Statistical Analysis Plan

Study ID: ADG20-TRMT-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 Treatment of Ambulatory Participants with Mild or Moderate COVID-19 (STAMP)

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Adagio Therapeutics, Inc.

STATISTICAL ANALYSIS PLAN

ADG20-TRMT-001

A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ADG20 in the Treatment of Ambulatory Participants With Mild or Moderate COVID-19 (STAMP)

FINAL Version 1.0, 03 March 2022

Prepared by:

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
BLQ	below the limit of quantification
BMI	body mass index
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CTMS	PPD Clinical Trial Management System
DAIDS	Division of Allergy and Infectious Diseases
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
EUA	emergency use authorization
FAS	full-analysis set
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
IA	Interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IM	intramuscular
IRT	interactive response technology
ISR	injection site reaction

Abbreviation	Definition
IV	intravenous
KM	Kaplan-Meier
LAR	legally authorized representative
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
MNAR	missing not at random
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
OTC	over-the-counter
PASC	post-acute sequelae of SARS-CoV-2
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
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

Abbreviation	Definition
WGS	whole genome sequencing

1. INTRODUCTION

This SAP describes the planned analyses for ADG20-TRMT-001 (STAMP) based on the clinical study protocol, version 6.0, dated 02-Mar-2022. In addition to the information presented in the statistical analysis section of the protocol (Section 7), which provides the principal features of analyses for the study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not principal in nature and result from information that was not available at the time of protocol finalization.

The STAMP study is a randomized, double-blind, placebo-controlled, multi-center adaptive study of the safety, efficacy, PK, and antiviral activity of the mAb ADG20 in the treatment of ambulatory participants with mild or moderate COVID-19 with a high risk of disease progression based on age or co-morbid medical conditions. The study will be conducted in 2 phases with data review conducted by an iDMC throughout.

PPD Biostatistics and programming team, designee of Adagio Therapeutics, Inc., will perform the statistical analysis; SAS Version 9.4 or higher will be used. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail. Any additional analysis outside of the planned analysis following the Day 29 database soft lock or the final database lock that are not performed by PPD are not included in the SAP.

The STAMP 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 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 efficacy data collected in participants with a non-Omicron variant of SARS-CoV-2 and safety data collected in all participants. The efficacy in participants with an Omicron variant of SARS-CoV-2 will be exploratory. With this analysis plan, the primary efficacy and safety analyses are planned 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

The objectives and endpoints are presented in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ADG20 compared to placebo in the treatment of mild or moderate COVID-19 in participants at high risk of disease progression	COVID-19-related hospitalization or all-cause death through Day 29
To evaluate the safety and tolerability of ADG20 compared to placebo through Day 29 in participants with mild or moderate COVID-19 and high risk of disease progression	Assessment of safety through Day 29 based on: • The incidence of TEAEs • Incidence of solicited injection site reactions through Day 4 • Changes from baseline in clinical laboratory tests (ie, CBC with differential, serum chemistry, coagulation) • Changes from baseline in vital signs (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure)
Secondary	
To evaluate the effect of ADG20 on the following clinical parameters in participants with mild or moderate COVID-19 and high risk of disease progression • Severity of COVID-19 • COVID-19-related emergency room visits, COVID-19-related hospitalizations, or all-cause death • Time to sustained resolution of COVID-19 symptoms • COVID-19-related medically attended visits • Time to sustained recovery of COVID-19 symptoms • All-cause mortality	• Severe/critical COVID-19 or all-cause death through Day 29 • COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29 • Time to sustained resolution of COVID-19 symptoms through Day 29 • COVID-19-related medically attended visit (telemedicine, physician office, urgent care center, emergency room, hospitalization) or all-cause death through Day 29 • Time to sustained recovery defined as sustained improvement or resolution of COVID-19 symptoms through Day 29 • All-cause death through Day 29, Day 60, and Day 90

Objectives	Endpoints
To evaluate the effect of ADG20 on SARS-CoV-2 viral load and clearance in participants with mild or moderate COVID-19 and high risk of disease progression	• Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Day 7 (±1) assessed by RT-qPCR from NP samples • Viral load >5 log_{10} copies/mL on Day 7 (±1) based on NP samples • Duration of SARS-CoV-2 viral shedding from Day 1 through Day 29 assessed by RT-qPCR from saliva samples • Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Days 3, 5, 7, 11, and 14 assessed by RT-qPCR from saliva samples • SARS-CoV-2 viral clearance (Days 5, 7, 11, 14, 21, and 29) assessed by RT-qPCR from saliva samples (and BLQ/not detected or not detected for NP samples for Day 7) • SARS-CoV-2 viral load AUC assessed by RT-qPCR from saliva samples from baseline to Day 29
To evaluate the long-term safety and tolerability of ADG20 compared to placebo in participants with mild or moderate COVID-19 and high risk of disease progression	Assessment of safety based on: • The incidence of TEAEs • Changes from baseline in clinical laboratory tests (ie, CBC with differential, serum chemistry, coagulation) • Changes from baseline in vital signs (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure)
To evaluate the PK of ADG20 following IM administration	PK parameters of ADG20: As data permit, C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, CL, Vd, and $T_{1/2.}$ Additional PK parameters may be calculated
To evaluate the immunogenicity (ADAs) to ADG20	Incidence of ADAs against ADG20
To evaluate the emergence of resistance to ADG20	Genotypic characterization of viral isolates for reduced susceptibility to ADG20, with phenotypic evaluation as appropriate
Exploratory	
To evaluate the effect of host or viral biomarkers on clinical outcomes	Effect of baseline SARS-CoV-2 specific antibody response on select clinical outcomes
To identify a persistently high viral load threshold for risk of adverse clinical outcomes	The level of viral load leading to the following adverse clinical outcomes: • COVID-19-related hospitalization or all-cause death through Day 29 • COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29 • Severe/critical COVID-19 or all-cause death through Day 29

Objectives	Endpoints
To evaluate the development of symptomatic COVID-19 or asymptomatic infection in household contacts of study participants after participant receipt of study drug	• Participants with symptomatic COVID-19 among household contacts • Participants with asymptomatic SARS-CoV-2 infection among household contacts
To evaluate the effect of ADG20 on the following parameters • COVID-19-related mortality • Time to improvement of COVID-19 symptoms • Post-acute sequelae of SARS-CoV-2 infection	• COVID-19-related death through Day 29 • Time to improvement of COVID-19 symptoms through Day 29 • Incidence of PASC at Day 60, Day 90, and Month 6

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; CBC=complete blood count; CL=clearance; C_{max}=maximum plasma concentration; IM=intramuscular; NP=nasopharyngeal; PASC=post-acute sequelae of SARS-CoV-2 infection; PK=pharmacokinetic; RT-(q)PCR=(quantitative) reverse transcription-polymerase chain reaction; TEAEs=treatment-emergent adverse events; $t_{½}$=plasma concentration half-life; T_{max}=time to reach C_{max}; Vd=apparent volume of distribution.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

ADG20-TRMT-001 is a randomized, double-blind, placebo-controlled, multi-center adaptive study of the mAb ADG20 in the treatment of ambulatory participants with mild or moderate COVID-19. The study will evaluate the safety, efficacy, PK, and antiviral activity of ADG20 300 mg IM versus placebo. A total of approximately 1084 participants are planned to be enrolled in the study at approximately 100 to 115 sites globally.

Participants with laboratory confirmed mild or moderate COVID-19 with symptom duration of 5 days or less prior to randomization and a positive SARS-CoV-2 test taken within 5 days or less prior to randomization will be enrolled. Participants will be randomized 1:1 to receive a single dose of ADG20 or placebo by IM injection. Randomization will be stratified by age (age 12 to 17, 18 to 65, and >65 years) and country.

Study drug will be administered at the study site. As a precaution for acute worsening of disease, hypersensitivity, and/or ISRs, participants will be observed after study drug administration, as described in the protocol (Section 6.4.1). Each participant will receive a single dose of study drug or placebo at the Day 1 Visit. After Day 1, participants will be followed via telemedicine visits, phone calls, or in-person visits, as indicated in the Schedule of Events (Appendix M), through Month 14/EOS.

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 available safety data, and other clinical study data, to ensure the benefit/risk remains favorable (refer to Appendix L and below for

details). Details regarding iDMC membership, conduct, ongoing safety monitoring, decision-making, and communication will be provided in the iDMC Charter. PPD is not responsible for producing iDMC reports and will complete analyses after the database locks (Day 29 and Month 14) as detailed below. Pausing guidelines triggering iDMC ad hoc reviews are described in Section 5.8.1.9.

To evaluate the safety profile of ADG20 and to make recommendations regarding enrollment of adolescents and pregnant and breastfeeding women in Phase 3 and postdose monitoring duration, an administrative IA will be reviewed by the iDMC after approximately 200 participants are enrolled in Phase 2.

Following completion of enrollment and completion of the Day 29 visit for all participants (or if it is known that a participant will not have a Day 29 visit), the database will be frozen (soft-locked) to conduct the primary Day 29 analysis. All decisions regarding the analysis will be made in a blinded fashion and the SAP will be finalized (signed) prior to unblinding. The study will be unblinded to Sponsor personnel not working directly with the site staff after this freeze, and an unblinded data analysis will be performed. All site staff, certain Sponsor personnel (or designee) working directly with the site staff, and participants, will remain blinded to individual participant study drug assignment.

The database will be locked for the final safety analysis after all participants have been followed through the Month 14 visit (or if it is known that the Month 14 visit will not occur).

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(s), and/or to address protocol amendments.

3.3. Study Duration

The study duration for each participant will be approximately 14 months. Each participant, regardless of study phase, will receive a single dose of ADG20 or placebo at the Day 1 visit. Participants will have telemedicine visits (via video or phone) and in-person clinic or at-home visits through Day 29. Participants will continue long-term follow-up through Month 14, with additional visits for safety laboratory tests at Day 90 and at Month 6.

3.4. Study Assessments

The Schedule of Assessments is provided in Appendix M. Efficacy and safety assessments will be conducted by site staff, and by participants with at home assessments and collections.

3.4.1. Clinical Efficacy Assessments

Participants will be asked to complete the COVID-19 Symptom Diary (includes global impression questions) daily from Day 1 to Day 29. The investigator (or designee) will assign an overall COVID-19 severity grade for each visit through Day 29. At scheduled visits on Days 3, 5, 7, 11, 14, 21, 29, 60, 90, and at Months 6, 11, and 14, participants (or guardians/LARs) will be asked to report any medically attended visits. Medically attended visits include telemedicine visits not specified in the protocol, emergency room or urgent care center visits, hospitalization, or visits to a physician's office. COVID-19-related medically attended visits include visits for

attention to worsening signs or symptoms attributed to COVID-19 in the opinion of the investigator. The participant's survival status (known to be dead or alive) should be determined at the planned time for any missed visit through Month 14, or at the time that the participant is thought to be lost to follow-up. At Day 29, participants will be asked about household transmission of SARS-CoV-2 and symptomatic COVID-19.

During the long-term follow-up period (LTFU), participants will be asked questions about their overall health status, including return to usual health and usual activities and any ongoing symptoms associated with COVID-19.

