Summary Document

Topic: A Comparison of Vaccine Efficacy Elements in Advanced Stage Clinical Trial Protocols

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Overview:

This document summarizes key aspects related to the assessment of vaccine efficacy in four US based and one UK based, published COVID-19 (C-19) Phase 3 efficacy trial protocols. They cover efficacy objectives, C-19 case definitions, efficacy endpoints, censoring of early C-19 cases, null hypothesis, statistical methods, number of C-19 cases required for the primary efficacy endpoint analysis, and assumed C-19 background attack rates justifying the estimated sample size.

One C-19 case definition is included in Novavax' UK protocol, two are included in the US-based Moderna, Janssen, and BioNTech/Pfizer protocols, while the AstraZeneca/Oxford's US protocol also includes a third case definition. Each protocol has a unique protocol-specific C-19 case definition; this constitutes the primary efficacy endpoint (i.e. C-19 irrespective of disease severity) in four of the protocols (Moderna, BioNTech/Pfizer, AstraZeneca/Oxford, Novavax), but is a secondary in the Janssen protocol; Janssen's primary endpoint is moderate to severe/critical C-19 only. All four US-based protocols include the US-FDA harmonized case definition as secondary endpoint, which mirrors the CDC case definition and may be updated as new information is made available. They also include a secondary endpoint evaluating efficacy based on censoring of cases occurring prior to 14 days after the second dose to align endpoints across COVID-19 vaccine studies and allow for cross trial comparisons.

AstraZeneca/Oxford's US protocol includes a third case definition (i.e. secondary efficacy endpoint) based on the University of Oxford-defined symptom criteria that mirrors the current UK Public Health England case definition. None of the protocols define moderate or severe C-19 according to the WHO definition. All the protocols define severe C-19 according to the US-FDA recommended definition.

Two of the protocols include a Burden of Disease (BoD) endpoint. BoD is included as an exploratory efficacy endpoint in the Moderna protocol where scores of 0, 1, 2, and 3 represent asymptomatic SARS-CoV-2, symptomatic C-19 without hospitalization, hospitalization, and death, respectively. The Janssen protocol includes BoD as a secondary efficacy endpoint where 0, 1, and 2 represent asymptomatic SARS-CoV-2, mild and moderate C-19, and severe C-19 respectively, similar to the BOD endpoint discussed in the Mehrothra publication[1]. A separate Summary Document on BoD[2] has been published by CEPI.

There is a lack of guidelines and global consensus on which symptoms should trigger C-19 diagnostic work up. This is reflected in the trial protocols as significantly different triggering symptoms are included and are generally reflective of the protocol-defined case definitions.

