Statistical Analysis Plan

Study ID: ADG20-PREV-001

Official Title of Study: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ADG20 in the Prevention of COVID-19 (EVADE)

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Adagio Therapeutics, Inc.

STATISTICAL ANALYSIS PLAN

ADG20-PREV-001

A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ADG20 in the Prevention of COVID-19 (EVADE)

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SPONSOR APPROVAL

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	body mass index
CBC	complete blood count
CI	confidence interval
CLI	COVID-19 like illness
COVID-19	coronavirus disease 2019
DAIDS	Division of AIDS
eCRF	electronic case report form
EOS	end of study
FAS	full analysis set
FDA	US Food and Drug Administration
ICF	informed consent form
iDMC	independent data monitoring committee
IM	intramuscular(ly)
IRT	interactive response technology
ISR	injection site reaction
KM	Kaplan-Meier
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
MAR	missing at random
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MI	multiple imputation
NP	nasopharyngeal
PCR	polymerase chain reaction
PCS	potentially clinically significant
PK	pharmacokinetic
PPS	per-protocol set
PT	preferred term
RT-PCR	reverse transcription polymerase chain reaction
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

1. INTRODUCTION

This SAP describes the planned analyses of study ADG20-PREV-001 (EVADE) based on the clinical study protocol, version 5.0, dated 02-Mar-2022. This SAP provides statistical analysis details/data derivations to supplement the information presented in the statistical analysis section of the protocol.

The EVADE study is a phase 2/3, multicenter, double-blind, placebo-controlled, randomized study of the mAb ADG20 in the prevention of symptomatic COVID-19 in adults and adolescents with no known history of SARS-CoV-2 infection but whose circumstances place them at increased risk of acquiring SARS-CoV-2 infection and developing symptomatic COVID-19. This objective will be independently evaluated in 2 cohorts: (1) participants with reported recent exposure to an individual diagnosed with a SARS-CoV-2 infection (Cohort A, PEP) and (2) participants with no reported recent exposure to SARS-CoV-2 (Cohort B, PrEP). An iDMC will monitor the study to evaluate the benefit versus risk and to ensure that the scientific integrity of the study is maintained.

The EVADE study was impacted by the emergence and global spread of the SARS-CoV-2 B.1.1.529 (Omicron) variant, which was first detected in South Africa and Botswana in November 2021. In vitro assessments of the neutralization activity of ADG20 demonstrated markedly reduced activity against authentic Omicron virus compared with prior variants such that ADG20 is unlikely to demonstrate adequate efficacy against SARS-CoV-2 infections caused by the Omicron variant. As a result, enrollment in Cohort A (PEP) and Cohort B (PrEP) of the study was suspended on 11-Jan-2022 as Omicron had become or was likely to become the predominant variant in regions enrolling the trial.

In response to this global event, the analysis plan for this study was updated to analyze data collected prior to the emergence of Omicron while efficacy and safety post-Omicron continue to be monitored in the study. Therefore, the primary efficacy analysis is focused on evaluating ADG20 300 mg IM treatment in the population randomized prior to the emergence of the Omicron variant. With this analysis plan, the primary efficacy and short-term safety analyses are planned for both cohorts after a database soft lock. A final safety analysis will occur after all enrolled participants have been followed through 14 months/EOS or have discontinued.

2. OBJECTIVES

For Cohort A (PEP), in participants with no known history of SARS-CoV-2 infection and reported recent exposure to SARS-CoV-2, the following objectives and endpoints apply (Table 1):

Table 1. Objectives and Endpoints: Cohort A (PEP)

Objectives	Endpoints
Primary (Cohort A [PEP])	
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in all randomized participants without current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.
To evaluate the safety and tolerability of ADG20 compared with placebo following intramuscular administration in all treated participants.	Assessment of safety based on: • Incidence of treatment-emergent adverse events. • Incidence of solicited injection site reactions through Day 4. • Changes from baseline in clinical laboratory tests (ie, complete blood count with differential and serum chemistry). • Changes from baseline in vital signs (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure).
Secondary (Cohort A [PEP])	
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in each of the following populations: • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 diagnosis. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through Day 28 in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through Day 28. Supplementary: • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through Day 28.

To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months. <u>Supplementary:</u> • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months, in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through 3 months. <u>Supplementary:</u> • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in all randomized participants with prior but not current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. <u>Supplementary:</u> • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection, in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	• Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by RT-qPCR (nasal sample) on Days 8 and 15. • Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology through Day 28.
To evaluate the impact of ADG20 compared with placebo on viral load in all randomized participants with asymptomatic SARS-CoV-2 infection detected by RT-qPCR (nasal sample) at baseline via surveillance.	• Peak post-baseline SARS-CoV-2 viral load as measured by RT-qPCR • SARS-CoV-2 viral load as assessed by RT-qPCR change from baseline to Day 8 and Day 15.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.

COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

ADA=antidrug antibody; AUC =area under the plasma concentration–time curve; $AUC_{0\text{-}inf}$: AUC extrapolated to infinite time; $AUC_{0\text{-}last}$=AUC from zero up to the last concentration ≥lower limit of quantification; CL=clearance; CLI=COVID-19-like illness; C_{max}=maximum plasma concentration; PEP=post-exposure prophylaxis; RT-(q)PCR=(quantitative) reverse transcription-polymerase chain reaction; $t_{½}$=plasma concentration half-life; T_{max}=time to reach C_{max}; V_{ss}=apparent volume of distribution at steady state.

For Cohort B (PrEP), participants with no known history of SARS-CoV-2 infection and no known recent exposure to SARS-CoV-2, but whose circumstances put them at increased risk of exposure to SARS-CoV-2 and symptomatic COVID-19, the following objectives and endpoints apply (Table 2).

Table 2. Objectives and Endpoints: Cohort B (PrEP)

Objectives	Endpoints
Primary (Cohort B [PrEP])	
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the safety and tolerability of ADG20 compared with placebo following intramuscular administration.	Assessment of safety based on: • Incidence of treatment-emergent adverse events. • Incidence of solicited injection site reactions through Day 4. • Changes from baseline in clinical laboratory tests (ie, complete blood count with differential and serum chemistry). • Changes from baseline in vital signs (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure).

Objectives	Endpoints
Secondary (Cohort B [PrEP])	
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in all randomized participants without current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through 3 months.
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months, in each of the following populations: • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants without current SARS-CoV-2 infection at baseline.	Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months. Supplementary: • Time from randomization to first SARS-CoV-2 infection. • Probability of SARS-CoV-2 infection through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in all randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months in all randomized participants.	Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection (based on serology) in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.

Objectives	Endpoints
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

ADA=antidrug antibody; AUC =area under the plasma concentration–time curve; $AUC_{0\text{-inf}}$: AUC extrapolated to infinite time; $AUC_{0\text{-last}}$=AUC from zero up to the last concentration ≥lower limit of quantification; CL=clearance; CLI=COVID-19-like illness; C_{max}=maximum plasma concentration; PrEP=pre-exposure prophylaxis; RT-(q)PCR=(quantitative) reverse transcription-polymerase chain reaction; $t_{½}$=plasma concentration half-life; T_{max}=time to reach C_{max}; V_{ss}=apparent volume of distribution at steady state.

Exploratory endpoints for Cohort A (PEP) and Cohort B (PrEP) are provided in Table 3.