3.4.2. Virologic Efficacy Assessments

Blood will be collected on Day 1 to test for SARS-CoV-2 antibodies. Two NP swabs will be collected on Day 1 for SARS-CoV-2 RT-qPCR, SARS-CoV-2 sequencing, and a respiratory panel assessment. One NP swab will be collected on Day 7 for SARS-CoV-2 RT-qPCR and SARS-CoV-2 sequencing. Saliva samples for SARS-CoV-2 RT-qPCR will be collected at the site on Days 1, 7, and 29, and by participants at home on Days 3, 5, 11, 14, and 21.

3.4.3. PK and ADA Assessments

On Day 1, a blood sample for PK assessment will be collected prior to study drug administration. Blood samples for PK assessment will also be collected on Days 7, 29, 90, and at Month 6 and Month 11. Blood samples for determination of ADA (and neutralizing antibody) against ADG20 will be collected on Days 1, 29, and 90, and at Months 6 and 11.

3.4.4. Safety Assessments

Safety will be assessed in an ongoing manner. Blood samples for safety laboratory assessments (hematology, serum chemistry, and coagulation) will be collected on Days 1, 7, 29, and 90, and at Month 6. A complete physical examination will be conducted at screening, and a targeted, symptom-directed review of changes in health based on reported AEs or ongoing signs/symptoms of COVID-19 will be conducted at Days 7, 29, and 90, and at Month 6 and Month 11. Vitals signs (including temperature, heart rate, respiratory rate, seated blood pressure, and SpO_2 will be assessed by site staff after study drug dosing and on Days 7, 29, and 90, and at Month 6 and Month 11 (see Appendix M). Measurements of temperature, SpO_2, and heart rate are to be taken by the participant daily through Day 29.

AEs occurring from when the participant signs the ICF until the Month 14 visit, or withdrawal from the study, 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. AESIs (as defined in Section 5.8.1.4) will be recorded through Day 4. 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.

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 5.8.

3.5.1. Clinical Efficacy Endpoints

COVID-19-related hospitalization or all-cause death through Day 29 (primary endpoint): COVID-19-related hospitalizations include 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, intensive care units, acute care facilities created for COVID-19 pandemic hospitalization needs, or other acute care facilities).
- **Through Day 29** is defined as the admission date for the hospitalization or acute care facility occurring from Day 1 (postdose) up to and including Day 29.
- **All-cause death** is defined as death for any reason from Day 1 (postdose) through Day 29.

Severe/critical COVID-19 or all-cause death through Day 29: All-cause death is defined as death for any reason from Day 1postdose) through Day 29. Severity is based on the investigator's assessment of severity (eCRF COVID-19 Severity Assessment) per the following protocol definitions:

- **Severe COVID-19** is defined as having a positive test by standard RT-PCR assay or equivalent test plus the following:
  - Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress including the need for initiation of oxygen therapy.
  - Clinical signs suggestive of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level or ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) <300 mm Hg.
  - No criteria for critical severity.
- **Critical COVID-19** is defined as having a positive test by standard RT-PCR assay or equivalent test plus evidence of critical illness, defined by at least one of the following:
  - Respiratory failure based on resource utilization requiring at least one of the following:
    - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation, or clinical diagnosis of respiratory failure (ie, clinical need for one of the preceding therapies, but the preceding therapies cannot be administered in setting of resource limitations).

- Shock (defined by systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors). **Note**: Shock is per investigator diagnosis/assessment.
- Multiorgan dysfunction/failure.

Note: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

Regardless of investigator's assessment of severity, severe/critical COVID-19 will be imputed for participants who met the primary efficacy endpoint definition in the analysis.

COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29: Defined as any stay in a hospital or acute care facility regardless of duration (includes emergency rooms, intensive care units, acute care facilities created for COVID-19 pandemic hospitalization needs, or other acute care facilities) for attention to worsening signs or symptoms attributed to COVID-19 in the opinion of the investigator or all-cause death through Day 29.

COVID-19-related medically attended visits or all-cause death through Day 29: Defined as for the primary efficacy endpoint, but also includes any medically attended visits, in-person, or telemedicine, not specified in the protocol. These include unscheduled in-person or telemedicine visits conducted by the investigator for the purpose of evaluating worsening signs or symptoms attributed to COVID-19 or emergency room, urgent care center or physician office visits, or hospitalization for attention to worsening signs or symptoms attributed to COVID-19, in the opinion of the investigator.

Time to sustained recovery (improvement or resolution) of COVID-19 symptoms through Day 29: Defined as the time from the first dose date to the earliest date when sustained improvement or sustained resolution of COVID-19 symptoms is met (as detailed below) through Day 29. COVID-19 symptoms assessed include fever, chills, cough, sore throat, congestion, shortness of breath/difficulty breathing at rest, shortness of breath/difficulty breathing with exertion, muscle or body aches, fatigue, headache, nausea, vomiting, and diarrhea. Loss of taste/smell is excluded from this analysis.

Time to sustained improvement of COVID-19 symptoms through Day 29: Defined as the time from the first dose date to the first date when all of the above symptoms are scored as moderate or severe at baseline are scored as mild or absent, all of the above symptoms scored as mild or absent at baseline are scored as absent, and with no symptom worsening or new symptoms, except for cough, fatigue, and headache which may be mild or absent, through Day 29.

Time to sustained resolution of COVID-19 symptoms through Day 29: Defined as time from the first dose date to the first date when all of the above symptoms are scored as absent with no symptom recurrence or new symptoms, except cough, fatigue, and headache which may be mild or absent, through Day 29.

Censoring rules for time to COVID-19 symptoms through Day 29 analysis:

- Participants who are randomized but not treated are censored at Day 1.

- Participants who have any COVID-19-related hospitalization (≥24 hours) or all-cause death through Day 29 (as defined in the primary endpoint) will be censored at Day 30.
- Participants who have not been followed through Day 29 visit (discontinuation from study or incomplete follow-up at the time of analysis) will be censored at the last contact date.
- Participants who have completed the Day 29 visit and do not experience a defined event through Day 29 will be censored at Day 30.

Table 2 provides further programming details.

Table 2: Criteria for Sustained Improvement and Sustained Resolution of COVID-19 Symptoms Through Day 29

COVID-19 Symptoms	Baseline Severity	Criteria for Sustained Improvement	Criteria for Sustained Resolution
Fever, chills, sore throat, congestion, shortness of breath/difficulty breathing at rest, shortness of breath/difficulty breathing with exertion, muscle or body aches, nausea, vomiting, diarrhea	Moderate/Severe	Mild/Absent with no worsening (moderate/severe)	Absent with no recurrence or new symptoms (mild/moderate/severe)
	Mild	Absent with no recurrence or new symptoms (mild/moderate/severe)	
	Absent		
Cough, fatigue, headache	Moderate/Severe	Mild/Absent with no worsening (moderate/severe)	Mild/Absent with no worsening (moderate/severe)
	Mild		
	Absent		

All-cause mortality through Day 29, Day 60, and Day 90: Defined as death for any reason from Day 1 (postdose) to Day 29, Day 60, and Day 90. In the overall survival analysis, participants who are alive or lost to follow-up at the time of analysis will be censored at the date of last contact.

COVID-19-related mortality through Day 29: Defined as death directly due to COVID-19 or any death for which COVID-19 or COVID-19 complications contributed to the death, as determined by the investigator, a formal autopsy report or death certificate, as recorded on the Death eCRF.

3.5.2. Virologic Endpoints

For all virologic assessments, the confirmatory retest (reflex) result should be used for analysis if present. If a participant has multiple assessments on the same date with different accession numbers, the accession number on the record with the highest viral load value should be used to select records for analysis. If viral load values are the same, the accession number on the record with the lowest value of MBSEQ will be used to select records for analysis.

Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Day 7 assessed by RT-qPCR from NP sample: Change from baseline is defined as the viral load at the Day 7 assessment from NP sample minus the viral load at baseline from NP sample.

Viral load >5 (log_{10} copies/mL) on Day 7 assessed by RT-qPCR from NP sample: A second cutoff of high viral load will also be examined: viral load >4 (log_{10} copies/mL) on Day 7 assessed by RT-qPCR from NP sample.

Duration of SARS-CoV-2 viral shedding from Day 1 through Day 29 assessed by RT-qPCR from saliva samples: Duration of SARS-CoV-2 viral shedding will be analyzed based on the time to SARS-CoV-2 viral clearance, which is defined as time from the first dose date to the first date the viral load is not detected, ie, below the limit of detection (LOD), and sustained through Day 29. Participants who do not have the defined event or who discontinue study prior to Day 29 are censored at the earlier date of the last viral load assessment or Day 30. Deaths occurring prior to Day 29 will be censored at Day 30.

Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Days 3, 5, 7, 11, 14, 21, and 29 assessed by RT-qPCR from saliva samples: Change from baseline is defined as the viral load from saliva samples at the Day 3, 5, 7, 11, 14, 21, or 29 assessment minus the viral load from saliva sample at baseline.

Proportions of SARS-CoV-2 viral clearance (Days 3, 5, 7, 11, 14, 21, and 29) assessed by RT-qPCR from saliva samples: In the mFAS-S, the cumulative proportion of participants with viral clearance (viral load not detected and sustained through Day 29) at Days 3, 5, 7, 11, 14, 21, and 29 will be assessed by RT-qPCR from saliva samples. Participants who have died or discontinued study prior to Day 29 are assumed to have no viral clearance.

Proportion of SARS-CoV-2 viral load BLQ/not detected or not detected at Day 7 assessed by RT-qPCR from NP samples: In the mFAS-NP, the proportion of participants with viral load BLQ/not detected or not detected at Day 7 assessed by RT-qPCR from NP samples.

SARS-CoV-2 viral load AUC assessed by RT-qPCR from saliva samples through Day 29: Defined as AUC of SARS-CoV-2 viral load from baseline through Day 29 from saliva samples at Days 3, 5, 7, 11, 14, 21, and 29. AUC is calculated using the trapezoidal method.

3.6. Treatments

After randomization, participants will receive a single 300 mg dose (up to 3 mL) of ADG20, or matching placebo, administered via IM injection.

3.7. Dose Adjustment/Modifications

As only a single dose is administered to each participant, there are no subsequent dose adjustments and/or modifications.

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 dose of study drug. If the date of dosing is missing, the date of randomization will be used instead.

Unless otherwise specified, the display precision for the summary statistics of all numerical variables will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will 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 the calendar day that study drug is administered. Subsequent study days are calculated as the date of assessment/event – date of injection + 1. If a participant is not dosed, the date of randomization is used to define Study Day rather than the date of injection.

Time-to-event variables are defined from the date of dosing. If a participant is not dosed, the date of randomization is used.

All summaries involving diary data will be based on distinct diary date entries.

Unscheduled visits: Unscheduled visit measurements will be included in the analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- 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.

Visit windowing rules: Assessments collected on the nominal visits per the protocol schedule will be included in by-visit summaries and analysis. If an assessment is missing from a nominal visit, available assessments from the unscheduled visits within the protocol-defined target-study-day range may be mapped to the corresponding nominal visit. The assessment occurring closest to the target study day will be used. If there are multiple assessments equally distant to the target study day, the earliest assessment will be used.

All diary data will be summarized based on the actual day.

Incomplete/missing data:

Imputation rules for missing dates of prior/concomitant medications, including COVID-19 vaccinations and prohibited medications, and procedures are provided in Appendix C.

Imputation rules for missing AE are provided in Appendix D.