	Moderna[3]	BioNTech/Pfizer[4]	Janssen Vaccine (J&J)[5]	AstraZeneca/Oxford (US trial)[6]	Novavax[7]
Protocol	mRNA-1273-P301	C4591001	VAC31518COV3001	D8110C00001	2019nCoV-302
Version	Amendment 3	V1.0	Amendment 3	Amendment 2	2.0
Date	20 August 2020	Not defined	15 September 2020	17 September 2020	23 October 2020
ClinTrials.gov [NCT Nr]	NCT04470427	NCT04368728	NCT04505722	NCT04516746	NCT04583995
General Trial Design					
N (randomization ratio)	30,000 (1:1 – vaccine vs placebo)	43,998 (1:1 – vaccine vs placebo)	60,000 (1:1 – vaccine vs placebo)	30,000 (2:1 – vaccine vs placebo)	15,000 (1:1 – vaccine vs placebo)
Primary vaccination schedule	2 doses: Day 1 & Day 29	2 doses: Day 1 & Day 22	Single dose: Day 1	2 doses: Day 1 & Day 29	2 doses: Day 0 & Day 21
Baseline COVID-19 (C-19) serostatus	Both seropositive and seronegative; PCR negative	Both seropositive and seronegative; PCR negative	Both seropositive and seronegative; PCR negative	Both seropositive and seronegative; PCR negative	Both seropositive and seronegative; PCR negative
Key strata	○ ≥18 - <65 years – low risk (60-75%) ○ ≥18 - <65 years – high risk ○ ≥65 years	○ ≥12 - <16 years ○ ≥16 - ≤55 years ○ >55 years (>40%)	○ ≥18 - <65 / ≥65 years ○ Co-morbidities yes / no ○ Sites	○ ≥18 - ≤55 years ○ ≥56 - ≤69 years ○ ≥ 70 years	○ ≥18 - <65 years ○ ≥65 - ≤84 years ○ Sites
Countries	USA	USA, Argentina, Brazil, South Africa, Turkey	USA, Argentina, Brazil, Chile, Colombia, Mexico, Peru, Philippines, South Africa, Ukraine	USA, Chile, Peru	UK
Case Definitions					
Protocol-specific C-19 case definition	Primary efficacy endpoint definition: ○ Positive RT-PCR **AND** ○ **Any ≥1** of: cough, dyspnoea, or clinical/radiographic pneumonia **OR** ○ **Any ≥2** of: fever, chills, myalgia, headache, sore throat, anosmia, or ageusia	Primary efficacy endpoint C-19 definition: ○ Positive SARS-CoV-2 NAAT **AND** ○ **Any ≥1** of: fever, cough dyspnoea, chills, myalgia, anosmia or ageusia, sore throat, diarrhoea, or vomiting	Molecularly confirmed C-19 with: ○ **Any ≥1** of fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, myalgia, GI symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, anosmia, ageusia, red or bruised looking feet or toes, or shaking chills or rigors	Primary efficacy endpoint definition: ○ Positive RT-PCR **AND** ○ **Any ≥1** of: dyspnoea, SpO_2 ≤ 93% or requiring supplemental O_2, clinical/radiographic pneumonia **OR** ○ **Any ≥2** of: fever, cough, myalgia, fatigue, anosmia or ageusia, vomiting, or diarrhoea	Primary efficacy endpoint definition: ○ Positive RT-PCR **AND** ○ **Any ≥1** of: fever, cough, dyspnoea, fatigue, myalgia, headache, anosmia or ageusia, sore throat, congestion, runny nose, nausea, vomiting or diarrhoea
C-19 US-FDA harmonized case definition[8] *(symptoms in blue are not included in C-19 protocol definition)*	Secondary efficacy definition: CDC case definition ○ Positive RT-PCR **AND** ○ **Any ≥1** of: cough, dyspnoea, fever or chills, myalgia, headache, sore throat, anosmia or ageusia, *fatigue, nasal congestion or runny nose, nausea, vomiting, or diarrhoea*	Secondary efficacy definition: CDC case definition ○ Positive SARS-CoV-2 NAAT **AND** ○ **Any ≥1** of: fever, cough, dyspnoea, chills, myalgia, anosmia or ageusia, sore throat, diarrhoea, vomiting, *fatigue, headache, nasal congestion or runny nose, or nausea*	Secondary efficacy definition: CDC case definition ○ Positive RT-PCR **AND** ○ **Any ≥1** of: cough, dyspnoea, fever or chills, myalgia, headache, sore throat, anosmia or ageusia, fatigue, nausea or vomiting, diarrhoea, runny nose, or *nasal congestion*.	Secondary efficacy definition: CDC case definition ○ Positive SARS-CoV-2 NAAT ○ **Any ≥1** of: fever (≥ 38.0C) or *chills,* cough, dyspnoea, fatigue, myalgia, *headache,* ageusia or anosmia, *sore throat, nasal congestion or runny nose*, nausea or vomiting, or diarrhoea	Not defined
Mild C-19 definition	Not defined	Not defined	Molecularly confirmed C-19 with: ○ **Any ≥1** of: fever, sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, myalgia, GI symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, anosmia/ageusia, red or bruised looking feet or toes, or shaking chills/rigors	Not defined	Molecularly confirmed C-19 with: ○ **Any ≥1** of: fever, cough; **OR** ○ **Any ≥2** of: dyspnoea, fatigue, myalgia, headache, anosmia or ageusia, sore throat, congestion, runny nose, nausea, vomiting or diarrhoea
Moderate C-19 definition,	Not defined	Not defined	Molecularly confirmed C-19 with: ○ **Any ≥1** of: RR>20/min, abnormal SpO_2 > 93%, pneumonia, DVT, or dyspnoea **OR**	Not defined	Molecularly confirmed C-19 with: ○ **Any ≥1** of: fever, high fever (≥ 38.4°C), dyspnoea, RR 20-29/min, SpO2: 94% to 95%, pneumonia or