Table 3. Exploratory Objectives and Endpoints: Cohorts A and B

Objectives	Endpoints
To evaluate the impact of ADG20 compared with placebo on medically attended visits or death in participants with asymptomatic SARS-CoV-2 infection at baseline.	Proportion of participants with asymptomatic SARS-CoV-2 infection at baseline (defined by positive SARS-CoV-2 RT-PCR test and lack of symptoms of COVID-19) with medically attended visits (outpatient, telemedicine, or hospitalization) or death through Day 28.
To evaluate the impact of ADG20 compared with placebo on Health Resource Utilization in participants with RT-PCR-confirmed symptomatic COVID-19.	Health Care Resource Utilization of participants who develop COVID-19 (eg, incidence and duration of ICU stay and incidence of emergency room visits).
To evaluate the emergence of resistance to ADG20.	Genotypic characterization of viral isolates for reduced susceptibility to ADG20, with phenotypic evaluation as appropriate.
To evaluate the impact of ADG20 compared with placebo on COVID-19 vaccination-induced immune response in a subset of participants.	Pre- and post-vaccination SARS-CoV-2 neutralizing antibody titers in participants who choose to receive COVID-19 vaccine during the study.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

The EVADE study is designed as a master protocol for multiple independent cohorts. Cohort A and B described below are the focus of this document.

- Cohort A (PEP): Participants with reported, recent exposure to an individual testing positive for SARS-CoV-2 (index case) randomized 1:1 to receive a single 300 mg IM dose of ADG20 or placebo
- Cohort B (PrEP): Participants with no known recent exposure but whose circumstances put them at increased risk of exposure to SARS-CoV-2 and symptomatic COVID-19 randomized 1:1 to receive a single 300 mg IM dose of ADG20 or placebo

The randomization will be assigned in a blinded manner using a centralized IRT system in accordance with a pre-generated randomization schedule. A participant is considered randomly assigned when a randomization transaction is recorded in the IRT. A separate randomization list will be created for each cohort. The randomization will be stratified by the following factors:

- Geographic region (United States/Western Europe, Central/Eastern Europe, and Rest of the World)
- Age/risk for severe/critical COVID-19 (12 to <55 years and low risk, 12 to <55 years and high risk, and aged ≥55 years)

3.2. iDMC, Interim, and Final Analyses

An iDMC will provide safety oversight for all parts of the study. The iDMC will meet at designated timepoints and on an ad hoc basis to review cumulative safety data and other clinical study data to ensure the benefit/risk remains favorable. Details regarding iDMC membership, conduct, ongoing safety monitoring, decision-making, and communication will be provided in the iDMC Charter.

Cohort A and Cohort B enrollment was suspended on 11-Jan-2022; these cohorts will not reopen, thus enrollment in these cohorts is complete. A database soft lock will be performed to evaluate the primary efficacy and short-term safety objectives. All study participants, site staff, and certain sponsor personnel (or designee) working directly with the site will stay blinded to the individual treatment assignment until the final database lock after the Month 14 visit.

Plans for additional database locks or analyses may be revised during the study to adapt to unexpected issues in study execution and/or data that affect planned analyses and/or to address regulatory authority request, and/or to address protocol amendments.

3.3. Study Duration

The study duration for each participant enrolled in the study will be approximately 14 months.

For Cohort A, the study consists of a Screening Period of up to 5 days, a 1-month Study Period (including dosing on Day 1), a 5-month follow-up period, and an 8-month long-term follow-up (LTFU) Period through Month 14 or withdrawal.

For Cohort B, the study consists of a Screening Period of up to 21 days, a 6-month Study Period (including dosing on Day 1), and an 8-month LTFU Period through Month 14 or withdrawal.

3.4. Study Assessments

Each participant in Cohort A and B will receive a single 300 mg IM dose of ADG20 or placebo at the Day 1 Visit. Participants will record any ISRs using an e-Diary (or paper back-up) daily on Day 1 postdose through Day 4. All participants will undergo assessments as indicated in the protocol Schedule of Assessments (SoA).

3.4.1. Clinical Efficacy Assessments

In each cohort, surveillance for symptomatic COVID-19 will be performed via phone calls to the participant by the site. Participants reporting COVID-19-like illness (CLI) symptoms will be contacted by the site to determine whether their symptoms meet criteria for a CLI visit. If CLI symptoms are confirmed by the site, the participant will enter the CLI Period and have an initial CLI visit within 48 hours. Participants who enter the CLI Period will be assessed as described in the protocol CLI SoA.

The occurrence of RT-PCR-confirmed COVID-19 and concomitant therapies associated with COVID-19 will be captured for the duration of the study. Every effort will be made to capture information from any medical visits (eg, visits to the primary care providers, emergency department/urgent care clinic visits, hospitalizations) related to COVID-19 or its complications for the purpose of Health Care Resource Utilization analysis.

3.4.2. Virologic Efficacy Assessments

Samples for SARS-CoV-2 and other virology assessments will be collected during the study as follows:

- A nasopharyngeal swab for central testing will be collected by the site on Day 1 and CLI Day 1. A saliva sample for central RT-PCR testing may be self-collected on CLI Day 1 if an in-person visit with site personnel cannot be conducted.
- Saliva will be collected by site personnel or by participant self-collection at home (using a kit provided by the site) to quantify viral load on CLI Day 1 as indicated in the CLI SoA.
- Nasal swabs for central SARS-CoV-2 RT-qPCR testing will be collected from participants in Cohort A (PEP) on Days 1 (predose), 8, and 15 (self-collected) to detect any asymptomatic infections.
- Blood samples will be collected for central SARS-CoV-2 serology testing to detect antibodies to the nucleocapsid (N) protein and/or the Spike (S) protein predose. Post-baseline blood samples will be collected for SARS-CoV-2 serology testing to detect antibodies to the nucleocapsid (N) protein to monitor participants for asymptomatic infection.
- Any known positive local RT-PCR test result obtained during the study period, whether within or outside of the study, should also be recorded on the local SARS-CoV-2 eCRF.

3.4.3. PK and ADA Assessments

Blood samples for analyses of PK and ADA will be collected as described in the protocol SoA.

3.4.4. Safety Assessments

Safety will be assessed in an ongoing manner. Adverse events occurring from when the participant signs the ICF until the Month 14 visit or withdrawal will be recorded. Only study procedure-related AEs occurring before randomization will be recorded. Other AEs, including SAEs and MAAEs will be collected through Month 14. Any AESI, as defined in Section 5.6.1.4, will be recorded. Participants will record ISRs using the Injection Site Reaction Diary starting after dosing on Day 1 through Day 4. Investigators (or designee) will follow all ISRs that are ongoing beyond Day 4 to resolution. Hypersensitivity reactions and ISRs that occur after Day 4 will be recorded as AEs.

Clinical laboratory samples will be collected at Screening (baseline), on Day 8, Day 28, Month 6, and Month 12. For participants who enter the CLI Period, clinical laboratory samples will also be collected at CLI Day 1 and CLI Day 28.

Vital signs will be collected at baseline, on Day 1 before and after dosing, Day 8, Day 28, Month 6, and Month 12. For participants who enter the CLI Period, vital signs will also be collected by site personnel on CLI Day 1 and CLI Day 28 and will be self-collected and reported by the participant daily on CLI Days 2 to 21.

3.5. Study Endpoints

Study endpoints and corresponding objectives are shown in Section 2. Definitions of the key clinical and virologic endpoints are provided below. Safety endpoints are defined in Section 5.6.

3.5.1. Clinical Efficacy Endpoints

RT-PCR-confirmed symptomatic COVID-19: laboratory-confirmed (RT-PCR) SARS-CoV-2 infection and an onset of symptoms as defined below occurring no more than 14 days from the date of the positive RT-PCR test sample collection. Central or local (in the absence of central test) RT-PCR tests from NP, saliva, or nasal samples are acceptable. Any COVID-19-related hospitalization ≥24 hours with a positive local SARS-CoV-2 test (within 14 days) or all-cause death are also counted toward the endpoint. The date of event is the earliest date of RT-PCR-confirmed COVID-19 symptom onset, COVID-19-related hospitalization, or all-cause death. The protocol defined COVID-19 symptoms are as follows:

- At least ONE of the following respiratory signs/symptoms:
  - Clinical evidence of pneumonia (eg, SpO2 ≤94% on room air, requiring new initiation of supplemental oxygen or radiographic evidence of pneumonia)
  - New or worsening dyspnea/shortness of breath.

