Topic: A Comparison of Study Population Inclusion and Exclusion Criteria reported in Advanced Stage Clinical Trial Protocols

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Overview:

This document summarizes the inclusion/exclusion criteria for study populations in five published COVID-19 (C-19) Phase 3 efficacy trial protocols and one summary document published by CEPI on the inclusion of at-risk populations in C-19 efficacy trials. Trial participants should meet all inclusion criteria and no exclusion criteria. These criteria cover areas such as age, comorbidities, reproductive health, baseline SARS-CoV-2 serostatus, race, and ethnicity.

The BioNTech/Pfizer protocol includes a minimum enrolment age of 12 years, while only subjects aged ≥18 years are included in the Moderna, Janssen, AstraZeneca (AZ)/Oxford, and Novavax protocols. No upper age limit is defined in the US-based protocols (BioNtech/Pfizer, Moderna, Janssen, and AZ/Oxford); however, the UK-based Novavax protocol defines an upper limit of 84 years for recruitment.

All protocols and the CEPI document recommend enrolment of subjects with stable pre-existing health conditions, but the definition of stable disease differs. Underlying comorbidities include for example obesity, diabetes, hypertension, cardiovascular diseases, and chronic respiratory, liver and kidney disease. The definition of stable disease in the Moderna, Janssen, and AZ/Oxford protocols and the CEPI document requires no therapy change or hospitalization for worsening of comorbidities for three months prior to enrolment, whilst the BioNtech/Pfizer and Novavax protocols require six and four weeks of stable treatment, respectively. The AZ/Oxford and Novavax protocols allow for inclusion of mild to moderate, well-controlled comorbidities.

Use of appropriate contraception by female subjects is required for 28 days prior to enrolment in all protocols, and this must be continued until 28 days after the second dose in the BioNTech/Pfizer protocol, two months after the second dose in the AZ/Oxford protocol, and three months after a single dose in the Janssen protocol and second dose in the Moderna and Novavax protocols. The latter protocols also consider representative enrolment of racial and ethnic minorities.

The Moderna, AZ/Oxford, and Novavax protocols recommend exclusion of subjects with a known history of SARS-CoV-2 infection. The Pfizer/BioNTech protocol excludes previous C-19, while all protocols enrol without knowing baseline SARS-CoV-2 serostatus. The Janssen protocol recommends unique exclusion criteria for underlying conditions for stage 1A and 2A of enrolment. The CEPI document, similar to the US-FDA guidance, recommends that trials do not screen for or exclude participants with history or laboratory evidence of prior SARS-CoV-2 infection. All protocols recommend the inclusion of HIV positive subjects on stable antiretroviral treatment.