			○ **Any ≥2** of: fever, HR>90, shaking chills/rigors, cough, malaise, headache, myalgia, GI symptoms, anosmia/ageusia, red or bruised looking feet or toes		LRTI by chest x-ray or chest CT, adventitious sounds on lung auscultation
Severe C-19 definition	Protocol-defined symptomatic C-19 PEE **AND** severe clinical illness defined as ≥1 of: ○ Respiratory rate (RR) ≥ 30/min ○ Heart rate (HR) ≥ 125 BPM ○ SpO_2 ≤ 93% or PaO_2/FIO_2 <300 **OR** ARDS **OR** shock **OR** organ failure **OR** ICU/CCU admission **OR** death	Confirmed C-19 with clinically severe systemic illness defined as ≥1 of: ○ RR ≥30/min ○ HR ≥125 BPM ○ SpO_2 ≤93% or PaO_2/FIO_2 <300 **OR** respiratory failure **OR** shock **OR** organ failure **OR** ICU/CCU admission **OR** death	Molecularly confirmed C-19 with clinically severe systemic illness defined as ≥1 of: ○ RR ≥30/min ○ HR ≥125 BPM ○ SpO_2 ≤93% or PaO_2/FIO_2 <300 **OR** respiratory failure **OR** shock **OR** organ failure **OR** ICU/CCU admission **OR** death	RT-PCR confirmed C-19 with clinically severe systemic illness defined as ≥1 of: ○ RR ≥30/min ○ HR ≥125 BPM ○ SpO_2 ≤93% or PaO_2/FIO_2 <300 **OR** respiratory failure **OR** shock **OR** organ failure **OR** ICU/CCU admission **OR** death	Molecularly confirmed C-19 with: **Any ≥1** of: ○ RR ≥30/min ○ HR ≥125 BPM ○ SpO2: ≤ 93% or PAO2/FIO_2 < 300 **OR** high flow oxygen therapy or NIV/NIPPV **OR** mechanical ventilation **OR** organ failure **OR** ICU **OR** death
Symptoms to trigger PCR & case work-up	○ Respiratory symptoms or fever of any duration (cough, dyspnoea, temp ≥38ºC) ○ Defined C-19 symptoms ≥ 48 hrs (chills, myalgia, headache, sore throat, anosmia, ageusia, rhinorrhoea, nasal congestion, fatigue, nausea, vomiting, or diarrhoea)	○ Fever ○ New or increased cough ○ New or increased dyspnoea ○ Chills ○ New or increased myalgia ○ New ageusia/anosmia ○ Sore throat ○ Diarrhoea ○ Vomiting ○ A diagnosis of C-19 outside the trial	○ **Any ≥1** new onset, unexplained, fever, sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, myalgia, GI symptoms, cough, chest congestion, dyspnoea, runny nose, wheezing, skin rash, eye irritation or discharge, chills, anosmia/ageusia, red or bruised looking feet or toes, SpO2 ≤95%, HR ≥ 90 BPM, neurological symptoms, skin rash, confusion, bluish lips or face, thrombosis, or clinically suspected C-19	○ Symptoms of any duration: tachypnoea, dyspnoea, fever ○ Additional CDC-defined C-19 symptoms lasting ≥ 48 hrs: chills, cough, myalgia, body ache, headache, sore throat, anosmia, ageusia, rhinorrhoea, nasal congestion, fatigue, nausea, vomiting, or diarrhoea	**Any ≥1** of: ○ Fever ○ New onset cough ○ New onset dyspnoea ○ New onset fatigue ○ New onset myalgia ○ New onset headache ≥ 48 hours ○ New onset anosmia/ageusia ○ Acute Sore throat, congestion, runny nose ○ New onset nausea, vomiting or diarrhoea ≥ 48 hours
Primary Efficacy Analysis					
Primary efficacy objective and primary efficacy endpoint (PEE)	Prevention of first occurrence of protocol-defined symptomatic C-19 **regardless of disease severity** – See protocol-specific C-19 definition above	Efficacy against (first) confirmed symptomatic C-19 **regardless of disease severity**, assessed in those without evidence of infection before vaccination, and separately in those with and without evidence of infection before vaccination defined for the primary efficacy endpoint. See protocol-specific C-19 definition above.	Prevention of first occurrence of **moderate to severe/critical** C-19 – defined for the primary efficacy endpoint as: ○ Positive RT-PCR or other NAAT **AND** ○ Moderate C-19 (**Any ≥1** of: RR>20/min, abnormal SpO_2 > 93%, pneumonia, DVT, or dyspnoea **OR Any ≥2** of: fever, chills/rigors, cough, malaise, headache, myalgia, Gastrointestinal symptoms, anosmia/ageusia, or limb rashes) **OR** ○ Severe/critical C-19	Prevention of first case of symptomatic C-19 **regardless of disease severity** - defined for the primary efficacy endpoint. See protocol-specific C-19 definition above.	Prevention of first case of symptomatic C-19 **regardless of disease severity** – defined for the primary efficacy endpoint as: ○ Positive RT-PCR **AND** ○ Mild C-19 **OR** ○ Moderate C-19 **OR** ○ Severe C-19
Analysis set PEE	Per-protocol set, modified ITT ○ As randomized ○ All doses received (Grade 3 Adverse Reaction post dose 1 is contraindication for dose 2) ○ No significant Protocol Deviations (PDs) ○ PCR & anti-N-ab negative at baseline	Evaluable Efficacy population: ○ As randomized ○ All doses received (Grade 3 Adverse Reaction post dose 1 is contraindication for dose 2) ○ No significant PDs	Per-protocol set ○ As randomized ○ SARS-CoV-2 negative at baseline ○ No major PDs	Full Analysis Set ○ As randomized ○ Received 2 doses ○ Not seropositive at baseline	Per-protocol set ○ As randomized ○ SARS-CoV-2 negative at baseline ○ Receive 2 doses ○ No major PDs before first C-19 episode
Censoring of early C-19 cases PEE	All cases up to 14 days post 2nd dose	All cases up to 7 days post 2nd dose	All cases up to 14 days post vaccination (Day 15)	All cases up to 14 days post 2nd dose	All cases up to 7 days post 2nd dose
Target Vaccine Efficacy (VE) point estimate PEE	60%	60%	60%; success: ≥50%	≥ 50%	60%
Null hypothesis (H0) (lower bound 95% CI VE)	H0: VE ≤ 30%	H0: VE ≤ 30%	H0: VE ≤ 30%	H0: VE ≤ 30%	H0: VE ≤ 30%