  OR

- At least TWO of the following systemic symptoms:
  - Fever ≥38 °C (≥100.4 °F)

- Cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)
- Headache
- Sore throat

RT-PCR-confirmed SARS-CoV-2 infection: determined by positive central RT-PCR testing after randomization (including Day 1). The date of event is the sample collection date of the first positive central RT-PCR testing after randomization (including Day 1).

Serology-confirmed SARS-CoV-2 infection: determined by positive central serology testing after randomization with a negative central serology at baseline. The date of event is the first sample collection date of positive central serology testing after randomization.

SARS-CoV-2 infection regardless of symptoms (asymptomatic or symptomatic): determined by any of the following outcomes during the study. The date of event is the earliest date of these events.

- RT-PCR-confirmed symptomatic COVID-19
- RT-PCR-confirmed SARS-CoV-2 infection
- Serology-confirmed SARS-CoV-2 infection

3.5.2. Other Clinical and Virologic Endpoints

For randomized participants with RT-PCR-confirmed symptomatic COVID-19, the following clinical and virologic parameters will be evaluated through CLI Day 28:

- **Maximum severity of COVID-19:** mild, moderate, or severe/critical COVID-19 as assessed by the investigator based on the criteria outlined in Appendix 5 of the protocol. Participants with COVID-19-related hospitalization or COVID-19-related death through CLI Day 28 are included as severe/critical.
- **Duration of COVID-19:** time to sustained resolution of COVID-19 symptoms. The following assessed COVID-19 symptoms will be included in the time to event analysis: fever, chills, cough, sore throat, congestion, shortness of breath/difficulty breathing, muscle or body aches, fatigue, headache, nausea, vomiting or diarrhea. Loss of taste/smell is not considered for this endpoint. Time to sustained resolution of COVID-19 symptoms is defined as time from the onset date of symptomatic COVID-19 to the first date when all of the above symptoms are scored as none with no symptom recurrence or new symptoms, except cough, fatigue, and headache that may be mild or none, through CLI Day 28.
- **COVID-19-related medically attended outpatient visits:** includes in-person or telemedicine visits not specified by the protocol and lasting <24 hours. These include unscheduled in-person or telemedicine visits conducted by the investigator for the purposes

of evaluating worsening signs or symptoms attributed to COVID-19 or emergency room, urgent care center, or physician office visits, for attention to worsening signs or symptoms attributed to COVID-19, in the opinion of the investigator.

- **COVID-19-related hospitalization:** includes visits for attention to worsening signs or symptoms attributed to COVID 19, in the opinion of the investigator. Hospitalization is defined as ≥24 hours of acute care in a hospital or acute care facility (includes emergency rooms, ICUs, acute care facilities created for COVID-19 pandemic hospitalization needs, or other acute care facilities).
- **COVID-19-related mortality:** COVID-19-related mortality is defined as death directly due to COVID-19 or any death in which COVID-19 or COVID-19 complications contributed to the death, as determined by the investigator, a formal autopsy report or death certificate.
- **All-cause mortality:** death due to any cause.
- **SARS-CoV-2 viral load (NP sample):** assessed by RT-qPCR from NP sample collected on CLI Day 1.
- **SARS-CoV-2 viral load (saliva sample):** assessed by RT-qPCR from saliva sample collected on CLI Day 1.

3.6. Treatments

After randomization, participants enrolled in Cohort A and B will receive a single 300 mg dose of ADG20 or matching placebo administered via IM injection.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. General Rules and Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of participants (n), mean, SD, median, first and third quartiles, minimum (min), and maximum (max).

Categorical variables will be summarized using frequency counts and percentages.

Baseline value, unless specified otherwise, is defined as the last non-missing measurement (scheduled or unscheduled) collected on or before the date of dosing. If the date of study dosing is missing, the date of randomization will be used instead.

A row denoted “Missing” may be included in count tabulations as needed to account for dropouts and missing values. The denominator for all percentages will be the number of participants in the treatment group within the analysis set of interest, unless otherwise specified.

Change from baseline is defined as the value at the post-baseline visit minus the value at the baseline visit.

Study Day 1 is denoted the day that study drug is administered. Subsequent study days are calculated as: date of assessment/event – date of dosing + 1. If a participant is not dosed, the date of randomization is used to define Study Day rather than the date of dosing.

Time-to-event parameters are defined from the date of randomization.

Unscheduled visit measurements will be included in analysis as follows:

- In the derivation of baseline measurements.
- In the derivation of maximum/minimum change from baseline values and worst post-baseline values for safety analyses.
- In individual participant data listings as appropriate.

Incomplete/missing data:

Imputation rules for missing dates of medications and AEs will be used (see Appendix A).

Data that are continuous in nature but are reported in the form of $<x$, $>x$, $\leq x$, or $\geq x$ (where x is considered as the limit of quantitation) will be set to limit of quantitation value with the following exceptions:

- For viral load data:
  - Viral load values reported as detected but BLQ of the PCR assay (<714 copies/mL) are imputed with half of the LLOQ of the PCR assay (ie, 357 copies/mL)
  - Viral load values reported as not detected are imputed with 1 copy/mL (ie, 0 $\log_{10}$ copies/mL)
  - Viral load values reported as $>7.1\times10^7$ copies/mL are imputed to 7.1×10^7 copies/mL
  - All viral load analyses will use both observed and the above imputed viral load data. Listings present observed viral load data.
- For PK concentrations:
  - For predose samples, the sampling time will be set to zero or labelled *Predose*.
  - For postdose samples, the nominal (scheduled) sampling time will be used in summary tables and mean concentration figures and actual sampling times will be used for all figures of individual concentrations.
  - All concentration values below the LLOQ will be set to zero for summary tables/figures and missing in individual plots.

Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups: The following treatment groups will be used for summary purposes: ADG20, Placebo.

All analyses and data summaries for efficacy will be provided by treatment group using the appropriate analysis sets, unless otherwise specified.

All data listings and tables displaying participant data that contain an evaluation date will display study day. Listings will be sorted by Subject ID and treatment.

4.2. Sample Size

Cohort A (PEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 28 days after randomization. The original sample size of 1078 participants was planned with 90% power, 2-sided alpha 0.05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 5% per 28 days in the placebo group and 1.5% in the ADG20 group. A sample size of 1270 participants was planned to account for 15% participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort A on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 is not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort A will only include events through 28 days after randomization or the emergence of Omicron, whichever is earlier. Prior to suspension of enrollment, 487 participants were randomized in Cohort A, of which approximately 377 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 346 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative pre-Omicron). The primary efficacy population yielded approximately 14 events through 28 days or emergence of Omicron, whichever is earlier, for the analysis. With 14 events, any observed efficacy >68% will be statistically significant at 2-sided α=0.05.

Cohort B (PrEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 3 months. The original sample size of 4628 participants was planned with 84% power, 2-sided alpha 0.05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 1% per 3 months in the placebo group and 0.3% in the ADG20 group. A sample size of 5142 participants was planned to account for 10% participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort B on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 is not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort B will only include events through 3 months after randomization or the emergence of Omicron, whichever is earlier. Prior to suspension of enrollment, 2101 participants were randomized in Cohort B, of which approximately 1646 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 1424 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative and seronegative pre-Omicron). A higher than expected aggregate attack rate resulted in sufficient number of cases to enable this cohort to be a fully powered study to detect clinically meaningful and statistically significant treatment differences. Based on 3.6% aggregate attack rate, 974 participants in a 1:1 randomization ratio provides 90% power to detect a statistically significant treatment effect when the true RR is 0.3 with 2-sided $\alpha = 0.05$. Therefore, the current sample size of 1424 provides sufficient statistical power to carry out the primary efficacy analysis, as well as preliminary evaluation of safety.