Data that are continuous in nature but are reported in the form $<x$, $>x$, $\leq x$, 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 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)
  - All viral load analyses will use both observed and imputed viral load data. Listings present both observed and imputed viral load.
- For PK concentrations
  - Serum concentrations that are BLQ will be treated as zero for PK analyses, except for BLQ values observed between 2 quantifiable concentrations, which will be set to missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. Missing concentrations will be treated as missing in the PK parameter calculations.
- Efficacy endpoint data will be imputed as detailed in Section 5.5.
- 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/displays for efficacy will be provided by treatment group using the appropriate analysis population unless otherwise specified.

Individual participant listings of all data represented on the eCRFs and laboratory data will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety data. 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

The primary analysis is the comparison of the ADG20 arm versus the placebo arm with respect to proportion of participants infected with a non-Omicron variant of SARS-CoV-2 with a COVID-19-related hospitalization or all-cause death through Day 29.

The original required sample size was calculated based on the following assumptions obtained from a review of data from studies of other mAbs in participants with a high risk for disease progression leading to hospitalization or death prior to widespread emergence of both the Delta and Omicron variants (AstraZeneca 2022; Eli Lilly and Company 2022; GlaxoSmithKline 2021; Regeneron 2022). The original sample size of 1084 participants was planned with 90% power, 2-sided alpha .05, and a 1:1 randomization ratio to detect a statistically significant risk reduction with a true efficacy of relative risk reduction 70% and a 5% event rate in the placebo arm.

At the time of enrollment suspension in January 2022, a total of 399 participants were randomized. Of them, approximately 320 participants will be included in the primary efficacy population of participants with a non-Omicron variant of SARS-CoV-2. Based on blinded monitoring of the primary endpoint outcomes, an aggregate event rate of approximately 9% was observed, indicating a higher placebo event rate than previously assumed and providing approximately 80% power to test the primary endpoint in the primary efficacy population given an estimated placebo event rate of 12% and the same efficacy assumption.

4.3. Randomization, Stratification, and Blinding

After completing the screening assessments, participants will be randomly assigned at the Day 1 visit to receive one of the following (1:1 randomization):

- ADG20 300 mg administered IM
- Placebo administered IM

Randomization will be assigned in a blinded manner using IRT, in accordance with a pre-generated randomization schedule, generated by SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina), linking sequential participant randomization numbers to treatment codes. Randomization will be stratified by age (age 12 to 17, 18 to 65, and >65 years) and country; it will also use an appropriate block size, known only by the statistician. A participant is considered randomized when a randomization transaction has been recorded in the IRT.

The main goal of the stratification by country is to promote the balance in important prognostic and predictive factors across the two treatment groups within a country to help increase comparability of the two treatments rather than incorporating stratification into the analyses to increase the precision of the estimates. Therefore, the country term will not be included as strata in the statistical models.

A participant's treatment assignment will not be unblinded to site staff, sponsor personnel (or designee) working directly with the site staff, or participants until the end of the study (Month 14 of Phase 3) unless medical treatment of the participant depends on knowing the study treatment the participant received. If the blind needs to be broken due to a medical emergency, the investigator may unblind an individual participant's treatment allocation.

Details of blinding are provided in Section 5.5 of the protocol and in the PPD Work Process Flow for Maintaining the Blind.

4.4. Multiplicity Adjustments

To control the overall type I error rate at .05 (2-sided), a hierarchical testing procedure will be used, such that testing for the key secondary analyses difference will proceed only if the treatment difference is statistically significant in the primary analysis.

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 when applicable.

4.5. Analysis Sets

4.5.1. Screen Failures

Screen failures are defined as participants who consent to participate in the study but who are not subsequently randomly assigned to treatment. Minimal information collected includes date of informed consent (and assent, where applicable for adolescents), reason for screen failure, and AE information. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A participant is considered enrolled once the participant has been randomized.

4.5.2. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized participants regardless of whether the participant received study drug. Participants will be analyzed based on the treatment they are randomized to, irrespective of which treatment was actually received.

4.5.3. SARS-CoV-2 Variant Specific Analysis Sets

WGS will be used to determine a participant's SARS-CoV-2 infecting variant (Delta, Omicron, and others) based on the NP or saliva sample collected at baseline; if the baseline sample is missing, the available post-baseline NP or saliva sample will be used. Any participants with a missing WGS result will be classified as suspected non-Omicron or Omicron variant by comparing their randomization date with the date of the first WGS-confirmed Omicron participant enrolled from the same country. If there is no WGS-confirmed Omicron participant enrolled from the same country in the study, the date of emergence of Omicron in the country, based on publicly available epidemiology data will be used (see Appendix E). A final clinical and virological review (with adjudication as needed) may be performed.

Modified Full Analysis Set with Non-Omicron SARS-CoV-2 Variant (mFAS-non-Omicron): will include all randomized participants with COVID-19 due to WGS-confirmed or suspected non-Omicron SARS-CoV-2 variants, regardless of whether the participant received study drug. The mFAS-non-Omicron is the primary efficacy population.

Modified Full Analysis Set with Omicron SARS-CoV-2 Variant (mFAS-Omicron): will include all randomized participants with COVID-19 due to WGS-confirmed or suspected Omicron SARS-CoV-2 variant, regardless of whether the participant received study drug.

4.5.4. Modified Full Analysis Set-PCR

Modified Full Analysis Set-PCR (mFAS-PCR): will include all randomized participants with a positive baseline quantitative SARS-CoV-2 RT-PCR based on either an NP swab or saliva sample and who received study drug. Participants will be analyzed based on the treatment they are randomized to, irrespective of what treatment was actually received.

Two sub-populations of the mFAS-PCR will be defined:

- **mFAS-NP**: will utilize the baseline NP swab to determine a positive SARS-CoV-2 PCR
- **mFAS-S**: will utilize the baseline saliva sample to determine a positive SARS-CoV-2 PCR.

mFAS-non-Omicron-PCR: is the subset of the mFAS-non-Omicron with a positive baseline SARS-CoV-2 RT-PCR. The subpopulations mFAS-non-Omicron-NP and mFAS-non-Omicron-S based on sample type used to determine a positive SARS-CoV-2 PCR (as defined above) will also be analyzed.

mFAS-Omicron-PCR: is the subset of the mFAS-Omicron with a positive baseline SARS-CoV-2 RT-PCR. The subpopulations mFAS-Omicron-NP and mFAS-Omicron-S based on sample type used to determine a positive SARS-CoV-2 PCR (as defined above) will also be analyzed.

4.5.5. Per-Protocol Set

The PPS includes all participants in the mFAS-non-Omicron who had no significant protocol deviations (as defined in Section 5.1.2) that affect the efficacy assessments, received the full dose of study drug as randomized, and for whom the primary efficacy endpoint was assessed (ie, it is known whether or not the participant had a COVID-19-related hospitalization or all-cause death through Day 29). Protocol deviations are tracked in the PPD CTMS. The Sponsor will perform blinded review of all significant protocol deviations prior to database lock to determine if the deviation excludes the participant from the PPS.

4.5.6. 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.

4.5.7. Immunogenicity Set

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

4.5.8. PK Analysis Set

The PK Analysis Set includes all participants in the Safety Set who had at least one measurable ADG20 concentration post-administration of study drug. Where participants experience issues that may affect exposure to study drug (eg, dosing errors, etc), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK analysis set on a case-by-case basis. All participants excluded from the PK analysis set will be documented in the data listings.

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 and number and percentage (based on total screened) of screen failure participants
- Number and percentage of participants randomized
- Number and percentage (based on total randomized) of participants randomized and not treated

Reason for screen failure will also be summarized by number and percentage of participants with percentage based on the number of Screen Failure participants. The possible reasons for screen failure are:

- Failure to meet randomization criteria
- Physician decision
- Withdrawal by participant/guardian/LAR
- Other

The number and percentage (based on total number in the FAS) of participants randomized will be presented for all analysis sets.

The following summary will be presented in the FAS, the mFAS-non-Omicron, and the mFAS-Omicron analysis sets:

- The number and percentage of participants completing and not completing dosing
- The reasons for not completing dosing (ie, reasons for treatment discontinuation) as recorded in the eCRF and chosen from the following list:
  - Adverse Event
  - Investigator’s discretion
  - Protocol Deviation

  - Withdrawal by parent/guardian
  - Withdrawal by participant
  - Other
- The number and percentage of participants who completed the study through Days 29, 60, and 90 and through Months 6, 11, and 14
- The number and percentage of participants who discontinued from the study (early termination) prior to Day 29, prior to Month 6, and prior to Month 14.
- The reasons for early discontinuation as recorded in the eCRF and selected from the following list:
  - Death
  - Participant's request
  - Withdrawal of consent
  - Lost to Follow-up
  - Other

Participant disposition data will also be presented in listings, including a listing of participants by analysis set, and a listing of participants excluded from the Per Protocol Set.

5.1.2. Protocol Deviations

All protocol deviations will be assessed according to a study deviation rules document that indicates whether each deviation is significant or non-significant. Significant deviations are defined as protocol deviations that affect the primary efficacy and safety assessments, the safety or mental integrity of a participant, or the scientific value of the study. Non-significant deviations are defined as protocol deviations that are identified but do not impact the endpoints, safety or mental integrity of a participant, or the scientific value of the trial project. Rules for defining significant protocol deviations will be developed, documented in the study deviation rules document, and finalized in a blinded manner before database lock.

The number and percentages of participants with at least one protocol deviation, one significant deviation and one non-significant deviation will be presented in the FAS by treatment group and overall. Significant protocol deviations will also be summarized by deviation type and subtype. A table will be provided for Day 29 and Month 14. A listing of all protocol deviations will be provided for all FAS participants.

5.2. Demographics and Clinical Characteristics

The following summary will be presented in the FAS, the mFAS-non-Omicron, and the mFAS-Omicron analysis sets.

5.2.1. Demographics

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 17, 18 to 65, >65, ≥50, >55, >70, and >75 years), country, sex (male, female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, and Multiple [if more than one race category is selected]), ethnicity (Hispanic or Latino, Not Hispanic or Latino), and BMI subgroups (for adults ≥25, ≥30, ≥40 kg/m^2; for adolescents ≥85th percentile for age and sex based on CDC growth charts for adolescents) (CDC 2001).

Participant demographics will be presented in a listing.

5.2.2. Clinical Characteristics

Risk factors for COVID-19 progression: The number and percentage of participants with each of the protocol-defined baseline risk factors for COVID-19 progression will be summarized separately for adults and adolescents. The number of participants with ≥1, ≥2 and ≥3 risk factors present at baseline will be summarized. Given differences in the definition of high risk for COVID-19 progression in this study and other mAbs that have received FDA EUA, a summary of the risk factors in the definition in the FDA EUA fact sheets may also be presented.

Duration of COVID-19 symptoms: The duration of symptom onset to randomization (defined as the time from date of onset of self-reported symptoms to the date of randomization) will be summarized with descriptive statistics and the number and percentage of participants with duration of symptoms of 0-3 days, 4-5 days, and >5 days. The duration of symptom onset to study drug administration will be summarized similarly.

COVID-19 symptoms: COVID-19 symptoms and their severity at baseline based on the symptom diary on Day 1 will be presented. The number and percentage of participants with at least 1 severe symptom, at least 1 moderate symptom and no severe symptoms, and those with only mild symptoms on Day 1 will be summarized.

COVID-19 severity: In addition, investigator-assessed COVID-19 severity (SARS-CoV-2 infection without symptoms, mild, moderate, severe, critical) will be presented as will a programmatic determination of baseline severity based on parameters collected in the eCRF and patient diary outlined in Table 3. The programmatic derived COVID-19 severity will be performed at baseline and for the maximum severity through Day 29.