VE statistical analysis method PEE	VE=1-Hazard Ratio using (stratified) Cox proportional hazards model	VE=100 x (1-IRR [illness rate-ratio vaccine to placebo]) using beta-binomial Bayesian model and incidence per 1,000 PY of follow-up	Truncated sequential probability ratio test	VE=1-RR using Poisson regression model	VE=1-RR using Poisson regression model
Number of planned interim analyses (IA) and statistical considerations	2 IA ○ 1st IA: 53 cases ○ 2nd IA: 106 cases ○ Objective of IA is early detection of VE > 30% ○ No intention to stop study early if efficacy is demonstrated at any IA ○ If efficacy is demonstrated at IA, subsequent IA or primary analysis will be considered supportive	1st IA performed at 94 cases. Final analysis planned at 164 cases[9] ○ VE will be declared if first primary objective is met ○ Study will stop for lack of benefit if predicted probability of success at final analysis or study success is <5%	Continuous (weekly) monitoring after 4 criteria are met: first 50% of subjects have ≥ 2 months of follow-up after vaccination; ≥ 6 C-19 cases for ≥ 60 years age group; ≥20 cases meeting PEE definition of moderate to severe/critical C-19; subset of ≥5 cases meeting primary endpoint definition of severe/critical C19. ○ If > 154 primary endpoints are observed before the 4 criteria are met, a single analysis will take place as soon as the conditions are met, using the full 2.5% one-sided significance level ○ If 4 criteria are met, health authority interaction will be triggered	1 IA ○ 150 cases ○ A statistically significant finding at IA (i.e. 2 sided 99.69% CI >30%) will not be considered a reason to stop study, but will be interpreted as early assessment of efficacy	2 IA ○ 1st IA: 66 cases ○ 2nd IA: 110 cases ○ Will be performed by an unblinded statistical team. ○ Based on communication received from statistical team, sponsor may stop study to unblind accrued data or continue study while maintaining blind for more robust safety and efficacy data.
Cases required for VE PEE	151 cases will provide 90% power to detect 60% reduction in hazard	Assuming a true VE of 60% and IA, 164 cases will provide 90% power to conclude true VE >30%	154 cases will provide 90% power to detect 60% reduction in hazard	150 cases to detect a VE of 60% with >90% power	152 cases to detect a VE of 60% with 90% power
Assumed background attack rate (incidence placebo arm)	0.75% / 6 months (1.5% / annum)	1.3% / annum	1.4% of moderate/severe C-19 during the first 3 months, with a 50% reduction in Month 4, and 62% reduction in the months thereafter	0.8% -timeframe not provided	1% to 5% / annum
Burden of Disease endpoint score (BoD score reflects the severity of symptoms. BoD endpoint is based on post SARS-CoV-2 infection follow-up.)	Uninfected/Asymptomatic infection = 0 Symptomatic without hospitalization = 1 Hospitalization = 2 Death = 3	Not defined	Uninfected/Asymptomatic infection = 0 Mild & Moderate C-19 = 1 Severe C-19 = 2	Not defined	Not defined
Selected secondary and exploratory endpoints					
Secondary efficacy objectives	○ Prevention of all C-19 (secondary, US-FDA harmonized C-19 case definition) ○ Prevention of all serologically confirmed SARS-CoV-2 infection regardless of symptomatology or C-19 severity ○ Prevention of severe C-19 ○ VE against C-19 death	○ Prevention of all symptomatic C-19 regardless of severity according to the secondary US-FDA harmonized C-19 case definition in those seronegative at baseline, and regardless of baseline serostatus ○ Prevention severe C-19 in those seronegative at baseline, and regardless of baseline serostatus ○ Prevention of confirmed C-19 regardless of disease severity, assessed in those without evidence of infection before vaccination, and separately in those with and without evidence of infection before vaccination[4]	○ Prevention moderate to severe/critical C-19 regardless of baseline serostatus ○ Prevention of mild C-19 ○ Prevention of C-19 hospitalization ○ Prevention of all SARS-CoV-2 infections regardless of symptomatology. ○ BoD endpoint for symptomatic C-19 to be evaluated.	○ Prevention of first symptomatic C-19 regardless of severity according to the secondary US-FDA harmonized C-19 case definition ○ Prevention of all symptomatic C-19 regardless of severity according to the secondary Oxford C-19 case definition (**Any ≥1** of: fever, cough, dyspnoea, anosmia, ageusia) ○ Prevention of severe/critical C-19 ○ Prevention of C-19-related Emergency Department visits ○ Prevention of SARS-CoV-2 infection as measured by anti-N-ab seroconversion	○ Key secondary endpoint: Prevention of first symptomatic moderate or severe C-19 in those seronegative at baseline ○ Prevention of all symptomatic C-19 regardless of severity or baseline serostatus ○ Prevention of hospitalization, ICU admission or mechanical ventilation regardless of baseline serostatus ○ Prevention of mild C-19 regardless of baseline serostatus