4.3. Multiplicity Adjustments

In each cohort, to control the overall type I error rate (alpha) at 0.05 (2-sided), a hierarchical testing procedure will be used for primary and key secondary efficacy endpoints, such that testing for the key secondary analyses difference will proceed only if the treatment difference is statistically significant in the primary efficacy analysis. The first key secondary hypotheses will be tested if the null hypothesis for the primary endpoint is rejected at 2-sided 0.05 level. The subsequent key secondary hypotheses will be tested if the null hypothesis for the preceding key secondary endpoint is rejected at 2-sided, .05 level.

Analyses of the other secondary and exploratory endpoints will be conducted to support the findings of the primary and key secondary efficacy analyses without accounting for multiple comparisons. Nominal p-values and 95% CIs will be computed for these secondary and exploratory efficacy analyses.

4.4. Analysis Sets

Analysis sets used in this study are defined below. In the efficacy analysis, participants will be analyzed based on the treatment they are randomized to, irrespective of what they actually might have received. In the safety analysis, participants will be analyzed based on the study drug received.

4.4.1. Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomly assigned to treatment. A participant is considered enrolled once the participant has been randomized.

4.4.2. Full Analysis Set

The Full Analysis Set (**FAS**) will include all randomized participants regardless of whether the participant received study drug.

4.4.3. Modified Analysis Sets

The Modified Full Analysis Set (**mFAS**) will include all randomized participants without prior or current SARS-CoV-2 infection at baseline based on central tests (baseline RT-PCR-negative and seronegative). If either central RT-PCR or central serology is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.

The modified Full Analysis Set-1 (**mFAS-1**) will include all randomized participants without current SARS-CoV-2 infection at baseline based on central tests (baseline RT-PCR-negative regardless of serostatus). If central RT-PCR is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.

The modified Full Analysis Set-2 (**mFAS-2**) will include all randomized participants with prior infection but without current SARS-CoV-2 infection at baseline based on central tests (baseline RT-PCR-negative and seropositive). No imputation is performed if any baseline test is missing.

The modified Full Analysis Set-3 (**mFAS-3**) is similarly defined as mFAS (baseline RT-PCR-negative and seronegative) except that no imputation is performed if any baseline test is missing. Select analyses of mFAS will be repeated in mFAS-3 as the sensitivity analysis.

4.4.4. Pre-Emergence of Omicron Analysis Set

The Pre-Emergence of Omicron Analysis Set (**pre-Omicron**) will include all participants randomized on or prior to 30-Nov-2021, allowing participants to be followed a minimum of 2 weeks through 15-Dec-2021 when Omicron became the predominant variant. The pre-Omicron Analysis Set will be used in combination with the modified analysis sets to define the **primary efficacy population** for each cohort, as follows:

- Cohort A (PEP): baseline RT-PCR negative participants in the pre-Omicron Analysis Set (**mFAS-1 pre-Omicron**)
- Cohort B (PrEP): baseline RT-PCR-negative and seronegative participants in the pre-Omicron Analysis Set (**mFAS pre-Omicron**)

4.4.5. Post-Emergence of Omicron Analysis Set

The Post-Emergence of Omicron analysis set (**post-Omicron**) will include participants randomized after 30-Nov-2021 until the end of enrollment (11-Jan-2022) and will be used to evaluate activity against the Omicron variant.

4.4.6. Per-Protocol Set

The Per-Protocol Set (**PP**) includes all randomized participants who receive the full dose of study drug, do not have missing data for the primary efficacy endpoint, and have no other important protocol deviation, as determined and documented by the Sponsor before database freeze/lock and unblinding, that could impact the assessment of efficacy. Participants will be analyzed based on the study drug they are randomized to.

4.4.7. Safety Set

The Safety Set will include all participants who received any amount of study drug. All safety analyses will be conducted in this analysis set. Participants will be analyzed based on the study drug actually received.

4.4.8. Immunogenicity Set

The Immunogenicity Set includes all participants who received any study drug and had a valid immunogenicity test result before the dose of study drug and at least 1 valid result after the dose of study drug.

4.4.9. PK Analysis Set

The PK Analysis Set includes all participants in the Safety Set who have at least two measurable ADG20 concentration post-administration of study drug.

5. STATISTICAL ANALYSES

5.1. Participant Disposition

5.1.1. Disposition

Participant disposition will be summarized for all screened participants, in the following categories:

- Number of screened participants
- Number of screen failure participants
- Number of participants randomized (FAS)
- Number and percentage of participants treated
- Number and percentage of participants randomized by analysis sets
- Number and percentage of participants by the reasons for study discontinuation
- Number and percentage of primary cause of death

All percentages will be based on the number of randomized participants. Participant disposition data will also be presented in listings.

Cumulative follow-up time will also be summarized for randomized participants:

- Ongoing participants: data cut-off date - randomization date + 1
- Discontinued or completed study participants: end of study date – randomization date + 1.

5.1.2. Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis before any unblinded analysis is performed, and important deviations that are considered to have an impact on the efficacy assessment will lead to the relevant participant being excluded from the PP analysis set.

The number and percentages of participants with important deviations will be presented in the FAS by treatment group and overall. Important protocol deviations will also be summarized by deviation category. A listing of all protocol deviations will be provided for all FAS participants.

5.2. Demographics and Clinical Characteristics

5.2.1. Demographics/Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg), height (cm), BMI (kg/m^2). BMI is calculated as (body weight in kilograms) / (height in meters)^2. The number and percentage of participants will be provided for the following categorical variables: age group (age 12 to <18, 18 to <55, 55 to <75, and ≥75 years), sex, race, ethnicity, stratified geographic region, stratified age/risk of severe COVID-19 (≥12 to <55 years and low risk, ≥12 to <55 years and high risk, and ≥55 years), baseline SARS-CoV-2 status by central RT-PCR, baseline SARS-CoV-2 status by central serology, and risk factors for COVID-19 disease progression on adults and on adolescents. In addition, a derived baseline high risk of progression to severe COVID-19 based on eCRF medical history/concomitant medication will be summarized.

Participant demographics/baseline characteristics will be presented in a listing.

5.3. Medical History

Medical history will be coded using MedDRA Version 24.0 or higher. The number and percentage of participants with any medical history will be summarized by treatment arm using SOC and PT ordered alphabetically by SOC and by descending participant count in the ADG20 arm for PT within SOC.

Participant medical history data including specific details will be presented in a listing.

5.4. Treatments and Medications

5.4.1. Prior and Concomitant Medication

Prior medications are defined as any medication with a start date before screening (date of informed consent) and stop date before the date of administration of the study drug. Concomitant medications are defined as any medication used on or before screening and with a stop date on or after the date of administration of the study drug, are ongoing, or are taken on or after the date of administration of the study drug.

Medications with partially missing dates will be imputed to categorize as prior or concomitant medication (Appendix A). If no classification to prior or concomitant can be conclusively determined, the medication will be considered concomitant. All medications will be coded according to the World Health Organization drug dictionary (WHODrug March 2021 or higher).

The number and percentages of participants with at least one prior/concomitant medication will be summarized by treatment group. The number and percentages of all prior/concomitant medications will be summarized by treatment group, WHODrug ATC level 2, and PT. All summaries will be performed using the FAS. A listing of prior/concomitant medications will be provided.

The number and percentages of participants with at least one prohibited concomitant medication for the prevention of COVID-19 or receiving a COVID-19 vaccine based on a sponsor medical adjudication will be summarized by treatment group in the FAS. The number and percentages of

these medications will also be summarized by WHODRUG ATC level 2 and PT, and a listing of prohibited medications will be provided.

5.4.2. Study Treatments

In Cohorts A and B, a single 300 mg dose of ADG20 or matching placebo will be administered by IM injection. Summaries of study treatment will be presented for the Safety Set. The number and percentage of participants that received a full dose (300 mg) and did not receive a full dose will be presented.

A total volume of 3 mL ADG20/placebo is administrated using the 100 mg/mL formulation in both US and non-US study sites. The US sites switched during the study to administer a total volume of 2 mL ADG20/placebo using the 150 mg/mL formulation. The non-US sites continued to administer 3 mL using the 100 mg/mL formulation.

