systemic reactions in the vaccine compared to 17 in the placebo group (mostly fever)



Unsolicited Adverse Events up to 28 Days After Any Vaccination		
	mRNA-1273, N=15185 (%)	Placebo, N=15166 (%)
All	23.9	21.6
Severe	1.5	1.3
Fatal	<0.1	<0.1
Leading to discontinuation from study vaccine	0.3	0.5
Medically attended	9	9.7

Unsolicited Adverse Events Reported by at Least 1% of Participants up to 28 Days After Injection		
	mRNA-1273, N=15185 (%)	Placebo, N=15166 (%)
Nervous system	4.5	4.1
Headache	3.1	3
Respiratory, thoracic, mediastinal	3.5	3.8
Cough	1.1	1
Oropharyngeal pain	1	1.3
Gastrointestinal	3.1	2.9
Diarrhea	1.2	1.1
Musculoskeletal and connective tissue	4.4	4.1
Arthralgia	1.4	1.1
Myalgia	1.3	1.2
General disorders and administration site	6.6	4.1
Fatigue	2.4	2.2
Injection site pain	1	0.4

- 13 deaths occurred during the study (6 in mRNA-1273 group and 7 in placebo group) and all were deemed to be unrelated to the vaccine
- Delayed injection-site reactions (those with onset on or after day 8) were noted in 244 participants (0.8%) after the first dose and in 68 participants (0.2%) after the second dose. Reactions were characterized by erythema, induration, and tenderness, and they resolved over the following 4 to 5 days.

Pregnancy

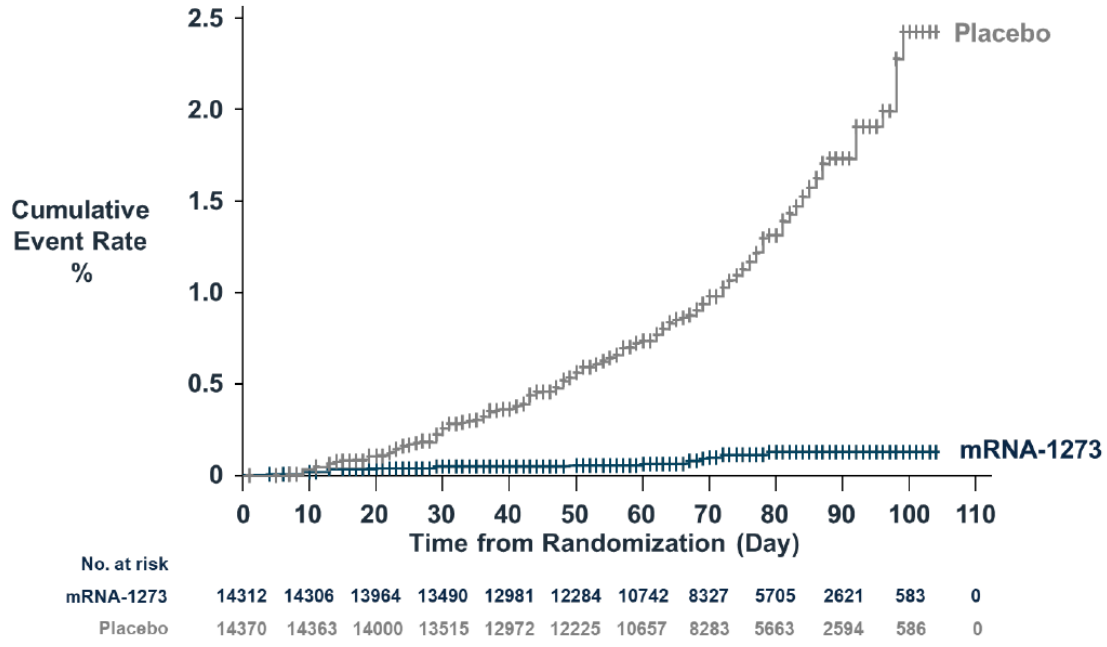
- To be enrolled in the study female subjects had to have a negative pregnancy test at enrollment and agree to use effective contraception for at least 3 months after final vaccination
- 13 pregnancies have been reported (6 in mRNA-1273 group and 7 in placebo group)
    - 10/13 were ongoing with no reported complications (all complications were in placebo group)