	ModeRNA[1]	BioNTech/Pfizer[2]	Janssen Vaccine (J&J)[3]	AstraZeneca/Oxford (US trial)[4]	Novavax (UK trial)[5]	CEPI Summary Document[6]
Protocol	mRNA-1273-P301	C4591001	VAC31518COV3001	D8110C00001	2019nCoV-302	Not defined
Version	Amendment 3	V1.0	Amendment 3	Amendment 2	V 1.0	V 1.0
Date	20 August 2020	Not defined	15 September 2020	17 September 2020	24 August 2020	15 July 2020
ClinTrials.gov [NCT Nr]	NCT04470427	NCT04368728	NCT04505722	NCT04516746	NCT04583995	Not applicable
Estimated enrolment	30,000	43,998	60,000	30,000	9000	Not defined
General criteria						
Age strata	○ ≥18-65, >65	○ ≥12 - <16, ≥16 - ≤55, >55	○ ≥18 to <60; ≥60	○ ≥18 - ≤55; ≥56 - ≤69; ≥ 70	○ ≥18 - ≤64; ≥ 65- ≤84	○ Not applicable
Stable disease definition (inclusion criteria)	○ Enrol pre-existing stable medical conditions defined as: Disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrolment	○ Enrol pre-existing stable medical conditions defined as: Disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment ○ Specific criteria: HIV HBV HCV	○ Enrol pre-existing stable medical conditions defined as: Disease with stable, well controlled signs and symptoms and stable dose for ≥12 weeks before enrolment and expected to remain stable for the duration of the study	○ Enrol pre-existing stable medical conditions defined as: Disease not requiring change in therapy / hospitalization for worsening disease during 3 months prior to enrolment. ○ Include mild / moderate, but not severe, well-controlled comorbidities.	○ Enrol pre-existing stable medical conditions defined as: Diseases not requiring hospitalisation; with no organ function deterioration and no new treatments or major dose adjustments 4 weeks prior to enrolment. ○ Include mild or moderate, but not severe, well-controlled comorbidities	○ Enrol pre-existing controlled/stable medical conditions defined as: Diseases on the same medication for ≥3 months prior to enrolment
Female participant reproductive health inclusion criteria	○ Not pregnant/breastfeeding ○ Not a WOCBP ○ Contraceptive use/abstain 28 days before Day1 ○ Contraceptive use ≥3 months after Dose 2 ○ Not breastfeeding	○ Not pregnant/breastfeeding **AND** ○ Any ≥1 of Not a WOCBP; WOCBP using contraceptive ≥28 days after last dose	○ Not a WOCBP **OR** ○ WOCBP on contraceptive for 3 months after vaccination ○ Negative pregnancy test at screening, Day 1	○ Not a WOCBP **OR** ○ WOCBP with negative pregnancy test on day of screening, Day 1; **AND** ○ One contraceptive 28 days prior to Day 1	○ Not pregnant or breastfeeding ○ WOCBP heterosexually inactive from 28 days prior to enrolment through 3 months after last dose **OR** ○ Contraceptive use from 28 days prior to enrolment through 3 months after last dose	○ Not defined
Baseline SARS-CoV-2 serostatus	○ Enrol without baseline SARS-CoV-2 serostatus screening ○ Exclude those with known *history* of SARS-CoV-2 infection	○ Enrol without baseline SARS-CoV-2 serostatus screening ○ Exclude previous clinical or microbiological *diagnosis* of COVID-19	○ Enrol without baseline SARS-CoV-2 serostatus screening ○ In high seroprevalence areas a screening serologic test for past or current SARS-CoV-2 infection at the sponsor's discretion, to restrict seropositive subjects	○ Enrol without baseline SARS-CoV-2 serostatus screening ○ Excludes those with known *history* of laboratory-confirmed SARS-CoV-2 infection	○ Enrol without baseline SARS-CoV-2 serostatus screening ○ Exclude history of laboratory-confirmed COVID-19 infection at any time prior to randomisation	○ Individuals with a history or laboratory evidence of prior SARS CoV-2 infection should not be excluded from efficacy trials
Race	○ Aim to enrol a representative sample from racial minorities	○ Enrolment targets not defined	○ Aim to enrol a good representation of race	○ Enrolment targets not defined	○ Enrol from racial minorities	○ Enrolment targets not defined
Ethnicity	○ Aim to enrol a representative sample from ethnic minorities	○ Enrolment targets not defined	○ Aim to enrol a good representation of ethnicity	○ Enrolment targets not defined	○ Enrol from ethnic minorities	○ Enrolment targets not defined
Socioeconomic deprivation	○ Enrolment targets not defined	○ Enrolment targets not defined	○ Enrolment targets not defined	○ Enrolment targets not defined	○ Enrolment targets not defined	○ Include in efficacy trials
Comorbidities *(To Enrol **ALL** with stable disease- Definition as above.)*			**Exclusion criteria for Stage 1a/2a**			
Obesity	○ Enrol stable disease	○ Enrol stable disease	○ BMI ≥30kg/m2	○ Enrol stable disease	○ Enrol stable disease	○ Include all BMI ○ BMI strata for exploratory immunogenicity assessment by BMI
Diabetes	○ Enrol stable disease	○ Enrol stable disease	○ Diabetes (type 1, type 2, or gestational)	○ Enrol stable disease	○ Enrol stable disease	○ Enrol stable disease
Hypertension	○ Enrol stable disease	○ Enrol stable disease	○ Moderate to severe high blood pressure	○ Enrol stable disease	○ Enrol stable disease	○ Not defined
Cardiovascular disease	○ Enrol stable disease	○ Enrol stable disease	○ Serious heart conditions (heart failure, CAD, CHD, CMP, and pulmonary hypertension)	○ Exclude severe and/or uncontrolled cardiovascular disease	○ Exclude clinically significant chronic cardiovascular disease	○ Enrol stable disease
Chronic respiratory diseases	○ Enrol stable disease	○ Enrol stable disease	○ Moderate to severe asthma; chronic lung diseases such as COPD (including emphysema and chronic bronchitis); idiopathic pulmonary fibrosis; cystic fibrosis	○ Exclude severe and/or uncontrolled respiratory disease	○ Exclude clinically significant respiratory disease	○ Enrol stable disease