Descriptive statistics of the total volume (for the 2 mL or 3 mL regimen) and dose (mg) will be presented; mL is converted to mg as follows: 100×dose in mL for 100 mg/mL formulation; 150×dose in mL for 150 mg/mL formulation. A listing of study drug administration will be provided.

5.5. Efficacy Analyses

5.5.1. Primary Efficacy Analysis

Cohort A (PEP): The primary efficacy endpoint is the proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through Day 28 after randomization or emergence of Omicron (designated by 15-Dec-2021), whichever is earlier, in the mFAS-1 pre-Omicron analysis set.

Cohort B (PrEP): The primary efficacy endpoint is the proportion of participants with RT-PCR–confirmed symptomatic COVID-19 through 3 months after randomization or emergence of Omicron (designated by 15-Dec-2021), whichever is earlier, in the mFAS pre-Omicron analysis set.

In each cohort, the null and alternative hypotheses are the following:

H_0: $P_1 - P_0 = 0$

H_1: $P_1 - P_0 \neq 0$

P_1 and P_0 are the proportion of participants with primary endpoint outcome in the ADG20 and placebo groups respectively. Using the methodology described below, a standardized estimator for a binary outcome (primary estimand) will be estimated with adjustment for the following stratification factors: geographic region and age/risk of severe COVID-19.

The method described in Ge et al. (2011) computes a population-level estimate for the treatment difference (in terms of difference in proportion) and supports an adjustment for the predefined prognostic factors. The method relies on a logistic regression model, considering the ith participant, $i = 1, \ldots, n$, where n is the total number of participants, and let y_i denote the binary outcome for the primary endpoint (present =1 or absent =0). The treatment indicator will be denoted by t_i, where $t_i = 0$ corresponds to the placebo arm and $t_i = 1$ corresponds to the

treatment (ADG20) arm. The vector of prognostic factors for the ith participant will be denoted by $\boldsymbol{x}_i$. The model is given by:

$$\text{logit}\, p_i = \beta_0 + \beta_1 t_i + \boldsymbol{\beta}_2' \boldsymbol{x}_i,$$

where $p_i = P(y_i = 1)$, β_0 and β_1 are the intercept and slope, $\boldsymbol{\beta}_2$ is the vector of model parameters corresponding to the covariates and the prime denotes transposition.

After the model has been fitted to the data, the model parameters will be estimated (the estimates will be denoted by $\hat{\beta}_0$, $\hat{\beta}_1$ and $\widehat{\boldsymbol{\beta}}_2$, respectively). After that, two potential outcomes will be computed from the model for each participant. These outcomes represent the participant's outcomes if the participant has been assigned to the placebo and treatment arms:

$$p_{i0} = P(y_i = 1 | t_i = 0),$$

$$p_{i1} = P(y_i = 1 | t_i = 1).$$

The population-level estimates for the incidence rates will be defined as follows:

$$\hat{p}_0 = n^{-1} \sum_{i=1}^{n} p_{i0} \text{ and } \hat{p}_1 = n^{-1} \sum_{i=1}^{n} p_{i1}.$$

These estimates can be used to define an estimate for the treatment difference (difference in the incidence rates) or relative risk reduction in a straightforward manner, ie,

$$\hat{p}_1 - \hat{p}_0 \text{ and } 1 - \hat{p}_1 / \hat{p}_0$$

The variance of the estimated treatment difference or relative risk reduction will be estimated using the delta method based on the algorithm presented in Ge et al. (2011) (Appendix B).

The primary estimand will be analyzed using treatment policy strategy to handle the intercurrent events (ICEs) so that all available primary endpoint outcomes will be included. The ICEs include the use of rescue medications (eg, COVID-19 vaccine, COVID-19 mAb for the purposes of prevention) and subject level unblinding by Investigator prior to the primary endpoint outcome.

Participants with COVID-19-related hospitalization ≥24 hours with a positive local SARS-CoV-2 test (within 14 days) or all-cause death are counted toward the primary endpoint outcome (Section 3.5.1). Participants with missing primary endpoint outcome will be imputed as not having the primary endpoint outcome in the primary analysis.

The prognostic factors include the stratification factors (geographic region, age/risk of severe COVID-19), and baseline serostatus or baseline RT-PCR status when applicable.

The observed risk difference (placebo minus ADG20) with 95% CI (using the Miettinen-Nurminen method), observed relative risk reduction, standardized risk difference with 95% CI and associated p-values, and standardized relative risk reduction with 95% CI will be provided.

5.5.2. Sensitivity Analysis of Primary Estimand

Sensitivity Analysis 1: To assess the impact of participants with missing primary endpoint outcome, a sensitivity analysis will utilize multiple imputation (MI) under missing at random (MAR) assumption. The imputation model (using SAS PROC MI) will be informed by all the

observed outcomes for participants including treatment and covariates used in the primary analysis. Participants with missing primary endpoint outcome will be imputed using monotone logistic regression. Missing outcomes will be imputed multiple=100 times. The seed for reproducibility will be set to 2022. The final analysis model applied to the complete data set will be the same as that for the primary analysis. Treatment effect estimates from the individual completed data sets will be combined using Rubin's rules (using SAS PROC MIANALYZE).

Sensitivity Analysis 2: To assess the impact of the ICE, a supplementary estimand will be defined using hypothetical strategy to handle the ICE. If the participant had the primary endpoint outcome after the ICE, the primary endpoint outcome will be set to missing. The analysis will be carried out using MI methodology as described in Sensitivity Analysis 1.

Sensitivity Analysis 3: A sensitivity analysis based on the Cochran-Mantel-Haenszel (CMH) test will be performed. This test will be adjusted for the randomization stratified factors. The levels of stratification may be combined if deemed necessary.

Sensitivity Analysis 4: A sensitivity analysis will repeat the primary efficacy analysis in the PP analysis set.

5.5.3. Analysis of Time to First RT-PCR-confirmed Symptomatic COVID-19

The time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (event) will be analyzed by Kaplan-Meier (KM) methodology and stratified Cox Proportional Hazard model in each of mFAS/mFAS-1/FAS pre-Omicron analysis sets.

Analysis events are those dated on or prior to the following censoring date: end of study date, date of subject unblinding, date of subject receipt of COVID-19 vaccination or other preventive medication, and analysis cutoff date if applicable. When analyzing pre-Omicron analysis set, emergence of Omicron variant (15 Dec 2021) will be used for the analysis cut-off date.

Participants who did not meet the defined event on or prior to the above censoring date are censored at the earliest of each of these dates. The time from randomization to first RT-PCR-confirmed symptomatic COVID-19 will be calculated as date of event/censoring – date of randomization + 1.

Survival curves between ADG20 and placebo will be compared using a log-rank test stratified by stratification factors: geographic region and age/risk category. Probability of cumulative incidence (1 – survival probability) will be estimated based on the survival curves at the specific time points.

A stratified Cox Proportional Hazard model will be performed to estimate the hazard ratio adjusted for prognostic factors. The prognostic factors include the stratification factors (geographic region, age/risk of severe COVID-19), and baseline serostatus or baseline RT-PCR status when applicable. Comparison of the survival distributions will use the score test for the hazard ratio from the Cox model.

5.5.4. Key Secondary Endpoints and Analyses

Analyses of the key secondary endpoints (Table 4) will be conducted sequentially following a hierarchical testing order within each cohort.

For the binary endpoint, the analysis will use the same methodology as the primary efficacy analysis for determining a standardized estimator (standardized risk difference/standardized relative risk reduction) with adjustment for the prognostic factors. The prognostic factors include the stratification factors (geographic region, age/risk of severe COVID-19), and baseline serostatus or baseline RT-PCR status when applicable.

Table 4. Key Secondary Endpoints

Endpoint	Analysis Set
Cohort A (PEP)	
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier	mFAS-1 pre-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron, whichever is earlier	mFAS pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier	mFAS pre-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron whichever is earlier	FAS pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier	FAS pre-Omicron
Cohort B (PrEP)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier	mFAS-1 pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier	mFAS pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier	mFAS-1 pre-Omicron

5.5.5. Subgroup Analyses

The primary endpoint and key secondary endpoints will be analyzed in the following subgroups.