Efficacy of Study 301 (November 25 Dataset)

Primary Efficacy Endpoint: Vaccine Efficacy Starting 14 Days After Second Injection				
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)	P-value
Confirmed COVID-19 cases	11	185	94.1% (89.3-96.8%)	<0.0001
Person-years	3304.9	3273.7	-	-
Incidence per 1,000 person-years	3.33	56.51	0.94 (0.89-0.97)	-

- Median follow-up of 63 days

Kaplan-Meier Estimates of Time to First Occurrence of COVID-19 Starting After Randomization, mITT – Interim Analysis



Secondary Efficacy Endpoint: Cases of Severe COVID-19 Starting 14 Days After Second Injection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Cases of severe COVID-19	0	30	100% (N/A-100%)
Secondary Efficacy Endpoint: Cases of COVID-19 with Less Restrictive Definition of COVID-19 Starting 14 Days After Second Injection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Cases of COVID-19	11	221	95.1% (91.1-97.3%)

Secondary Efficacy Endpoint: Cases of COVID-19-Related Deaths Starting 14 Days After Second Injection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Cases of COVID-19	0	1	100% (N/A-100%)

Secondary Efficacy Endpoint: Cases of COVID-19 Starting 14 Days After First Injection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Cases of COVID-19	11	225	95.2% (91.2-97.4%)

Secondary Efficacy Endpoint: Cases of COVID-19 Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Cases of COVID-19	12	187	93.6% (88.6-96.5%)

Vaccine Efficacy from Dose 1 by Time Period			
First COVID-19 Occurrence	mRNA-1273, N=996	Placebo, N=1079	Vaccine Efficacy (95% CI)
After dose 1	7	39	80.2% (55.2-92.5%)
After dose 1 to 14 days after dose 1	5	11	50.8% (-53.6-86.6%)
>14 days after dose 1	2	28	92.1% (68.8-99.1%)

Subgroup Analysis of COVID-19 Cases Starting 14 Days After Second Injection			
	mRNA-1273, N=14134	Placebo, N=14073	Vaccine Efficacy (95% CI)
Age (years)			
18-64	7/10551	156/10521	95.6% (90.6-97.6%)
≥65	4/3583	29/3552	86.4% (61.4-95.2%)
Age and risk			
18-64 and not at risk	5/8396	121/8403	95.9% (90-98.3%)
18-64 and at risk	2/2155	35/2118	94.4% (76.9-98.7%)
≥65	4/3583	29/3552	86.4% (61.4-95.2%)
Sex			
Male	4/7366	87/7462	95.4% (87.4-98.3%)
Female	7/6768	98/6611	93.1% (85.2-96.8%)
At risk for severe			
Yes	4/3206	43/3167	90.9% (74.7-96.7%)
No	7/10928	142/10906	95.1% (89.6-97.7%)
Race and ethnicity			
White	10/9023	144/8916	93.2% (87.1-96.4%)
Communities of color	1/5088	41/5132	97.5% (82.2-99.7%)

Asymptomatic Infections as Measured by Scheduled Nasopharyngeal Swabs Prior to Second Injection		
	mRNA-1273, N=14134	Placebo, N=14073
Positive swab results with no documented COVID-19 symptoms	14	38

- Nasopharyngeal swabs were collected pre-dose 1 and pre-dose 2
- Approximately 2/3 fewer positive swabs in the vaccine group compared to placebo group, which suggests that some asymptomatic infections start to be prevented after the first injection

Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization[7]

Press Release 11/30/20 (Grade 4[S,E])

- Primary efficacy analysis of the Phase 3 study of mRNA-1273 confirms the high efficacy observed at the first interim analysis
- Efficacy

	Placebo	mRNA-1273	Efficacy (%)
Total Cases	185	11	94.1
Severe Cases	30	0	100

    - The primary endpoint is based on the analysis of confirmed COVID-19 cases starting 2 weeks following the second dose of vaccine
    - There has been 1 COVID-related death in the study in the placebo group
    - Efficacy was consistent across age, gender, race, and ethnicity
    - The 196 cases included 33 older adults 65+ and 42 participants from diverse communities
- Safety
    - No serious safety concerns have been identified
    - The most common adverse reactions include injection site pain, fatigue, myalgia, arthralgia, headache, and erythema/redness at injection site
    - Adverse reactions increased in severity after the second dose of the vaccine
- Looking forward
    - Moderna will submit for an Emergency Use Authorization (EUA) with the FDA today
    - They expect to have approximately 20 million doses of mRNA-1273 available in the US by the end of 2020 and 500 million to 1 billion doses globally in 2021

Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study[8]

Press Release 11/16/20 (Grade 4[S,E])

- Enrollment
  - >30,000 participants
  - Ages 18 and older
  - >7,000 participants over 65
  - >5,000 participants under 65 with high risk chronic diseases (diabetes, obesity, cardiac disease)
  - 11,000 participants from communities of color
- Endpoints
  - Primary: prevention of symptomatic COVID-19
  - Secondary: prevention of severe COVID-19, prevention of infection by SARS-CoV-2
- First Interim Analysis (11/16/20)

	Placebo	mRNA-1273	P-value
Confirmed cases	90	5	<0.0001
Severe cases	11	0	-

  - Reported vaccine efficacy: 94.5%

Safety Data (as reported by DSMB)	
Grade 3 (severe) events (>2% frequency)	Frequency (%)
First dose	
Injection site pain	2.7
Second dose	
Fatigue	9.7
Myalgia	8.9
Arthralgia	5.2
Headache	4.5
Pain	4.1
Erythema/redness at injection site	2.0

  - The majority of adverse events were mild or moderate in severity
- Moderna intends to submit for Emergency Use Authorization with the FDA in the coming weeks based on final analysis of 151 cases and median follow-up of more than 2 months

An mRNA Vaccine against SARS-CoV-2- Preliminary Report[9]

Phase 1 Clinical Trial (Grade 2^S)

Adverse Events for 18-55 Years Old, 100 µg		
	First Dose (n=15), %	Second Dose (n=15), %
Local AEs	93	100
Erythema/Redness	13	13
Induration/Swelling	13	7
Pain	93	100
Systemic AEs	67	100
Fever	0	40
Arthralgia	13	13
Fatigue	27	80
Chills	7	80
Headache	27	60
Myalgia	7	43
Nausea	0	47

- Adverse events were solicited for 7 days following vaccination
- All systemic AEs were mild or moderate
- Systemic or local AEs occurring in more than half of participants
    - Fatigue
    - Chills
    - Headache
    - Myalgia
    - Pain at injection site
- There were 90 unsolicited AEs reported but none were serious
- One patient from lower dose group withdrew before second dose due to transient urticaria related to first dose

Adverse Events for Older Adults, 100 µg Dose		
First Dose		
	56-70 Years (n=10), %	>70 Years (n=10), %
Local AEs	80	80
Systemic AEs	30	30
Second Dose		
Local AEs	90	100
Systemic AEs	80	80

- Most common solicited adverse events were headache, fatigue, myalgia, chills, and injection-site pain
- Adverse effects were more common after second dose
- Symptoms typically occurred on the day of vaccination or 1 day afterward and resolved quickly
- One systemic adverse event was classified as severe (fatigue in >70 years group)
- All unsolicited adverse events that were deemed by investigators to be related to the vaccine were mild

Ad26.COV2.S (Johnson & Johnson)

Safety and Immunogenicity of the Ad26.COV2.S COVID-19 Vaccine Candidate: Interim Results of a Phase 1/2a, Double-Blind, Randomized, Placebo-Controlled Trial[10]

Phase 1/2 Clinical Trial (Grade 2^S)

	Age 18-55 (n=402), %	Age ≥65 (n=394), %
Any AE	72	46
Local AEs	58	27
Systemic AEs	64	36
Fever	19	4
Grade 3 or higher AEs	11	1

- Adverse events were solicited for 7 days following vaccination
- Most common AEs were headache, fatigue, and myalgia
- All fevers occurred within 2 days of immunization and resolved within 1-2 days
- No participants discontinue the study due to an AE
- No grade 4 adverse events in any group
- 12 patients reported unsolicited AEs in the 28-day follow-up period that were considered by investigators to be related to the vaccine
    - All but 1 (worsening HTN) resolved during follow-up period
- One participant was hospitalized overnight with a fever due to suspicion of COVID-19 but recovered within 12 hours (fever judged to be vaccine-related)