Table 3: Programmatic Determination of COVID-19 Severity

Protocol Defined COVID-19 Severity	Programmatic Determination
Critical COVID-19, as defined in Section 2.2.2 of the protocol	Positive local RT-PCR test at baseline, and one of the following: • Any concomitant procedure entry of: endotracheal intubation and mechanical ventilation, high-flow oxygen (>20 L/min with FIO_2 ≥50%), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation • Any AE entry of: respiratory failure, shock, multisystem organ failure/dysfunction, ARDS, or acute lung injury
Severe COVID-19, as defined in Section 2.2.2 of the protocol	Positive local RT-PCR test at baseline, none of the criteria for critical COVID-19, and one of the following: • Any of the following signs/symptoms: shortness of breath at rest, RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO_2 ≤93%. • Concomitant procedure of oxygen therapy • COVID-19 related MAV hospitalization (≥24 hours) or ICU admission.
Moderate COVID-19, as defined in Section 2.2.2 of the protocol	Positive local RT-PCR test at baseline, none of the criteria for severe or critical COVID-19, and any of the following signs/symptoms: shortness of breath with exertion worse than usual, RR ≥20 and <30 breaths per minute, heart rate ≥90 and <125 beats per minute
Mild COVID-19, as defined in Section 2.2.2 of the protocol	Positive local RT-PCR test at baseline, none of the criteria for moderate, severe, or critical COVID-19, and any of the following symptoms: fever, chills, cough, sore throat, congestion, muscle or body aches, fatigue, headache, nausea, loss of taste or smell, vomiting, diarrhea.

SARS-CoV-2 test: The number and percentage of participants with a local SARS-CoV-2 test performed, and for those with a test performed, the specimen type, assay type, and result will be presented. The duration from the local positive SARS-CoV-2 test (defined as the time from date of the test performed to the date of randomization) will be summarized with descriptive statistics and summarized categorically (0 days, 1-2 days, 3-5 days, >5 days). Baseline SARS-CoV-2 RT-qPCR results from the sample collected by NP swab and from the saliva sample will be presented as will descriptive statistics of the baseline viral load (log_{10} copies/mL) from each sample type. Baseline qualitative serology (SARS-CoV-2 antibody) status will be summarized based on qualitative serology assay (positive, negative). Baseline overall serology status based on three serology assays (qualitative, IgA, and IgG) will be summarized (positive if at least one serology assay is positive, missing if all three assays are missing, negative otherwise). Results of the baseline MNT test assay (not detected, detected) will be summarized.

Respiratory pathogen test: The presence of additional pathogens on Day 1 from the respiratory pathogen panel assay will be summarized.

SARS-CoV-2 variant: The number and percentage of participants with baseline isolates by PANGO lineage and CDC classification as variant of concern, variant of interest, variant being monitored, or other variants identified (CDC 2021) will be summarized in the FAS based on SARS-CoV-2 sequencing data. If baseline sequencing data are missing, available post-baseline sequencing data may be used. Participants without sequencing data will be summarized by suspected non-Omicron or Omicron variant (see Section 4.5.3).

Participant clinical characteristics will be presented in a listing.

5.3. Medical History

Medical history documentation will include all medical conditions, surgeries, or drug allergies within the prior year. Also, any clinically significant abnormalities found during the Screening physical exam should be documented as medical history. Medical history will be coded using the MedDRA version 23.1 or higher. The number and percentage of participants with any medical history will be summarized by treatment arm using SOC and PT, with SOCs and PTs within each SOC sorted in descending order of frequency in the ADG20 arm. Percentages will be calculated based on number of participants in each treatment group in the FAS and the mFAS-non-Omicron. If the same medical history (based on PT) is reported for the same participant more than once, the medical history is counted only once for the PT.

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

A prior medication is defined as any medication that is taken within 30 days prior to dosing of study drug. A concomitant medication is defined as any medication that has a stop date that is on or after the date of study drug dosing or is ongoing after dosing.

All medications used within 30 days prior to the date of randomization up to and including Day 60 will be collected on the CRF. In addition, any concomitant medications related to AEs and any vaccinations received will be recorded for the entire length of the study (ie, through Month 14). 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 by participant will be provided.

The number and percentages of participants with at least one prohibited concomitant medication (refer to ADG20-TRMT-001 Designated Background Standard of Care document) for the treatment of COVID-19 or receiving a COVID-19 vaccine will be summarized by treatment group in the FAS and the mFAS-non-Omicron. The number and percentages of these medications will also be summarized by treatment group, WHODrug ATC level 2 and PT, and a listing of prohibited medications by participant will be provided.

Medications with missing dates will follow the imputation rules in Appendix C to categorize as prior, concomitant, or prohibited up through Day 29. Medications are sorted by decreasing frequency of ATC Level 2 in the ADG20 arm, then by decreasing frequency of PT in the ADG20 arm.

5.4.1.1. Concomitant Procedures

A listing of concomitant procedures as collected on the eCRFs will be provided.

5.4.1.2. Study Treatments

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. Descriptive statistics of the total volume (mL) and dose (mg) will be presented; mL is converted to mg as follows: 100×dose in mL. A listing of study drug administration and of study drug exposure exceptions (study drug not administered, full dose not administered, and/or study drug not received as randomized) will be provided.

5.5. Efficacy Analyses

5.5.1. Primary Efficacy Analysis

The primary efficacy endpoint is the incidence of COVID-19-related hospitalization or all-cause death through Day 29 in the mFAS-non-Omicron analysis set. The null and alternative hypotheses are the following:

H_o: $P_1 - P_0 = 0$

H_1: $P_1 - P_0 \neq 0$

P_1 and P_0 are the proportion of participants with COVID-19-related hospitalization or all-cause death through Day 29 in the ADG20 and placebo groups respectively. Using the methodology as described below (with additional details in Appendix J), a standardized estimator for a binary outcome (standardized risk difference/standardized relative risk reduction) will be estimated with adjustment for the following prognostic factors: age (continuous), sex (categorical), baseline qualitative serostatus (categorical: positive, negative), BMI (continuous), and baseline viral load from NP sample (continuous as $\log_{10}$ copies/mL). For all efficacy analysis models, missing baseline serostatus will be imputed as positive and missing baseline BMI and viral load will be imputed as the average of all participants with non-missing data at baseline. Age is a randomization stratification factor and, thus, cannot be missing.

Appendix I summarizes the main estimation and sensitivity analyses for the primary estimand (Estimand 1a). The main estimation for Estimand 1a will use available data for COVID-19 hospitalization or all-cause death through Day 29, implemented in the mFAS-non-Omicron analysis set. Missing status on COVID-19-related hospitalization or all-cause death will be imputed as not having a COVID-19 hospitalization or all-cause death. The number and percentages of participants who experience and do not experience a COVID-19-related hospitalization or all-cause death will be summarized by treatment group, including summaries of missing data, COVID-19-related hospitalizations, and all-cause death. 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.

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 pre-defined prognostic factors. The method relies on a logistic regression model that includes COVID-19-related hospitalization or all-cause death present or absent as the dependent variable and treatment and prognostic factors as independent variables. To define this model, consider 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 (COVID-19-related hospitalization or all-cause death, 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 prognostic factors 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 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, i.e.,

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

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 J).

5.5.1.1. Sensitivity Analyses of Primary Estimand

A sensitivity analysis will utilize multiple imputation (MI) under missing at random (MAR) assumption which uses all participants with available primary endpoint data through Day 29. The imputation model (using PROC MI) will be informed by the observed outcomes for participants through Day 29 including treatment and the prognostic factors listed above. Participants with missing information on the primary endpoint will be imputed using monotone logistic regression. Further variables will be considered for inclusion in the MI model on the basis they may inform missingness or be correlated with the endpoint. Missing outcomes will be imputed multiple=100 times. The seed for reproducibility will be set to 2020. 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 via PROC MIANALYZE.

A sensitivity analysis using control-based imputation will also be conducted. Missing primary endpoint status through Day 29 will be imputed using monotone logistic regression as stated above but informed only by the placebo group. This will be implemented by the MNAR statement with the option MODELOBS =(TRT=0), where TRT=0 indicates the placebo group.

Additional sensitivity analyses include:

- Repeat the primary efficacy analysis in the PPS analysis set.
- Repeat the primary efficacy analysis with baseline overall serostatus (categorical as positive; negative) as covariate instead of baseline qualitative serostatus. Any missing baseline overall serostatus will be imputed as positive.

5.5.2. Supplemental Estimand Analyses

Appendix I provides an overview of the main estimation and sensitivity analyses for the supplementary estimand (Estimand 1b). Estimand 1b utilizes a hypothetical strategy for the intercurrent event of receipt of prohibited treatments (refer to ADG20-TRMT-001 Designated Background Standard of Care document) for COVID-19 (IcEV3).

For participants with IcEv3, if the participant has not had a COVID-19-related hospitalization or death prior to the intercurrent event, the primary endpoint will be set to missing. Missing data for the supplementary analysis will be carried out using an MI based strategy that includes the following three steps:

- Step 1. Missing outcomes will be imputed multiple times (M=100) based on the intercurrent event handling strategy
- Step 2. The logistic regression analysis model presented above will be applied to each completed data set with terms including the prognostic factors and treatment variable and estimates of the treatment effect and associated standard error will be computed.
- Step 3. The individual completed sets will be combined using Rubin's rules to produce a single inferential statement (treatment effect, standard error, and p-value) via PROC MIANALYZE.

The imputation model will be informed by the observed outcomes from participants who either did not experience the intercurrent event or met the primary endpoint prior to receiving prohibited medication. The imputation model will include the prognostic factors as listed in Section 5.5.1. Further variables will be considered for inclusion in the MI model on the basis they may inform missingness or be correlated with the endpoint.

The final analysis model applied to the complete data set will be the same as that for the primary analysis.

5.5.2.1. Sensitivity Analyses of Supplemental Estimand

A sensitivity analysis using control-based imputation will be conducted. The analysis will impute the binary primary endpoint for participants who received prohibited medications to treat

COVID-19 using PROC MI. Missing primary endpoint status through Day 29 will be imputed using monotone logistic regression as stated in the sensitivity analyses for the primary analysis but informed only by the placebo group. This will be implemented by the MNAR statement with the option MODELOBS =(TRT=0), where TRT=0 indicates the placebo group.

5.5.3. Key Secondary Endpoints and Analyses

Appendix H provides an overview of the main estimation and sensitivity analyses for the key secondary estimands (Estimand 2 and Estimand 3).

To control the overall type I error rate at .05 (2-sided), a hierarchical testing procedure will be used, such that testing for the key secondary analyses difference will proceed only if the treatment difference is statistically significant in the primary analysis.

The key secondary endpoints will be tested in the following order:

1. Severe/critical COVID-19 or all-cause death through Day 29
2. COVID-19-related emergency room visit, COVID-19-related hospitalization, or all-cause death through Day 29
3. Time to sustained resolution of COVID-19 symptoms through Day 29

For binary endpoints, the analysis will use the same methodology as the primary efficacy endpoint for determining a standardized estimator for a binary outcome (standardized risk difference/standardized relative risk reduction) with adjustment for the following prognostic factors: age (continuous), sex (categorical), baseline serostatus (categorical as positive; negative), BMI (continuous) and baseline viral load (continuous as $\log_{10}$ copies/mL) and will be conducted on the mFAS-non-Omicron analysis set. Similar to the primary analysis, the standard error of the standardized estimator will be estimated using the delta method.