- Sex (male, female)
- Stratified geographic region (United States and Western Europe, Central and Eastern Europe, Rest of the World) from IRT
- Stratified age/risk of severe COVID-19 (aged ≥12 and <55 years and low risk, aged ≥12 and <55 and high risk, aged ≥55 years) from IRT

- Derived age/risk of severe COVID-19 (aged ≥12 and <55 years and derived low risk, aged ≥12 and <55 and derived high risk, aged ≥55 years) from eCRF
- Derived high risk for severe COVID-19 (yes, no): aged ≥12 and <55 and derived high risk, plus aged ≥55 years

For the binary endpoint, the analysis will use the same methodology as the primary efficacy analysis with age (continuous) as covariate to estimate the standardized relative risk reduction and 95% CI for each subgroup with at least 5 total events. Subgroups with less than 5 total events will be summarized descriptively. A forest plot will be provided, which displays the point estimate and 95% CI of the estimate. Missing age will be imputed as the average of non-missing value at baseline in the FAS. Additional prognostic factors may be added to the model if there is no issue of model convergence, such as baseline serostatus or baseline RT-PCR status when applicable.

5.5.6. Additional Secondary Endpoints and Analyses

Analyses of other secondary endpoints (Table 5) will be conducted to support the findings of the primary and key secondary efficacy endpoints. The results of these analyses will be considered descriptive in nature and will be analyzed without any procedures to account for multiple comparisons. In addition to these analyses, listings will be provided.

Table 5. Additional Secondary Endpoint Analyses

Endpoint	Analysis Set
Cohort A (PEP)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier	mFAS-1/mFAS/FAS pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier	mFAS-1/mFAS/FAS pre-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 and 3 months after randomization or emergence of Omicron, whichever is earlier	mFAS-2 pre-Omicron
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) on Days 8 and 15 after randomization	mFAS-1 pre-Omicron
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology through Day 28	mFAS-1 pre-Omicron
Peak post-baseline SARS-CoV-2 viral load as measured by RT-qPCR (nasal sample)	participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) on Days 8 and 15
SARS-CoV-2 viral load assessed by RT-qPCR (nasal sample) change from baseline to Day 8 and Day 15	participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) at baseline, Day 8, and Day 15

Endpoint	Analysis Set
Cohort B (PrEP)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier	FAS pre-Omicron
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier	FAS pre-Omicron
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6	mFAS pre-Omicron
Cohort A (PEP), Cohort B (PrEP)	
Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28	participants with RT-PCR-confirmed symptomatic COVID-19
All-cause mortality through CLI Day 28	
COVID-19-related mortality through CLI Day 28	
Time from reported symptom onset to sustained resolution of symptomatic COVID-19 through CLI Day 28	
Viral load from CLI Day 1 sample assessed by RT-qPCR.	
Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28	
Proportion of participants with COVID-19-related hospitalizations through CLI Day 28	

5.5.7. Exploratory Endpoint Analyses

Analyses of exploratory endpoints (Table 6) will be conducted to explore additional efficacy signals for hypothesis generation.

Table 6. Exploratory Endpoint Analyses

Endpoint	Analysis Set
Cohort A (PEP)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 (regardless of variant)	mFAS-1/mFAS/FAS pre-Omicron
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS pre-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 (regardless of variant)	mFAS-1/mFAS/FAS post-Omicron
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS post-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 (regardless of variant)	mFAS-1/mFAS/FAS
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS

Endpoint	Analysis Set
Cohort B (PrEP)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months (regardless of variant)	mFAS-1/mFAS/FAS pre-Omicron
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS pre-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months (regardless of variant)	mFAS-1/mFAS/FAS post-Omicron
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS post-Omicron
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months (regardless of variant)	mFAS-1/mFAS/FAS
Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 (regardless of variant)	mFAS-1/mFAS/FAS
Cohort A (PEP), Cohort B (PrEP)	
Proportion of participants with asymptomatic SARS-CoV-2 infection at baseline (defined by positive central SARS-CoV-2 RT-PCR test and lack of symptoms of COVID-19) with medically attended visits (outpatient, telemedicine, or hospitalization) or death through Day 28	Descriptive summary
Health Care Resource Utilization of participants who develop COVID-19: incidence and duration of ICU stay and incidence of emergency room visits	Descriptive summary
Genotypic characterization of viral isolates for reduced susceptibility to ADG20: proportion of participants with baseline and post-baseline (treatment-emergent) variations at critical amino acid positions associated with ADG20 resistance (≥15% and ≥50% allele frequencies)	Descriptive summary
Pre- and post-vaccination SARS-CoV-2 neutralizing antibody titers in participants who choose to receive COVID-19 vaccine during the study	Descriptive summary

5.6. Safety Analysis

5.6.1. Solicited and Unsolicited Adverse Events

5.6.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to the study drug. AEs occurring from when the participant signs the ICF until the Month 14 (EOS) visit or discontinuation from study will be recorded. Only study procedure-related AEs occurring before randomization will be recorded. All AEs will be followed to adequate resolution. MedDRA Version 24 or higher will be used to code all AEs.

5.6.1.2. Injection Site Reactions

Intramuscular ISRs will be recorded in the Injection Site Reaction Diary and graded using the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007), as described in Appendix 1 of the protocol.

Participants will be instructed to record the worst severity experienced (Table 7) during each recording period (prior 24 hours) of the following local (solicited) AEs through Study Day 4, and, if applicable, whether medication was taken to relieve the symptoms:

- Injection site pain or tenderness
- Erythema/redness at the site of injection
- Induration/swelling at the site of injection

Table 7. Grading of Injection Site Reactions

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening[a] (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

Note: In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[a] Pain/tenderness are not expected to be life-threatening but can still meet Grade 4 criteria based on ER visit or hospitalization

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

For summaries combining ISRs and other AEs, ISRs will be mapped to MedDRA SOC and PT as shown in Table 8.

Table 8. Injection Site Reaction Mapping to MedDRA Coding

Injection Site Reaction Term	System Organ Class	Preferred Term
Pain	General disorders and administration site conditions	Injection site pain
Tenderness	General disorders and administration site conditions	Injection site pain
Erythema	General disorders and administration site conditions	Injection site erythema
Redness	General disorders and administration site conditions	Injection site erythema
Induration	General disorders and administration site conditions	Injection site induration
Swelling	General disorders and administration site conditions	Injection site swelling
Necrosis	General disorders and Administration site conditions	Injection site necrosis
Exfoliative dermatitis	Skin and subcutaneous tissue disorders	Dermatitis exfoliative

An ISR that is reported on multiple days will be considered one ISR with the start date defined as the date the ISR was first reported, and the end date defined as the date the ISR is reported as not

occurring (ie, none) in the diary or the date of resolution for the ISR Resolution eCRF. Maximum severity will be assigned.

5.6.1.3. Treatment Emergent Adverse Events

A TEAE is defined as any AE that has an onset during or after the administration of study drug through the Month 14 visit, or any preexisting condition that has worsened during or after the administration of study drug through the Month 14 Visit. Because solicited AEs (ISRs in participants receiving IM injection) are expected to occur after the administration of study drug, all solicited AEs will be considered study drug related TEAEs.

5.6.1.4. Adverse Events of Special Interest

For this study, AESIs are specified in the protocol as follows: Hypersensitivity reactions occurring within 4 days of study drug administration including, but not limited to, anaphylaxis, anaphylactic shock, bronchospasm, hypotension, loss of consciousness, generalized skin rash, angioedema, bronchoconstriction, allergic bronchial asthma, allergic rhinitis, allergic conjunctivitis, drug allergy, immune thrombocytopenia, autoimmune hemolytic anemia, rash, urticaria, and arthus reaction.