ChAdOx1 nCoV-19/AZD1222 (AstraZeneca)

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK[11]

Phase 3 Clinical Trial (Grade 1[E])

Efficacy

Primary Efficacy Analysis: Efficacy Against SARS-CoV-2 More Than 14 Days After a Second Dose				
	Total Cases	ChAdOx1 nCoV-19 Cases/N (Incidence rate per 1000 person-years)	Control* Cases/N (Incidence rate per 1000 person-years)	Vaccine Efficacy (95% CI)
All vaccine recipients	131	30/5807 (44.1)	101/5829 (149.2)	70.4% (54.8-80.6%)
LD/SD**	33	3/1367 (14.9)	30/1374 (150.2)	90% (67.4-97%)
SD/SD***	98	27/4440 (56.4)	71/4455 (148.8)	62.1% (41.0-75.7%)

*Control was MenACWY vaccine or saline

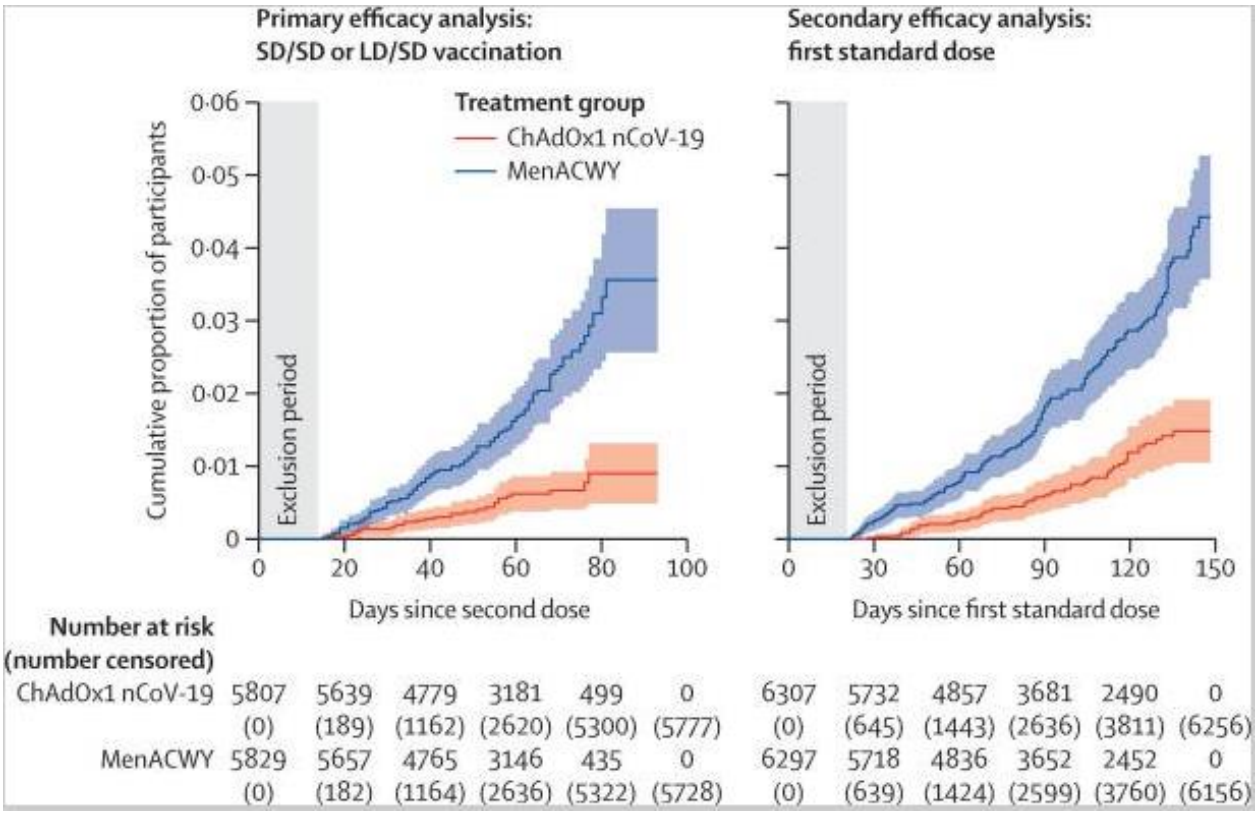
**LD/SD: Low dose for first dose, then standard dose for second dose