For the first key secondary endpoint, if the determination of investigator assessment of COVID-19 severity is missing at a visit, it will be imputed as not severe/critical COVID-19 (or all-cause death) unless the participant is hospitalized due to COVID-19 at the time of the visit. In this case, the assessment of COVID-19 severity will be imputed as severe/critical COVID-19. For the second key secondary endpoint, missing data will be imputed as not having a COVID-19-related emergency room visit, COVID-19-related hospitalization, or all-cause death through Day 29. The number and percentages of participants who experience the event and do not experience the event will be summarized by treatment group, including summaries of missing data, and each component of the endpoint. The observed risk difference (placebo minus ADG20) with 95% CI (using the Miettinen-Nurminen method), observed relative risk reduction, standardized risk difference between the ADG20 arm and placebo arm with 95% CI and associated p-values, and standardized relative risk reduction with 95% CI will be provided.

Time to sustained resolution in COVID-19 symptoms through Day 29 will be analyzed by KM methodology and stratified Cox Proportional Hazard model. Survival curves between ADG20 and placebo will be compared using a log-rank test stratified by age (categorical as 12-17, 18-65, and >65 years). A stratified Cox Proportional Hazard model will be used to estimate the hazard ratio where the model includes age (categorical as 12-17, 18-65, and >65 years) as stratification variable and sex (categorical), baseline serostatus (categorical), baseline BMI (continuous), and

baseline viral load (continuous as $\log_{10}$ copies/mL) as covariates. Comparison of the survival distributions will use the score test for the hazard ratio from the Cox model.

5.5.3.1. Sensitivity Analyses

For each of the two binary key secondary endpoints, sensitivity analyses will include MI under MAR, which uses all participants with available key secondary endpoint status through Day 29. The imputation model (using PROC MI) will be informed by the observed outcomes for participants through Day 29 including treatment and prognostic factors. Participants with missing information on each key secondary endpoint through Day 29 will be imputed using monotone logistic regression. Further variables will be considered for inclusion in the MI model on the basis that they may inform missingness or be correlated with the endpoint. 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 via PROC MIANALYZE.

An additional sensitivity analysis will repeat the key secondary efficacy analyses in the PPS analysis set.

5.5.4. Additional Secondary Endpoints and Analyses

Analyses of other secondary endpoints in the mFAS-non-Omicron analysis set 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, except as specifically noted. Analysis approaches for the other secondary endpoints (ie, non-key) are summarized in Table 4. In addition to these analyses, listings of viral load based on nasopharyngeal samples; viral load, viral clearance status, viral load AUC, and time to viral clearance based on saliva samples; and medically attended visits will be provided.

Table 4: Additional Secondary Endpoint Analyses

Endpoint	Statistical Analysis Methods
COVID-19-related medically attended visits and all-cause death through Day 29	The methods for the primary efficacy endpoint will be used except without applying multiplicity adjustments (see Section 5.5.1).
Time to sustained recovery in COVID-19 symptoms through Day 29	The methods for the analysis of time to sustained resolution of COVID-19 symptoms through Day 29 will be used (see Section **5.5.3**)
All-cause death through Day 29, Day 60, and Day 90	KM methodology will be used to analyze all-cause deaths. The probability of all-cause deaths by each of these time points will be estimated, along with 95% CIs for differences in the probabilities. Survival curves between ADG20 and placebo will be compared using a log-rank test. A Cox Proportional Hazard model will be used to estimate the hazard ratio. The model includes age (continuous), sex (categorical), baseline serostatus (categorical: positive, negative), baseline BMI (continuous), and baseline viral load (continuous as $\log_{10}$ copies/mL) as covariates. Comparison of the survival distributions will use the score test for the hazard ratio from this Cox model.

Endpoint	Statistical Analysis Methods
Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Day 7 (±1) assessed by RT-qPCR from NP samples	Observed NP baseline and post-baseline values are used to calculate change from baseline. ANCOVA with treatment group and the prognostic factors (with observed NP baseline) as in the primary efficacy endpoint analysis as covariates. The LS mean for the point estimate in each group and 95% CIs will be presented. The difference in LS means between the ADG20 group and the placebo group and 95% CIs for the differences will be determined. The analysis will be performed on the mFAS-non-Omicron-NP with available data at Day 7. In addition, two-sample t-test will be used to compare change from baseline viral load between treatment without covariate adjustment (unadjusted mean difference). If Day 7 value is missing, the earliest measurement closest to the Day 7 visit within 1 day (including scheduled and unscheduled visit) will be used.
Viral load >5 (log_{10} copies/mL) on Day 7 (±1) based on NP samples	The methods for the primary efficacy endpoint will be used. Analysis will be performed on the mFAS-non-Omicron-NP with available data at Day 7. Analysis will be repeated using a second definition of high viral load (viral load >4 log_{10} copies/mL).
Duration of SARS-CoV-2 viral shedding from Day 1 through Day 29 assessed by RT-qPCR from saliva samples	KM methodology will be used to analyze duration of viral shedding from Day 1 through Day 29 of SARS-CoV-2 RNA. KM curves, the number and percentage of censored observations and the median, 25th and 75th percentiles will be provided. Survival distributions will be compared between ADG20 and placebo using a log rank test stratified by age (categorical) and baseline serostatus. A stratified Cox Proportional Hazard model will be used to estimate the hazard ratio where the model includes age (categorical as 12-17 years, 18-65 years and >65 years) as a stratification variable and sex (categorical), baseline serostatus (categorical as positive; negative), baseline BMI (continuous) and baseline viral load (continuous as log_{10} copies/mL) as covariates. Comparison of the survival distributions will use the score test for the hazard ratio from this Cox model. Analyses will be performed on the mFAS-non-Omicron-S.
Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Days 3, 5, 7, 11, 14, 21, and 29 assessed by RT-qPCR from saliva samples	Observed saliva baseline and post-baseline values are used to calculate change from baseline. Mixed model for repeated measures with treatment group and the prognostic factors (with observed saliva baseline) in the primary efficacy endpoint analysis as covariates. The LS mean for the point estimate in each group and 95% CIs will be presented. The difference in LS means between the ADG20 group and the placebo group and the 95% CIs for the differences will be determined. A plot of the LS means with 95% CIs by Day assessed by treatment group will be presented. The analysis will be performed on the mFAS-Non-Omicron-S with available data at each timepoint. In addition, a two-sample t-test will be used to compare change from baseline viral load between treatment at each time point without covariate adjustment (unadjusted mean difference).
SARS-CoV-2 viral clearance (Days 3, 5, 7, 11, 14, 21, and 29) assessed by RT-qPCR from saliva samples (and BLQ/not detected or not detected for NP sample for Day 7)	In the mFAS-non-Omicron-S, the cumulative proportion of participants with viral clearance will be presented for each post-baseline time point. In the mFAS-non-Omicron-NP, the proportion of participants with viral load BLQ/not detected or not detected at Day 7 will be presented. The ADG20 arm will be compared to placebo using the analysis procedure outlined for the primary efficacy outcome. In addition, these analyses will be presented for the subgroups of participants with observed baseline NP viral load >5 and ≤5 log_{10} copies/mL.

Endpoint	Statistical Analysis Methods
SARS-CoV-2 viral load AUC (log_{10} copies/mL) assessed by RT-qPCR from saliva samples through Day 29	An ANCOVA will be used to compare ADG20 and placebo where the prognostic factors in the primary efficacy endpoint analysis will be used as covariates. Participants in the mFAS-non-Omicron-S will be included in this analysis. The AUC from Day 1 through Day 29 will be calculated according to the linear trapezoidal rule using the measured SARS-CoV-2 viral load above the lower limit of quantification. No AUC values will be calculated when Day 1 and/or Day 29 values are missing, or if there are more than 3 values missing in the profile. In addition, two-sample t-test will be used to compare viral load AUC between treatment without covariate adjustment (unadjusted mean difference).

5.5.5. Exploratory and Additional Efficacy Endpoints

To facilitate review of the composite endpoints in the mFAS-non-Omicron analysis set, tables will be provided summarizing medically attended visits and all-cause death, both before and after Day 29, and summarizing COVID-19-related hospital and ICU stays.

To explore efficacy and virological endpoints in the mFAS-Omicron analysis set, summary tables will be provided.

5.5.5.1. COVID-19-Related Duration of Hospitalization

For participants who did not die through Day 29, the sum of the duration of all COVID-19-related hospital stays through Day 29 will be summarized by category (>0 to <24 hours, 1-8 days, 9-15 days, 16-22 days, 23-29 days, >29 days) for each treatment group. The mean total number of days and standard deviation will also be presented. For purposes of the continuous summary, a hospital stay of less than 24 hours will be imputed as 0.5 days. A similar categorical and continuous summary will be presented for the subset of ICU stays.

The number and percentage of participants who died on or prior to Day 29 will be presented by treatment group.

5.5.5.2. Exploratory Analysis of Omicron Analysis Set

Given the expected smaller sample size of the mFAS-Omicron analysis set, the following clinical endpoints will be summarized descriptively:

- COVID-19-related hospitalization or all-cause death through Day 29
- Severe/critical COVID-19 or all-cause death through Day 29
- COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29
- Time to sustained resolution of COVID-19 symptoms through Day 29
- COVID-19-related medically attended visit (telemedicine, physician office, urgent care center, emergency room, hospitalization) or all-cause death through Day 29

The following virological endpoints will be summarized descriptively unless otherwise specified:

- Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Day 7 (±1) assessed by RT-qPCR from NP samples, apply the same methodology in Table 4.
- Viral load >5 log_{10} copies/mL on Day 7 (±1) based on NP samples
- Duration of SARS-CoV-2 viral shedding from Day 1 through Day 29 assessed by RT-qPCR from saliva samples
- Change from baseline in SARS-CoV-2 viral load (log_{10} copies/mL) to Days 3, 5, 7, 11, 14, 21, and 29 assessed by RT-qPCR from saliva samples, apply the same methodology in Table 4.
- SARS-CoV-2 viral clearance (Days 3, 5, 7, 11, 14, 21, and 29) assessed by RT-qPCR from saliva samples (and BLQ/not detected or not detected for NP samples for Day 7)
- SARS-CoV-2 viral load AUC assessed by RT-qPCR from saliva samples from baseline to Day 29

5.5.6. Graphical Displays of Efficacy Endpoints

Forest plots for the standardized relative risk reduction for the primary and two binary key secondary endpoints will be provided. Additionally, adjusted, and unadjusted mean change from baseline in viral load will be depicted with forest plots, box and whisker plots and line plots.

Duration of viral shedding, time to sustained recovery of symptoms, time to symptom improvement, and time to symptom resolution will be presented using Kaplan-Meier plots and forest plots. Finally, a Kaplan-Meier plot for all-cause death will be provided.