Hypersensitivity reactions will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (NIAID 2017).

Determination of hypersensitivity reactions for participants throughout the study will be based on a sponsor medical adjudication based on the narrow and broad terms of the SMQs hypersensitivity, anaphylactic reaction, and angioedema.

All hypersensitivity reactions will be summarized through Day 4 and through Month 14.

5.6.1.5. Medically Attended Adverse Events

MAAEs are defined as AEs leading to medically attended visits that are not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason other than the illness under study (COVID-19). AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered MAAEs.

5.6.1.6. Serious Adverse Events

An SAE is defined as any event that:

- results in death
- is immediately life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (eg, intensive treatment in an ER or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or

development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor]).

5.6.1.7. Adverse Event Intensity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The intensity of all unsolicited AEs will be graded by the investigator according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (NIAID 2017). The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (Note: This grade is not specifically listed on each page of the grading table.)

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates). For SAEs, only one instance of the event would be reported with the highest severity grade.

Missing severity is not imputed.

5.6.1.8. Relationship of Adverse Events to Study Drug

All ISRs (solicited AEs) are considered related to study drug.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all unsolicited AEs. The relationship will be characterized using the following classification:

- **Not related:** There is not a reasonable possibility of a relationship to the study drug. The participant did not receive the study drug, temporal sequence of the AE onset relative to administration of the study drug is not reasonable, OR the AE is more likely explained by another cause than the study drug.
- **Related:** There is a reasonable possibility of a relationship to the study drug. There is evidence of exposure to the study dug. The temporal sequence of the AE onset relative to the administration of the study drug is reasonable. The AE is more likely explained by the study drug than by another cause.

If relationship is missing for an event, the event will be categorized as Related.

5.6.1.9. Analysis of Adverse Events and Injection Site Reactions

All AE and ISR analyses will be performed using the Safety Set. For all analyses of AEs/ISRs, if the same AE/ISR (based on PT) is reported for the same participant more than once, the AE/ISR

is counted only once for the PT and at the highest severity and by relationship to study drug. Percentages will be calculated out of the number of participants in the Safety Set. Missing and incomplete dates of AEs will be imputed as described in Appendix A. In addition to safety summaries, listings of AEs (with TEAE designated by *), SAEs, and ISRs will be presented.

Safety summaries through Month 14 will be presented. All summaries by SOC and PT will be sorted by descending participant count of SOC/PT in the ADG20 arm.

The AE/ISR summaries listed below will be provided:

- Overall summary of AEs (solicited and unsolicited) including the number/percentage of participants with:
  - a pre-treatment AE
  - a TEAE (and separately for unsolicited and solicited TEAEs)
  - a study drug related TEAE
  - a ≥Grade 3 TEAE
  - an SAE
  - a study drug related SAE
  - a TEAE leading to death
  - an MAAE
  - any hypersensitivity reaction (and separately for any hypersensitivity reaction through Day 4 [AESI])
- Incidence of TEAEs (including solicited ISRs) by SOC, PT, and treatment group
- Incidence of TEAEs (including solicited ISRs) occurring in >2% of participants in either arm by SOC, PT, and treatment group
- Incidence of MAAEs by SOC, PT, and treatment group
- Incidence of study drug related TEAEs (including solicited ISRs) by SOC, PT, and treatment group
- Incidence of TEAEs (including solicited ISRs) by maximum severity by SOC, PT, and treatment group
- Incidence of study drug related TEAEs (including solicited ISRs) by maximum severity by SOC, PT, and treatment group
- Incidence of solicited AEs (ISRs) by maximum severity based on the FDA toxicity scale through Day 4
- Incidence of SAEs by SOC, PT, and treatment group
- Incidence of hypersensitivity reactions by SOC, PT, and treatment group
- Incidence of hypersensitivity reactions by maximum severity by SOC, PT, and treatment group

5.6.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory and results will be graded at the laboratory according to DAIDS criteria, if applicable.

Descriptive statistics (based on SI units) for clinical laboratory test results (hematology, serum chemistry, and coagulation) will be presented by treatment group and time point assessed. Descriptive statistics for the change from baseline to each post-baseline time point for the laboratory parameters will also be summarized by treatment group. In addition, the number and percentage of participants with potentially clinically significant (PCS) laboratory parameters will be summarized for any time post-baseline and by time point assessed.

A shift table of the DAIDS toxicity grading from baseline to worst post-baseline will be provided. For tests with both high and low DAIDS toxicity criteria, shift will be summarized separately for the high and low direction. A PCS value is defined as any DAIDS grade 4 post-baseline or any increase of 2 or more DAIDS grades post-baseline, except for PCS low creatinine clearance, which is defined as any DAIDS Grade 4 post-baseline or any DAIDS grade shift from 0 to 3. Laboratory parameters not graded by DAIDS will be defined as PCS based on the criteria in Table 9.

Table 9. PCS Criteria for Clinical Laboratory Tests Not Graded by DAIDS

Parameter	SI Unit	PCS Low Limit	PCS High Limit
Basophils percent	%	—	>4.0 × ULN
Eosinophils percent	%	—	>4.0 × ULN
Monocytes percent	%	—	>4.0 × ULN
Hematocrit	%	<0.6 × baseline	>1.3 × ULN
Blood urea nitrogen	mmol/L	—	>1.3 × ULN
Chloride	mmol/L	<0.8 × LLN	>1.1 × ULN
Protein, total	g/L	<0.8 × LLN	>1.2 × ULN

LLN=lower limit of normal; PCS=potentially clinically significant; ULN=upper limit of normal.

All clinical laboratory values for participants with PCS will be provided in listings.

5.6.3. Vital Sign Measurements

Descriptive statistics for vital signs and for the change from baseline to each post-baseline time point will be presented by treatment group. The number and percentage of participants with a PCS vital sign parameter will be provided for any time post-baseline and by time point assessed. A PCS value is defined as meeting both criterion value and change from baseline provided in Table 10.

Table 10. PCS Criteria for Vital Signs

Vital Sign Parameter (Unit)	Flag	Criterion Value	Change from Baseline
Systolic blood pressure (mmHg)	High (CH)	≥180	Increase of ≥20 mmHg
	Low (CL)	≤90	Decrease of ≥20 mmHg
Diastolic blood pressure (mmHg)	High (CH)	≥105	Increase of ≥15 mmHg
	Low (CL)	≤50	Decrease of ≥15 mmHg
Heart Rate (bpm)	High (CH)	≥120	Increase of ≥15 bpm
	Low (CL)	≤50	Decrease of ≥15 bpm
Temperature (°C)	High (CH)	≥38 °C	Increase of ≥1 °C
	Low (CL)	<35 °C	Decrease of ≥1 °C
Respiratory Rate (breaths/min)	High (CH)	≥30 breaths/min	Increase of ≥10 breaths/min
	Low (CL)	≤8 breaths/minute	Decrease of ≥4 breaths/minute
Oxygen Saturation (SpO_2)	Low (CL)	≤93%	Decrease of ≥3%

bpm=beats per minute; CH=clinically high; CL=clinically low.

All vital sign data by participant for in-person visit will be presented in a listing.

5.6.4. Other Safety Data

Physical examination results will be included in data listings. Pregnancy testing data will be provided in a listing for all female participants.

6. PHARMACOKINETIC ANALYSES

All PK listings, individual concentration-time profiles, PK tables and figures, and all statistical analyses will be presented using the PK analysis set.

6.1. Data Handling

Data rounding specifications for PK data are documented in the PK TLF shells. Handling of missing data is detailed in Section 4.1.

6.2. Serum Concentrations

Serial blood samples will be collected at the following time points (with collection window) for PK assessment:

- Day 1 at baseline (predose)
- Day 8 (±2 days), Day 28 (+5 days), 6 months (±2 weeks), 12 months (±2 weeks)

Individual serum concentrations of ADG20 will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric mean CV%, median, minimum, and maximum) by time point.