Key exploratory efficacy objectives	○ VE against BoD ○ VE against all-cause mortality ○ VE against duration of C-19 symptoms	Not defined	○ VE in preventing of SARS-CoV-2 infection in participants with comorbidities	○ VE against all-cause mortality ○ VE against C-19 related deaths ○ VE in preventing C-19 related hospitalizations ○ VE in preventing C-19-related ICU admissions	○ VE against symptomatic all severity C-19 onset ≥14 days after dose 1 in those seronegative at baseline

Ab: Antibody; ARDS: Acute respiratory distress syndrome; BOD: Burden of disease; CI: Confidence interval; CCU: Critical care unit; C-19: Coronavirus disease 2019; CDC: US Centers for Disease Control and Prevention; DVT: Deep venous thrombosis; FDA: Food and Drug Administration; FiO_2: Fraction of inspired oxygen; GI: Gastrointestinal; H0: Null hypothesis; IA: Interim analysis; ICU: Intensive care unit; IRR: Incidence rate ratio; ITT: Intention to treat; NAAT: Nucleic acid amplification test; NIV: Non-invasive ventilation; NIPPV: Non-invasive positive pressure ventilation; PaO_2: Partial pressure of oxygen; PD: Protocol deviation; PEE: Primary efficacy endpoint; PY: Person years; RT-PCR: Reverse transcriptase- polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SpO_2: Peripheral capillary oxygen saturation; VE: Vaccine efficacy

References

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