5.5.6.1. Viral Load Effect on Adverse Clinical Outcomes

In order to identify a persistently high viral load threshold for risk of adverse clinical outcomes, the level of viral load leading to the following adverse clinical outcomes will be assessed in the mFAS-non-Omicron analysis set:

- COVID-19-related hospitalization or all-cause mortality through Day 29
- COVID-19-related emergency room visits, COVID-19-related hospitalization, or all cause death through Day 29
- Severe/critical COVID-19 or all-cause mortality through Day 29

An association between viral load (log_{10} copies/mL) and the adverse clinical outcome will be examined graphically. The viral load for participants with the adverse clinical outcome and box plot of viral loads for participants without the adverse clinical outcome will be presented for Days 3, 5, 7, 11, 14, 21, and 29. The number and percentage of participants with and without the adverse clinical outcome will be summarized by viral load categories at Days 3, 5, 7, 11, 14, 21, and 29. Viral load from saliva samples will be used for Days 3, 5, 7, 11, 14, 21, and 29, and also from NP swabs for Day 7.

5.5.6.2. Time to Sustained Improvement of COVID-19 Symptoms Through Day 29

KM methodology will be used to analyze time to sustained symptom improvement through Day 29 (Section 3.5.1) with respect to the mFAS-non-Omicron analysis set. Median time-to improvement by treatment group and 95% CIs will be reported. Survival curves between ADG20 and placebo will be compared using a log-rank test stratified by age (categorical as 12-17, 18-65, and >65 years). A stratified Cox Proportional Hazard model will be used to estimate the hazard ratio where the model includes age (categorical as 12-17, 18-65, and >65 years) as a stratification variable and sex (categorical), baseline serostatus (categorical: positive, negative), baseline BMI (continuous) and baseline viral load (continuous as $\log_{10}$ copies/mL) as covariates. Comparison of the survival distributions will use the score test for the hazard ratio from the Cox model. Refer to Appendix F for rules for missing symptom diary data.

5.5.6.3. Time to Sustained Recovery of COVID-19 Symptoms Through Day 29

KM methodology will be used to analyze time to sustained symptom recovery (improvement or resolution) through Day 29 (Section 3.5.1) with respect to the mFAS-non-Omicron analysis set. Median time to recovery by treatment group and 95% CIs will be reported. Survival curves between ADG20 and placebo will be compared using a log-rank test stratified by age (categorical as 12-17, 18-65, and >65 years). A stratified Cox Proportional Hazard model will be used to estimate the hazard ratio where the model includes age (categorical as 12-17, 18-65, and >65 years) as a stratification variable and sex (categorical), baseline serostatus (categorical: positive, negative), baseline BMI (continuous) and baseline viral load (continuous as $\log_{10}$ copies/mL) as covariates. Comparison of the survival distributions will use the score test for the hazard ratio from the Cox model. A forest plot of median time to sustained symptom recovery by selected subgroups will be presented. Refer to Appendix F for rules for missing symptom diary data.

5.5.7. Household Contacts

The number and percentage of participants with any documented asymptomatic SARS-CoV-2 or symptomatic COVID-19 infection in one or more household contacts as of Day 29 will be summarized by treatment group in the mFAS-non-Omicron analysis set. Among those participants with household contacts with asymptomatic and symptomatic infection, descriptive summary statistics for the number of household contacts with each type of infection will be summarized using percentages based on the number of participants with household contacts with documented asymptomatic or symptomatic COVID-19 infection.

These data will also be presented in a listing.

5.5.8. COVID-19-Related Mortality Through Day 29

The number and percentage of participants with a COVID-19 related death, with COVID-19 as the primary cause of death, and with COVID-19 or COVID-19 complications contributory to death will be summarized in the mFAS-non-Omicron by treatment group.

The listing of deaths will include a column for primary cause of death and if COVID-19 or COVID-19 complications were contributory to death.

5.5.9. Post-Acute Sequelae of SARS-CoV-2 Infection

During the long-term follow-up period, participants will be asked questions about their overall health status including return to usual health and usual activities and any ongoing symptoms associated with COVID-19 at the visits specified in the Schedule of Events (Appendix M). Symptoms reported on the Long-term Health Status Assessment eCRF will be considered PASC events. The number and percentage of participants with any PASC will be summarized by treatment group and in those participants with and without a COVID-19-related hospitalization through Day 29 with respect to the mFAS-non-Omicron. The number and percentage of participants reporting each symptom thought to be related to COVID-19 and the number and percentage of participants returning and not returning to usual health and usual activities will be summarized by treatment arm. The number of participants in each arm reporting no symptoms, 1 ongoing symptom and >1 ongoing symptom will be summarized at Day 60, Day 90, and Month 6. The overall severity of PASC symptoms will be presented (absent, mild, moderate, severe) by treatment arm and time point (Day 60, Day 90, and Month 6).

These data will also be presented in a listing.

5.6. Subgroup Analyses

The primary (Estimand 1a) and key secondary (Estimands 2 and 3) analyses will be repeated within the subgroups listed below in the mFAS-non-Omicron analysis set. Analyses of virologic endpoints will be repeated within selected subgroups as detailed below.

- age group (12-17, 18-65, >65, ≥50, >55, and >75 years)
- sex (male, female)
- race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multiple)
- time from symptom onset to the date of study drug administration (0-3, 4-5, >5 days)
- time from SARS-CoV-2 test to the date of study drug administration (0, 1-2, 3-5, >5 days)
- baseline SARS-CoV-2 status by RT-qPCR from NP swab (positive, negative).
- baseline viral load from NP swab (>5, ≤5 $\log_{10}$ copies/mL); viral load >5 and >4 $\log_{10}$ copies/mL) on Day 7 based on the NP sample will also be analyzed in these subgroups
- baseline qualitative serologic status (positive, negative) from the assay of antibodies to SARS-CoV-2 N antigen.
- baseline overall serologic status (positive, negative) from three assays: antibodies to N antigen, IgA to S (spike) trimer, IgG to S trimer; viral load >5 and >4 $\log_{10}$ copies/mL on Day 7 based on the NP sample will also be analyzed in these subgroups
- COVID-19 severity (mild, moderate)

- BMI (≥30 and ≥40 kg/m^2 for adults and ≥85th percentile by age and sex based on CDC growth charts for adolescents, <30 kg/m^2 for adults and <85th percentile by age and sex based on CDC growth charts for adolescents) (CDC 2001)
- Diabetes as collected on COVID-19 Risk Factors eCRF (yes, no)
- Cardiac disease as collected on COVID-19 Risk Factors eCRF (yes, no)
- WGS confirmed non-Omicron variant (Delta/Delta-like, etc)

Given the various sample sizes by subgroup, the standardized relative risk reduction will be estimated using the same methodology in Ge et al. (2011) from a logistic regression model fit to the binary endpoint with age (continuous) as covariate for each subgroup with at least 5 total events. Subgroups with less than 5 total events will be summarized descriptively.

5.7. Other Analyses

5.7.1. Resistance

Resistance to ADG20 in viral isolates obtained from participants will be characterized using genotypic methods, with phenotypic methods deployed as appropriate. Plans for analysis of resistance data will be provided in the Resistance Monitoring Plan. A summary of participants with baseline and post-baseline (treatment-emergent) variations at critical amino acid positions associated with ADG20 resistance (≥15% and ≥50% allele frequencies) and their associated virologic and clinical outcomes will be provided in the FAS.

5.7.2. Immunogenicity Analyses

Analyses will be conducted in the Immunogenicity Set. ADA status will be defined as positive or negative based on the confirmatory cut-off point. ADA results will be summarized by treatment arm at baseline (predose Day 1), Days 29 and 90, and Months 6 and 11. ADA status (positive or negative) is determined based on the confirmatory assay results.

Treatment-emergent ADA is defined as participants who had a negative ADA measurement at baseline (predose Day 1) and positive ADA post-baseline (Day 29, Day 90, Month 6, or Month 11) 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 patients with treatment-emergent ADA will be summarized by treatment arm. The frequency of neutralizing antibodies (if assessed) may also be summarized.

5.8. Safety Analysis

The primary safety objective of the study is to evaluate the safety and tolerability of ADG20 compared to placebo through Day 29 in participants with mild or moderate COVID-19 and high risk of disease progression. A secondary objective is to evaluate safety through Month 14. Safety assessments will include monitoring of AEs, clinical laboratory testing, and vital sign measurements.

5.8.1. Adverse Events

5.8.1.1. Unsolicited 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. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Exceptions to this reporting related to COVID-19 signs and symptoms are described in the protocol (Section 6.4.6.3.2). All AEs will be followed to adequate resolution. MedDRA version 24 or higher will be used to code all AEs.

5.8.1.2. Injection Site Reactions

Intramuscular ISRs will be recorded in the Injection Site Reaction Diary (refer to the protocol, Appendix 12.3) and graded using the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007).

Participants will be instructed to record the worst severity (Table 5) experienced during each recording period (prior 24 hours) of the following local (solicited) AEs through Day 4, and 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 5: Grading of Injection Site Reactions

Local Reaction to Injectable Product	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening[a]
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	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER 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

ER=emergency room.
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.

Erythema/redness and induration/swelling reported as <2.5 cm in greatest diameter will be classified as *Non-Graded*.

For summaries combining ISRs and other AEs, ISRs will be mapped to MedDRA SOC and PT as shown in Table 6.

Table 6: 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 with an 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.

5.8.1.3. 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.

5.8.1.4. Adverse Events of Special Interest

An AESI, which can be serious or nonserious, is defined as an AE or SAE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor or designee could be appropriate (ICH E2F; CIOMS VI).

For this study, AESIs are specified in the protocol as follows: Hypersensitivity reactions occurring through Day 4. Hypersensitivity reactions include but are 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, arthus reaction, etc.

Determination of hypersensitivity reactions will be based on a sponsor medical adjudication based on the narrow and broad terms of the 3 SMQs hypersensitivity, anaphylactic reaction, and angioedema.

All hypersensitivity reactions will be summarized through Day 4, through Day 29, and through Month 14/EOS. However, only those reactions occurring through Day 4 will be considered AESIs.

5.8.1.5. 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.

5.8.1.6. 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

5.8.1.7. Severity

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.)

Missing severity is not imputed.

Grading criteria for ISRs are provided in Section 5.8.1.2.

5.8.1.8. Relationship of Adverse Events 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 relatedness is missing for an event, the event will be categorized as Related.

All ISRs are considered related to study drug.

5.8.1.9. 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/ISR, 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 based on the number of participants in each treatment group in the Safety Set. Missing and incomplete dates of AEs will be imputed as described in Appendix D. In addition to safety summaries, listings of AEs (with TEAE designated by *), SAEs, and ISRs will be presented.

Safety summaries will be presented through Day 29 and overall. All summaries will be sorted by decreasing frequency 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
  - ≥Grade 3 TEAE
  - an SAE
  - a study drug related SAE
  - a TEAE leading to death

  - a study drug related TEAE leading to death
  - a TEAE leading to treatment discontinuation
  - 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 PT sorted by descending frequency of PT in the ADG20 arm
- Incidence of MAAE 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) and by maximum severity based on the FDA toxicity scale through Day 4 (only for Day 29 analysis)
- Incidence of SAEs by SOC, PT, and treatment group
- Incidence of SAEs excluding COVID-19 SAEs associated with the primary endpoint by SOC, PT, and treatment group; COVID-19-related PTs include COVID-19, COVID-19 pneumonia.
- Incidence of study drug related SAEs by SOC, PT, and treatment group
- For the Day 29 analysis only: incidence of solicited AEs (ISRs) summarized by maximum duration (defined as the end date-start date +1) of 1, 2, 3, 4, and >4 days for participants with any ISR and for each ISR type. Time from injection to report of first onset of any solicited ISR (in days) will also be summarized.
- Overall summary of hypersensitivity reactions including number and percentage of participants with:
  - any hypersensitivity reaction
  - a study drug related hypersensitivity reaction
  - a severe (≥Grade 3) hypersensitivity reaction
  - a serious hypersensitivity reaction
  - any hypersensitivity reaction by onset day category of first reaction (Day 1, 2, 3, 4, 5-8, 9-14, 15-21, 22-29, >29). Time from study drug administration to first onset of

hypersensitivity reaction and the duration of the hypersensitivity reaction for participants with hypersensitivity reactions (longest duration if multiple) will also be summarized.