***SD/SD: Standard dose for both doses

- 53.2% of participants in the LD/SD group received a second dose >12 weeks after the first (median 84 days) and only 0.8% received the second dose within 8 weeks
- The median interval between doses for the SD/SD group in the UK study was 69 days and the median interval between doses for the SD/SD group in the Brazil study was 36 days

Subgroup Comparison of Efficacy Against SARS-CoV-2 More Than 14 Days After a Second Dose				
	Total Cases	ChAdOx1 nCoV-19 Cases/N	Control Cases/N	Vaccine Efficacy (95% CI)
SD/SD <6 weeks between doses	28	9/1702	19/1698	53.4% (-2.5-78.8%)
SD/SD ≥6 weeks between doses	70	18/2738	52/2757	65.4% (41.1-79.6)

Secondary Efficacy Analysis: Efficacy Against SARS-CoV-2 More Than 21 Days First Standard Dose				
	Total Cases	ChAdOx1 nCoV-19 Cases/N (Incidence rate per 1000 person-years)	Control Cases/N (Incidence rate per 1000 person-years)	Vaccine Efficacy (95% CI)
UK	90	28/3060 (35.4)	62/3064 (78.5)	55.0% (29.7-71.1%)
Brazil	102	23/3247 (46.7	79/3233 (162.4	71.2% (54.2-81.9%)
Total	192	51/6307 (39.7)	141/6297 (110.5)	64.1% (50.5-73.9%)



Hospitalizations for COVID-19		
	ChAdOx1 nCoV-19 (N=12021)	Control (N=11724)
≤21 days after the first dose	2	6
>21 days after the first dose and ≤14 days after the second dose	0	5
>14 days after the second dose	0	5
Severe COVID-19		
≤21 days after the first dose	0	0
>21 days after the first dose and ≤14 days after the second dose	0	1
>14 days after the second dose	0	1

AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19[12]

Press Release 11/23/20 (Grade 4[S,E])

- Active clinical trials
  - COV002
    - Single-blinded, multicenter, randomized Phase 2/3 trial
    - 12,390 participants in the UK
    - Participants are >18 and healthy or with medically stable chronic diseases and are at an increased risk of being exposed to COVID-19
    - Participants receive one or two intramuscular doses of a half dose or full dose of AZD1222 or comparator (meningococcal vaccine MenACWY)
  - COV003
    - Single-blinded, multicenter, randomized Phase 3 trial
    - 10,300 participants in Brazil
    - Participants are >18 and healthy or with medically stable chronic diseases and are at an increased risk of being exposed to COVID-19
    - Participants randomized to receive two intramuscular doses of full dose AZD1222 or comparator (meningococcal vaccine MenACWY)
- Methods
  - Two different dosing strategies
    1. Half dose followed by a full dose at least one month apart
    2. Full dose followed by a full dose at least one month apart
- Preliminary results

	Efficacy (%)
Dosing Strategy 1 (n=2,741)	90
Dosing Strategy 2 (n=8,895)	62
Combined (n=11,636)	70

  - All results were statistically significant (p=<0.0001)
  - Results from this interim analysis were based on a total of 131 cases of COVID-19
  - Independent DSMB determined analysis met its primary endpoint showing protection of COVID-19 occurring 14 days or more after receiving 2 doses of the vaccine
  - There were no confirmed serious safety events related to the vaccine
- Looking forward
  - Clinical trials are also being conducted in the US, Japan, Russia, South Africa, Kenya and Latin America with a total expected enrollment of up to 60,000 participants globally
  - AstraZeneca expects a capacity of up to 3 billion doses of the vaccine in 2021

Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial[13]

Phase 2/3 Clinical Trial (Grade 2^S)

- Patients were instructed to complete a diary card to record local and systemic adverse reactions for 7 days after each dose

