Virginia COVID-19 Vaccine Advisory Workgroup
Safety/Efficacy Subcommittee
Summary of Available Safety/Efficacy Data for COVID-19 Vaccines
11/23/2020 update

1. BNT162b2 (Pfizer)

RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study[1]

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	33	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

***Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study*[2]**

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

***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

2. mRNA-1273 (Moderna)

An mRNA Vaccine against SARS-CoV-2- Preliminary Report[4]

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

***Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study*[5]**

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

3. 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*[6]**

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)

4. **ChAdOx1 nCoV-19/AZD1222 (AstraZeneca)**

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[7]

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

***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*[8]**

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

AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19[9]

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

5. NVX-CoV2373 (Novavax)

Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine[10]

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*[11]**

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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