- Incidence of hypersensitivity reactions by SOC, PT, and treatment group through Day 4, through Day 29, and through Month 14/EOS.
- Incidence of hypersensitivity reactions by SOC, PT, maximum severity, and treatment group, through Day 4, through Day 29, and through Month 14/EOS.
- Overall summary of AEs and the incidence of AEs (including solicited ISRs) by SOC and PT, by age group (12-17, 18-65, >65 years).

A listing will be provided of participants meeting any pausing guideline in the ADG20 arm, as described in Table 7.

Table 7: Study Pausing Guidelines

Phase	Pausing Guideline
Phase 2	• 2 or more participants with a study drug-related ≥Grade 3 hypersensitivity reaction • 2 or more participants with a ≥Grade 3 injection site reaction • Any study drug-related death • Any study drug-related SAE, including hypersensitivity reactions
Phase 3	• Any study drug-related death • Any study drug-related SAE, including hypersensitivity reactions

5.8.1.10. Adverse Events Leading to Treatment Discontinuation

Treatment discontinuation is collected on the End of Treatment eCRF. If the reason for treatment discontinuation is AE, the relevant AE number is also collected, and AEs recorded should match the cases on the AE eCRF where Action Taken is *Drug Withdrawn*. In the event of disagreement between these data sources, AE tables/listing will present data from the AE eCRF and disposition tables will present data from the End of Treatment eCRF. Given study treatment is a single dose, the incidence of AEs leading to treatment discontinuation is expected to be none/minimal.

5.8.1.11. Adverse Events Leading to Study Discontinuation

Study discontinuation is collected on the End of Study eCRF. *Adverse Event* is not collected as a possible reason for study discontinuation because the study only involves one dose of study drug, and the remainder of the study collects follow-up data (though an AE may lead to treatment discontinuation which the leads the participant/investigator to remove the participant from study). Therefore, no incidence table for TEAE leading to study discontinuation will be provided.

5.8.2. Death and Survival Status

Death status may derive from the Adverse Event, Survival Status, End of Treatment, or End of Study eCRFs. In each case, details are collected on the Death eCRF. In the event of data inconsistency, the Death eCRF data will be used. The number and percentage (based on the Safety Set) of participants who died will be summarized for primary cause of death (COVID-19,

Other Adverse Event, Unknown) and whether COVID-19 or COVID-19 complications contributed to the death by treatment group. Percentages of primary cause of death and whether COVID-19 contributed to the death will be based on the number of participants who died. A summary of AEs leading to death will also be provided by SOC and PT for the Safety Set.

A listing of death details as well as a listing of survival status for participants who discontinued the study early will also be provided.

5.8.3. Clinical Laboratory Evaluations

Blood samples for safety laboratory assessments (hematology, serum chemistry, and coagulation) will be collected on the days specified in the Schedule of Events (Appendix M). 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 Appendix K. Refer to Appendix B for handling of unscheduled and multiple in-window values. All clinical laboratory values for participants with PCS will be provided in listings.

5.8.3.1. Hematology

The following hematology parameters (CBC with differential) will be assessed per the Schedule of Events (Appendix M):

- Hemoglobin
- Hematocrit
- Erythrocyte count
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocyte (white blood cell) count
- Neutrophils

- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

5.8.3.2. Serum Chemistry

The following serum chemistry parameters will be assessed per the Schedule of Events (Appendix M):

- Glucose, non-fasting
- Calcium
- Albumin
- Total protein
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Urea nitrogen
- Creatinine (and calculated eGFR)
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Human chorionic gonadotropin (hCG) for females

5.8.3.3. Coagulation

The following coagulation parameters will be assessed per the Schedule of Events (Appendix M):

- Prothrombin time (PT)/International Normalized Ratio (INR)
- Partial thromboplastin time (PTT)/activated Partial thromboplastin time (aPTT)

5.8.4. Vital Sign Measurements

Vital signs, including temperature, heart rate, respiratory rate, seated blood pressure, and SpO_2 will be summarized using the site staff assessment.

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 separately for the time period of intensive monitoring post-study drug administration. PCS values are provided in Appendix K. Refer to Appendix B for handling of unscheduled and multiple in-window values.

All vital sign data by participant will also be presented in listings separately for in-person visit and eDiary. Vital Sign listings will include participant recordings and will list data by visit, date and timepoint.

5.8.5. Other Safety Data

Pregnancy testing data will be provided in a listing for all female participants whose fertility status (as collected on the Screening Fertility Status eCRF) is *Child-Bearing Potential* or *Unknown*.

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 7 (±1 day), Day 29 (+5 days), Day 90 (±14 days), Month 6 (±30 days), Month 11 (±30 days)
- Unscheduled

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.

In addition, individual serum concentrations of ADG20 will be presented in data listings and summarized by ADA status (positive/negative). Individual and mean concentration plots will also be presented by ADA status (treatment emergent ADA positive/negative).

6.3. Serum Pharmacokinetic Parameters

Serum concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, NJ). The PK parameters to be calculated for ADG20, where data permit, as listed in Table 8.

Table 8: 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 8, which will be listed and summarized, the parameters in Table 9 will also be listed to document the selection of data points used to estimate $T_{1/2}$ using non-compartmental procedures.

Table 9: 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.

In addition, serum PK parameters will be presented in data listings and summarized by ADA status (treatment emergent ADA positive/negative).

7. CHANGES IN THE PLANNED ANALYSIS

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

8. REFERENCES

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9. APPENDICES

APPENDIX A. STANDARDS FOR VARIABLE DISPLAY IN TFLS

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean, median, 25th percentile, and 75th percentile will be presented to one more significant figure than the original results; the SD will be presented to two more significant figures than the original results; the minimum and maximum will be presented to the same level of precision as the original results. P-values should be presented to 4 decimal places, unless otherwise specified.

Categorical Variables: Percentages will be presented to 1 decimal place. If the count is 0, the percentage will not be displayed. If the count equals the denominator, the percentage will be displayed as 100.

APPENDIX B. ANALYSIS VISIT WINDOWS

Assessments collected at scheduled or unscheduled visits will be mapped using the analysis visit windows listed in Table 10. All diary data will be analyzed using the actual day. Refer also to Section 4.1.

Table 10: Analysis Windows

AVISIT	AVISITN	Range of Trial Day	Target Day	If more than one value, which value is used for analyses
Screening	1	Day -2 to 1		Last value prior to administration of study drug
Day 1	2	Day 1	Day 1	Day 1
Day 3	4	Day 2 to Day 4	Day 3	Nominal visit. If none exist, then closest to target day.
Day 5	6	Day 4 to Day 6	Day 5	Nominal visit. If none exist, then closest to target day.
Day 7	8	Day 6 to Day 8	Day 7	Nominal visit. If none exist, then closest to target day.
Day 11	12	Day 9 to Day 13	Day 11	Nominal visit. If none exist, then closest to target day.
Day 14	15	Day 12 to Day 16	Day 14	Nominal visit. If none exist, then closest to target day.
Day 21	22	Day 18 to Day 23	Day 21	Nominal visit. If none exist, then closest to target day.
Day 29	30	Day 24 to Day 34	Day 29	Nominal visit. If none exist, then closest to target day.
Day 60	31	Day 53 to Day 67	Day 60	Nominal visit. If none exist, then closest to target day.
Day 90	32	Day 76 to Day 104	Day 90	Nominal visit. If none exist, then closest to target day.
Month 6	33	Day 150 to Day 210	Day 180	Nominal visit. If none exist, then closest to target day.
Month 11	34	Day 300 to Day 360	Day 330	Nominal visit. If none exist, then closest to target day.
Month 14	35	Day 360 to Day 480	Day 420	Nominal visit. If none exist, then closest to target day.

APPENDIX C. IMPUTATION RULES FOR MISSING DATES OF PRIOR/CONCOMITANT MEDICATIONS FLAGS

For inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

- If it cannot be determined whether the start date of a medication is prior to the administration of study drug, it will be assumed that the medication was received prior to the administration of study drug.
- If it cannot be determined whether the stop date of a medication is after administration of study drug, it will be assumed that the medication was received after the administration of study drug.

For medications that are prohibited from randomization to Day 29, incomplete start and stop dates will be imputed as follows:

- If year is missing, day and month are missing, or the date is completely missing, no imputation will be done.
- If year and month are present and day is missing, if the month is the same as the month of randomization and/or the Day 29 visit, then assume the medication was received from randomization to Day 29. Otherwise, the prohibited medication will be assumed to not have been received from randomization to Day 29.
- If year and day are present and month is missing, then assume the medication was received from randomization to Day 29.

APPENDIX D. IMPUTATION RULES FOR MISSING DATES OF AES

Imputation rules for missing or partial start dates and end dates of AEs are defined below:

Missing or partial start date:

- If only Day is missing, use the first day of the month, unless:
  - The AE end date is on/after the date of study drug administration or is missing/partial AND the start month and year of the AE coincide with the start month and year of study drug administration. In this case, use the date and time of study drug administration, even if AE time was collected.
- If Day and Month are both missing, use the first day of the year, unless:
  - The AE end date is on/after the date of study drug administration or is missing/partial AND the start year of the AE coincides with the start year of study drug administration. In this case, use the date and time of study drug administration, when time is available.
- If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of administration of study drug, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

Missing or partial end date: Missing or partial end dates will not be imputed.

Missing start time: If the AE occurs on the date of dosing and time is missing, the AE should be assumed to be treatment emergent.

APPENDIX E. DATES OF EMERGENCE OF OMICRON VARIANT BY COUNTRY

Country	Date of First Participant With WGS-Confirmed Omicron Variant from the Same Country	Epidemiology Date of the Emergence of Omicron from the Same Country[a]
Brazil	n/a	14-Dec-21
Bulgaria	21-Dec-21	
South Africa	10-Nov-21	
Germany	25-Nov-21	
Greece	29-Dec-21	
Poland	n/a	29-Dec-21
Ukraine	5-Jan-22	
Romania	28-Dec-21	

[a] Source: Date of reaching 10% Omicron of samples tested in a country.

For Brazil: Latif AA, Mullen JL, Alkuzweny M, et al. (2022a). BA.1 Lineage Report – Brazil. outbreak.info. Retrieved 1 March 2022 from: https://outbreak.info/situation-reports?xmin=2021-10-20&xmax=2022-01-21&loc=BRA&pango=BA.1&selected=BRA.

For Poland: Latif AA, Mullen JL, Alkuzweny M, et al. (2022b). BA.1 Lineage Report – Poland. outbreak.info. Retrieved 1 March 2022 from: https://outbreak.info/situation-reports?pango=BA.1&loc=POL&selected=POL.