Prime Vaccination			
	18-55 years (n=49), %	56-69 years (n=30), %	≥70 years (n=49), %
Local symptoms	88	73	30
Pain	61	43	20
Redness	0	0	2
Warmth	14	7	14
Itch	4	7	4
Swelling	0	0	4
Induration	0	0	2
Tenderness	76	67	49
Systemic symptoms	86	77	65
Feverish	43	10	10
Fever	24	0	0
Chills	35	10	4
Joint pain	33	17	14
Muscle ache	53	37	18
Fatigue	76	50	41
Headache	65	50	41
Malaise	41	27	24
Nausea	27	13	8
Boost Vaccination			
Local Symptoms	76	72	55
Pain	49	34	10
Redness	2	0	2
Warmth	12	14	4
Itch	12	3	2
Swelling	0	0	4
Induration	0	0	2
Tenderness	61	59	47
Systemic Symptoms			
Feverish	10	14	8
Fever	0	0	0
Chills	14	10	0
Joint pain	6	17	8
Muscle ache	35	24	18
Fatigue	55	41	33
Headache	31	34	20
Malaise	29	10	12

Nausea	8	21	6

- There were no severe local reactions to any dose of the vaccine
- Only 1 participant (1%) reported a severe systemic reaction after the prime dose and 7 participants (5%) reported a severe systemic reaction after the boost dose
- Fewer adverse events were reported after the boost vaccination than after the prime vaccination
- As of October 26, 2020, 13 serious adverse events have occurred, but none of them are considered to be related to the vaccine

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial[14]

Phase 1/2 Clinical Trial (Grade 2^S)

	N=487, %
Local AEs	
Pain after injection	67
Tenderness	83
Systemic AEs	
Fatigue	70
Headache	68
Muscle ache	60
Malaise	61
Chills	56
Feeling feverish	51
Temperature >38°C	18

- Adverse events were solicited for 7 days following vaccination
- Severity and intensity of local and systemic reactions was highest on day 1 after vaccination
- Pain after injection and tenderness were mostly mild to moderate
- All unsolicited adverse events considered to be potentially related to the vaccine occurring on days 0-28 were mild or moderate and resolved in the follow-up period
- Of unsolicited AEs days 0-28 post-vaccination, only headaches and oropharyngeal pain occurred in more than 2 patients
- Transient neutropenia was observed in 46% of participants

NVX-CoV2373 (Novavax)

Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine[15]

Phase 1/2 Clinical Trial (Grade 2^S)

First Dose		
	5 µg + Adjuvant (n=26), %	Placebo (n=23), %
Local AEs	69	40
Pain	39	13
Erythema/Redness	0	0
Induration/Swelling	0	0
Tenderness	65	30
Systemic AEs	46	39
Fever	0	0
Joint pain/Arthralgia	4	4
Fatigue	31	17
Malaise	12	9
Headache	23	30
Muscle pain/Myalgia	23	9
Nausea/Vomiting	4	4
Second Dose		
Local AEs	92	19
Pain	58	10
Erythema/Redness	4	5
Induration/Swelling	4	0
Tenderness	81	10
Systemic AEs	65	33
Fever	0	0
Joint pain/Arthralgia	27	10
Fatigue	46	14
Malaise	35	14
Headache	46	29
Muscle pain/Myalgia	46	14
Nausea/Vomiting	8	0

- No grade 4 AEs were reported
- 1 patient in 5 µg + adjuvant group had severe joint pain and fatigue
- No adverse event extended past 7 days after second vaccination
- Mean duration of events for first and second doses was 2 days or less
- Unsolicited adverse events were predominantly mild and there were no reports of serious adverse events
- Laboratory abnormalities
    - 10% had grade ≥2 laboratory abnormalities that showed no clinical manifestations
    - 5% had transient reductions in hemoglobin that resolved within 7-21 days
    - 3% had elevated liver enzymes that resolved within 7-14 days

Emergency Use Authorization for Vaccines Explained[16]

What is an Emergency Use Authorization (EUA)?

- An Emergency Use Authorization (EUA) is a mechanism to facilitate the availability and use of medical countermeasures, including vaccines, during public health emergencies. Under an EUA, FDA may allow the use of unapproved medical products, or unapproved uses of approved medical products in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain statutory criteria have been met, including that there are no adequate, approved, and available alternatives

Are the COVID-19 vaccines rigorously tested?