Individual serum concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Mean (SD) serum concentrations will be plotted by part, treatment, nominal time on both linear and semi-logarithmic scales.

6.3. Serum Pharmacokinetic Parameters

Serum concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ). The PK parameters to be calculated for ADG20, where data permit, are listed in Table 11.

Table 11. Calculated PK Parameters

Parameter	Definition
C_{max}	Maximum observed concentration.
T_{max}	Time of maximum observed concentration.
$AUC_{0\text{-last}}$	AUC from time 0 to the last measurable observed concentration (C_t), calculated using the linear trapezoidal rule.
$AUC_{0\text{-inf}}$	AUC from time 0 extrapolated to infinity, calculated as [$AUC_{0\text{-last}} + (C_t / \lambda_z)$].
$T_{1/2}$	Apparent terminal elimination half-life, calculated as: ln (2) / λ_z.
CL/F	Apparent total body clearance, calculated as: Dose / $AUC_{0\text{-inf}}$.
V_d/F	Apparent volume of distribution during the terminal phase (for IM dose), calculated as: Dose / [$\lambda_z \times AUC_{0\text{-inf}}$].

In addition to the PK parameters shown in Table 11, which will be listed and summarized, the parameters in Table 12 will also be listed to document the selection of data points used to estimate $T_{1/2}$ using non-compartmental procedures.

Table 12. PK Parameters for Data Selection

Parameter	Definition
λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included
λ_z lower	Lower bound used for the estimation of λ_z
λ_z upper	Upper bound used for the estimation of λ_z
Rsq (R2)	R2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where R2 ≥0.80
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-inf}}$ due to extrapolation; $AUC_{0\text{-inf}}$, CL/F and V_d/F values will be flagged and excluded from summary statistics where $\%AUC_{ext}$ >20%

Actual sampling times will be used for the estimation of all serum PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows).

Serum PK parameters will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean,

geometric CV, median, minimum, and maximum) by part, treatment. T_{max} will be summarized using number of observations, median, minimum, and maximum only.

7. IMMUNOGENICITY ANALYSIS

Immunogenicity analysis will be conducted in the Immunogenicity Set. ADA status will be defined as positive or negative based on the confirmatory assay. Baseline (predose Day 1) and Day 28, Month 6, and Month 12 ADA results will be summarized by treatment arm.

Treatment emergent ADA is defined as participants who had a negative ADA measurement at baseline (predose Day 1) and positive ADA post-baseline or participants who had a positive ADA measurement at baseline and a positive ADA measurement post-baseline with an ADA titer ≥4 times the baseline ADA titer. The number and percentage of participants with treatment-emergent ADA will be summarized by treatment group.

8. CHANGES IN THE PLANNED ANALYSIS

There are no changes to the analyses presented in the protocol.

9. REFERENCES

Ge M, Durham LK, Meyer D, et al. (2011). Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences. Drug Inf J. 45(4): 481-493. doi:10.1177/009286151104500409.

NIAID. (2017). Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1 July 2017. Retrieved 18 December 2020, from https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

10. APPENDICES

APPENDIX A. IMPUTATION RULES FOR MISSING DATES OF MEDICATIONS AND ADVERSE EVENTS

For missing dates of medications or AEs, the most conservative approach will be systematically considered. If the AE onset date is missing/incomplete, it is assumed to have occurred during the treatment or follow-up phase (ie, considered a TEAE) except if the partial onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered either a prior or concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (eg, xx-xxx-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the first dose of study drug or completely missing, then the start date will be estimated to be equal to the date of the first dose of study drug. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to be the last of the month (eg, xx-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last day of the year (eg, xx-xxx-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug, and the stop date will not be imputed.
- Missing or partial end dates will not be imputed for AEs.

APPENDIX B. ALGORITHM OF LOGISTIC REGRESSION METHOD

The method described in Ge et al. (2011) computes a population-level estimate for the treatment difference (in terms of risk difference in proportions) and supports an adjustment for the pre-defined prognostic factors.

With a data set of n participants,

binary response vector $Y = (y_1, y_2, ..., y_n)'$,

covariate matrix $X = (x_1, x_2, \ldots, x_n)'$,

a logistic regression model assumes $\text{logit}[P(y_i = 1 \mid x_i)] = \beta' x_i$, where $\text{logit}(p) = \ln[p/(1 - p)]$.

Let b denote the maximum likelihood estimate (MLE) of β, and its estimated variance-covariance matrix is V. The proportions of responders to both treatment and control, and their risk difference are estimated as follows.

First, create the new covariate matrix X_t from X by adjusting the column corresponding to treatment assignment such that all participants are in the treated group. Then calculate the vector of estimated probabilities of response to treatment $\widehat{P}_t$ from X_t and b, $\widehat{P}_t = \text{logit}^{-1}(X_t\, b)]$. Similarly, assume each participant is assigned to control and redo the above steps to get X_c and $\widehat{P}_c$.

Estimate Risk Difference (RD):

$$RD = \sum_{i=1}^{n} \frac{\hat{P}_{ti}}{n} - \sum_{i=1}^{n} \frac{\hat{P}_{ci}}{n}$$

where $\hat{P}_{ti}$ and $\hat{P}_{ci}$ are the i^{th} elements of $\hat{P}_t$ and $\hat{P}_c$ respectively.

The variance of the estimated risk difference:

$$Var(RD) = Var(\sum_{i=1}^{n} \frac{\hat{P}_{ti}}{n}) - 2cov\left(\sum_{i=1}^{n} \frac{\hat{P}_{ti}}{n}, \sum_{i=1}^{n} \frac{\hat{P}_{ci}}{n}\right) + Var(\sum_{i=1}^{n} \frac{\hat{P}_{ci}}{n})$$

The delta method can be used to estimate each component of the variance estimation.

Define A_t as a vector with elements $A_{ti} = \widehat{P}_{ti}(1 - \widehat{P}_{ti})$.

Similarly define A_c as a vector with elements $A_{ci} = \widehat{P}_{ci}(1 - \widehat{P}_{ci})$.

$d_t = (A_t' X_t)/n$

$d_c = (A_c' X_c)/n$

$SE = \sqrt{(d_t V d_t' + d_c V d_c' - 2\, d_c V d_t')}$

The confidence interval of RD is $RD \pm Z_{(1-\alpha/2)}\, SE$

Estimate Log Risk Ratio (RR):

$$\delta_1 = \log(RR) = log\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n} - log\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}$$

where $\hat{P}_{ti}$ and $\hat{P}_{ci}$ are the i[th] elements of $\hat{P}_t$ and $\hat{P}_c$ respectively.

The variance of the estimated log risk ratio:

$$Var(\delta_1) = Var(log\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}) - 2cov\left(log\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}, log\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}\right) + Var(log\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n})$$

Since,

$$Var\left(log\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}\right) \approx \left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}}\right)^2 Var\left(\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}\right) \approx \left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}}\right)^2 d_t V d_t'$$

$$Var\left(log\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}\right) \approx \left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}}\right)^2 Var\left(\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}\right) \approx \left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}}\right)^2 d_c V d_c'$$

$$2cov\left(log\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}, log\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}\right) \approx 2\left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ti}}{n}}\right)\left(\frac{1}{\sum_{i=1}^{n}\frac{\hat{P}_{ci}}{n}}\right) d_c V d_t'$$

$SE(\delta_1) = \sqrt{Var(\delta_1)}$

The confidence interval of logRR is $\delta_1 \pm Z_{(1-\alpha/2)}\, SE(\delta_1)$.

The confidence interval of RR is $\exp(\delta_1 \pm Z_{(1-\alpha/2)}\, SE(\delta_1))$.

The relative risk reduction and its confidence interval is

$(1 - \exp(\delta_1))$ and $[1 - \exp(\delta_1 + Z_{(1-\alpha/2)}\, SE(\delta_1)), 1 - \exp(\delta_1 - Z_{(1-\alpha/2)}\, SE(\delta_1))]$.