Chronic liver disease	○ Enrol stable disease	○ Enrol stable disease	○ Chronic liver disease, including cirrhosis	○ Exclude severe and/or uncontrolled liver disease	○ Exclude clinically significant hepatic disease	○ Enrol stable disease
Chronic kidney disease	○ Enrol stable disease	○ Enrol stable disease	○ Chronic kidney disease (with dialysis) ○ End stage renal disease	○ Exclude severe and/or uncontrolled kidney disease	○ Exclude clinically significant renal disease	○ Enrol stable disease
HBV	○ Enrol stable disease	Enrol if ○ HBsAg present for ≥6 months **AND** ○ HBeAg negative, anti-HBe positive; Serum HBV DNA <2000 IU/mL; Persistently normal ALT and/or AST levels; No necroinflammation from liver biopsy	○ HBV infection or chronic active HBV per medical history	○ Enrol stable disease	○ Exclude clinically significant HBV	○ Not defined
HCV	○ Enrol stable disease	○ Enrol if evidence of undetectable HCV RNA for ≥12 weeks following HCV treatment/undetectable HCV viral load	○ HCV infection per medical history	○ Enrol stable disease	○ Exclude clinically significant HCV	○ Not defined
Malignancies -Non haematological/Haematological	○ Enrol stable disease	○ Enrol stable disease	○ Malignancy ≤ 1 year before screening **AND** ○ Include squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix, malignancies with minimal risk of recurrence	○ Exclude history of primary malignancy **AND** ○ Include participants with history of childhood leukaemia; indolent prostatic CA, treated non-melanoma skin CA, lentigo maligna and uterine cervical carcinoma in situ, localized prostate CA	○ Exclude subjects with current diagnosis of or treatment for cancer **AND** ○ Include basal cell carcinoma of the skin and cervical carcinoma in situ	○ Include subjects with history or concurrent malignancy with a natural history or treatment unlikely to interfere with safety or efficacy of potential vaccine
Neurological disease	○ Enrol stable disease	○ Enrol stable disease	○ Parkinson's disease, GBS, encephalopathy, meningoencephalitis, or history of acute polyneuropathy	○ Exclude history of GBS / **ANY** demyelinating condition ○ Exclude severe and/or uncontrolled neurological disease	○ Exclude clinically significant or chronic neurological diseases requiring physician review for diagnosis and treatment e.g. MS, degenerative conditions, neuropathy, Parkinson's disease, AND ○ Include migraine or chronic headaches or nerve root compression stable on treatment for 4 weeks prior to enrolment	Not defined
HIV positive participants inclusion criteria	○ Stable ART **AND** ○ Viral load 50-500 copies/mL ○ CD4 count ≥350 cells/ µL	○ Stable ART use for ≥6 months **AND** ○ Viral load <50 copies/mL ○ CD4 count >200 cells/ µL ≤ 6 months before dose 1	○ Stable ART use for≥ 6 months **AND** ○ Viral load <50 copies/mL ○ CD4 count ≥300 cells/µL	○ Stable ART use	○ Include ART use **AND** ○ ≤ 6 months history viral load < 1000 copies/mL **OR** ○ CD4 count > 300 cells/ µL.	Not defined

ALT: Alanine aminotransferase; ART: Antiretroviral treatment; AST: Aspartate aminotransferase; CA: Cancer; CAD: Coronary artery disease; CHD: Congenital heart disease; CMP: Cardiomyopathies; COPD: Chronic obstructive pulmonary disease; GBS: Guillain-Barré syndrome; HCV: Hepatitis C Virus; HBV: Hepatitis B virus; HIV: Human Immunodeficiency Virus; MS: Multiple sclerosis; RNA: Ribonucleic acid; Stage 1a: enrol ≥18 to <60 years of age without comorbidities; Stage 1b: enrol ≥18 to <60 years of age with comorbidities; Stage 2a: enrol ≥60 years of age without comorbidities; Stage 2b: enrol ≥60 years of age with comorbidities; WOCBP: Women of Child Bearing Potential; YOA: Years of age

References

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