- Initially, in phase 1, the vaccine is given to a small number of generally healthy people to assess its safety at increasing doses and to gain early information about how well the vaccine works to induce an immune response in people
- In the absence of safety concerns from phase 1 studies, phase 2 studies include more people, where various dosages are tested on hundreds of people with typically varying health statuses and from different demographic groups, in randomized-controlled studies. These studies provide additional safety information on common short-term side effects and risks, examine the relationship between the dose administered and the immune response, and may provide initial information regarding the effectiveness of the vaccine
- In phase 3, the vaccine is generally administered to thousands of people in randomized, controlled studies involving broad demographic groups generates critical information on effectiveness and additional important safety data. This phase provides additional information about the immune response in people who receive the vaccine compared to those who receive a control, such as a placebo

What safety and effectiveness data are required to be submitted to FDA for an EUA request for a vaccine intended to prevent COVID-19?

- For an EUA to be issued for a vaccine, for which there is adequate manufacturing information to ensure quality and consistency, FDA must determine that the known and potential benefits outweigh the known and potential risks of the vaccine. An EUA request for a COVID-19 vaccine can be submitted to FDA based on a final analysis of a phase 3 clinical efficacy trial or an interim analysis of such trial
- From a safety perspective, FDA expects an EUA submission will include all safety data accumulated from phase 1 and 2 studies conducted with the vaccine, with an expectation that phase 3 data will include a median follow-up of at least 2-months (meaning that at least half of vaccine recipients in phase 3 clinical trials have at least 2 months of follow-up) after completion of the full vaccination regimen. In addition, FDA expects that an EUA request will include a phase 3 safety database of well over 3,000 vaccine recipients who have been followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen

What is the process that manufacturers are following to potentially make a COVID-19 vaccine available by EUA?

- When the phase 3 portion of the human clinical trial reaches a predetermined point that informs how well a vaccine prevents COVID-19, an independent data safety monitoring board will review the data and inform the manufacturer of the results. Based on the data and the interpretation of the data by this group, manufacturers decide whether and when to submit an EUA request to FDA, taking into consideration input from FDA
- After FDA receives an EUA request, our career scientists and physicians will evaluate all of the information included in the manufacturer's submission
- While FDA's evaluation is ongoing, we will also schedule a public meeting of our Vaccines and Related Biological Products Advisory Committee, which is made up of external scientific and public health experts from throughout the country. During the meeting, these experts, will discuss the safety and effectiveness data so that the public and scientific community will have a clear understanding of the data and information that FDA is evaluating to make a decision whether to authorize a COVID-19 vaccine for emergency use
- Following the advisory committee meeting, FDA's career professional staff will consider the input of the advisory committee members and continue their evaluation of the submission to determine whether the available safety and effectiveness and manufacturing data support an emergency use authorization of the specific COVID-19 vaccine in the United States

What are the plans for continued monitoring of COVID-19 vaccines authorized by FDA for emergency use?

- FDA expects vaccine manufacturers to include in their EUA requests a plan for active follow-up for safety, including deaths, hospitalizations, and other serious or clinically significant adverse events, among individuals who receive the vaccine under an EUA, to inform ongoing benefit-risk determinations to support continuation of the EUA
- FDA also expects manufacturers who receive an EUA to continue their clinical trials to obtain additional safety and effectiveness information and pursue licensure (approval)
- Post-authorization vaccine safety monitoring is a federal government responsibility shared primarily by FDA and the CDC, along with other agencies involved in healthcare delivery. There will be multiple, complementary systems in place with validated analytic methods that can rapidly detect signals for possible vaccine safety problems. The U.S. government has a well-established post-authorization/post-approval vaccine safety monitoring infrastructure that will be scaled up to meet the needs of a large-scale COVID-19 vaccination program. Some of these systems are the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the Biologics Effectiveness and Safety (BEST) Initiative, and Medicare claims data.

How will vaccine recipients be informed about the benefits and risks of any vaccine that receives an EUA?

- FDA must ensure that recipients of the vaccine under an EUA are informed that FDA has authorized the emergency use of the vaccine, of the known and potential benefits and risks, the extent to which such benefits and risks are unknown, that they have the option to accept or refuse the vaccine, and of any available alternatives to the product. Typically, this information is communicated in a patient "fact sheet." The FDA posts these fact sheets on our website

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