APPENDIX F. RULES FOR MISSING SYMPTOM DIARY DATA

Information about COVID-19 associated symptoms is collected in a daily COVID-19 Symptom Diary as described in the protocol (Section 6.3.1.1). Participants are asked to rate the severity over the last 24 hours as *None*, *Mild*, *Moderate*, or *Severe* for the following 11 symptoms: fever, chills, cough, sore throat, congestion, shortness of breath at rest, shortness of breath with exertion, muscle or body aches, fatigue, headache, and nausea. In addition, there are two questions regarding senses of taste and smell (same as usual, less than usual, none), two questions regarding frequency of vomiting or diarrhea (none, 1-2, 3-4, ≥5 times), two general status questions (yes, no), and one question regarding overall severity of symptoms.

All diary data will be listed. For analysis, the answers to the questions regarding taste and smell are mapped as following: absent/none=same as usual, mild/moderate=less than usual, severe=none and the two questions regarding frequency of vomiting diarrhea are mapped as following: absent/none=none, mild=1-2 times, moderate=3-4 times, and severe= ≥5 times.

The following algorithms for imputing missing data (none/mild/moderate/severe) will be applied. These algorithms apply independently to individual symptom assessments.

a. If a participant is hospitalized on or before Day 29 for a COVID-19-related hospitalization:
    - All existing data will be utilized (as the protocol indicates that the diary should be completed if feasible during hospitalization).
    - If a participant has no assessments during the hospitalization: for symptoms that were present prior to the hospitalization, the missing data are imputed as severe. If the symptom was not present at baseline or returned to absent (none) prior to the hospitalization, the symptom will be imputed as absent (none). Otherwise, if a participant has partial data available during the hospitalization: missing values are imputed as the maximum (worse) of the last observed or imputed value prior to the missing assessment and the next observed or imputed value after the missing assessment.

b. If a participant is hospitalized on or before Day 29 for a non-COVID-19-related hospitalization, missing values during hospitalization are imputed as the maximum (worse) of the last observed or imputed value prior to the missing assessment and the next observed or imputed value after the missing assessment.

c. If a participant discontinues from the study, is lost to follow up (LFU), or dies on or before Day 29, symptom ratings will not be imputed beyond the date of discontinuation/LFU/death.

d. If diary data are missing when a participant is not COVID-related hospitalized and remains on study (through Day 29), data will be imputed as follows:
    - The Day 1 assessment is baseline and is performed on-site prior to study drug dosing, so the assessment is not likely to be missing. If data are present for Day 1 and is missing for a sequence of consecutive days from Day 1 but with at least one subsequent score, impute the missing values through to the first available score with the value of the first available score (provided by the participant or imputed due to hospitalization). This is a conservative assumption, so that symptom improvement or resolution is less likely to be indicated early.

- If only the Day 1 assessment is missing (for a given symptom), the value will be imputed as the Day 2 value.
- For intermittent missingness during follow-up, impute the missing values as the worse of the last available value (actually provided by the participant or imputed due to hospitalization) before the missing value and the first available value (actually provided by the participant or imputed due to hospitalization) after the missing value, irrespective of length of sequence of missing values. If the last prior and the first subsequent value are equal, then symptom improvement or resolution is based on the assumption that the situation remained stable during the missing duration. If the last prior value is worse than the first subsequent one, then symptom improvement/resolution is delayed over the missing duration until improvement/resolution is confirmed. If the last prior assessment is better than the first subsequent value, then symptom improvement/resolution is reversed earlier.

e. If a participant has no period(s) of hospitalization and all post-Day 1 data are missing (for a given symptom) or all data, including Day1, are missing (for a given symptom), the symptom will not be imputed. If all data are missing for all symptoms, the participant will be excluded in the time-to-event analyses for improvement/resolution/sustained recovery.

f. Missing data for the questions regarding sense of taste and smell, frequency of vomiting or diarrhea, will be imputed using the values mapped to none/mild/moderate/severe.

g. Missing data will not be imputed for general status questions and overall severity of symptoms.

APPENDIX G. ESTIMANDS AND INTERCURRENT EVENTS

Label	Description
IcEv1 (Co-infection)	Co-infection with respiratory pathogens other than SARS-CoV-2 from administration of drug through Day 29
IcEv2 (Prohibited COVID-19 vaccine)	COVID-19 vaccine through Day 29 from administration of drug
IcEv3 (Prohibited treatments for COVID-19)	Use of prohibited treatments for COVID-19 from administration of drug through Day 29

APPENDIX H. PRIMARY AND KEY SECONDARY OBJECTIVES AND ESTIMANDS

Objective	**Primary**: To evaluate the efficacy of ADG20 compared to placebo in the treatment of mild or moderate COVID-19 in participants at high risk of disease progression	**Primary**: To evaluate the efficacy of ADG20 compared to placebo in the treatment of mild or moderate COVID-19 in participants at high risk of disease progression	**Key Secondary**: To evaluate the effect of ADG20 on the following clinical parameters in participants with mild or moderate COVID-19 and high risk of disease progression	**Key Secondary**: To evaluate the effect of ADG20 on the following clinical parameters in participants with mild or moderate COVID-19 and high risk of disease progression
Estimand Label	Estimand 1a (Primary)	Estimand 1b (Supplementary to Primary)	Estimand 2 (Key Secondary 1)	Estimand 3 (Key Secondary 2)
Estimand Description (*with Endpoint*)	Treatment difference (ADG20 – Placebo) in proportion of *COVID-19-related hospitalization or all-cause death through Day 29* regardless of co-infection with respiratory pathogens other than SARS-CoV-2, use of prohibited COVID-19 vaccine, or prohibited treatments for COVID-19	Treatment difference (ADG20 – Placebo) in proportion of *COVID-19-related hospitalization or all-cause death through Day 29* regardless of co-infection with respiratory pathogens other than SARS-CoV-2 or use of COVID-19 vaccine and assuming no intake of prohibited treatments for COVID-19	Treatment difference (ADG20 – Placebo) in proportion of participants experiencing *severe/critical COVID-19 or all-cause death through Day 29* regardless of co-infection with respiratory pathogens other than SARS-CoV-2, use of prohibited COVID-19 vaccine, or prohibited treatments for COVID-19	Treatment difference (ADG20 – Placebo) in proportion of participants experiencing *COVID-19-related emergency room visits, hospitalization, or all-cause death through Day* regardless of co-infection with respiratory pathogens other than SARS-CoV-2, use of prohibited COVID-19 vaccine, or prohibited treatments for COVID-19
Target Population	Adult and adolescent participants with laboratory confirmed mild or moderate COVID-19 who are at high risk of disease progression	Same as Estimand 1a	Same as Estimand 1a	Same as Estimand 1a
Endpoint	Incidence of COVID-19-related hospitalization or all-cause death through Day 29	Same as Estimand 1a	Incidence of severe/critical COVID-19 or all-cause death through Day 29	Incidence of COVID-19-related emergency room visits, hospitalizations, or all-cause death through Day 29
Treatment Conditions	IM ADG20, IM Placebo	Same as Estimand 1a	Same as Estimand 1a	Same as Estimand 1a
Population-Level Summary	Difference in proportion of COVID-19-related hospitalization or all-cause death through Day 29	Difference in proportion of COVID-19-related hospitalization or all-cause death through Day 29	Difference in proportion of severe/critical COVID-19 or all-cause death through Day 29	Difference in proportion of COVID-19-related emergency room visits, hospitalization, or all-cause death through Day 29

Objective	**Primary**: To evaluate the efficacy of ADG20 compared to placebo in the treatment of mild or moderate COVID-19 in participants at high risk of disease progression	**Primary**: To evaluate the efficacy of ADG20 compared to placebo in the treatment of mild or moderate COVID-19 in participants at high risk of disease progression	**Key Secondary**: To evaluate the effect of ADG20 on the following clinical parameters in participants with mild or moderate COVID-19 and high risk of disease progression	**Key Secondary**: To evaluate the effect of ADG20 on the following clinical parameters in participants with mild or moderate COVID-19 and high risk of disease progression
Estimand Label	Estimand 1a (Primary)	Estimand 1b (Supplementary to Primary)	Estimand 2 (Key Secondary 1)	Estimand 3 (Key Secondary 2)
IcEv1 (Co-Infection)	Treatment policy	Treatment policy	Treatment policy	Treatment policy
IcEv2 (Prohibited COVID-19 vaccine)	Treatment policy	Treatment policy	Treatment policy	Treatment policy
IcEv3 (Prohibited treatments for COVID-19)	Treatment policy	Hypothetical	Treatment policy	Treatment policy
Rationale for Strategies	Given the trial's confirmatory setting, interest lies in estimating treatment effects in participants who have access to prohibited concomitant therapy such as COVID-19 vaccines or treatments and regardless of co-infection with respiratory pathogens other than SARS-CoV-2, since this scenario reflects general clinical practice and the continuously evolving setting for preventing and treating COVID-19.	Interest lies in estimating the effectiveness of ADG20 against hospitalization or all-cause death without the influences of prohibited treatments for COVID-19.	Similar to Estimand 1a	Similar to Estimand 1a

APPENDIX I. OVERVIEW OF STATISTICAL METHODS: ESTIMATIONS OF ESTIMANDS AND SENSITIVITY ANALYSES

Estimand Label	Estimand Description	Main Estimation			Sensitivity Analysis
		Analysis Set	**Imputation/Data Handling Rules**	**Analysis Model/Method**	
Estimand 1a	Treatment difference (ADG20 – Placebo) in proportion of *COVID-19-related hospitalization or all-cause death through Day 29* regardless of intake of prohibited treatments for COVID-19	FAS	The endpoint will incorporate all available information through Day 29. Where participants have missing primary endpoint through Day 29, the status will be imputed as not having COVID-19-related hospitalization or all-cause death (ie, responder)	The endpoint will be analyzed using the methodology for determining a standardized estimator for a binary outcome, with adjustment for prognostic factors. The standard error of the standardized estimator will be estimated using the delta method (refer to Appendix K)	Multiple imputation under MAR assumption followed by calculation of standardized risk difference and 95% CI using Rubin's method. Control based imputation Per-protocol Set analysis
Estimand 1b	Treatment difference (ADG20 – Placebo) in proportion of *COVID-19-related hospitalization or all-cause death through Day 29* assuming no intake of prohibited treatments for COVID-19	FAS	In case of prohibited treatments for COVID-19, the primary endpoint will utilize multiple imputation under MAR assumption. The imputation model will be informed by the observed outcomes from participants who did not receive such medication (or received it after meeting the primary endpoint). The logistic model will include the prognostic factors.	Same as Estimand 1a	Hypothetical strategy of handling the ICEs.
Estimand 2	Treatment difference (ADG20 – Placebo) in proportion of participants experiencing *severe/critical COVID-19 or all-cause death through Day 29* in the target population	FAS	Same as Estimand 1a	Treatment difference in the proportion of participants with severe/critical COVID-19 or all-cause death through Day 29 will be presented and tested using the main analysis method outlined for Estimand 1a	

Estimand Label	Estimand Description	Main Estimation			Sensitivity Analysis
		Analysis Set	Imputation/Data Handling Rules	Analysis Model/Method	
Estimand 3	Treatment difference (ADG20 – Placebo) in proportion of participants experiencing COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29 in the target population	FAS	Same as Estimand 1a	Treatment difference in proportion of participants with COVID-19-related emergency room visits, COVID-19-related hospitalizations or all-cause death through Day 29 will be presented and tested using the main analysis method for Estimand 1a.	

APPENDIX J. 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 $X = (x_1, x_2, ..., x_n)'$, a logistic regression model assumes $logit[P(y_i = 1 \mid x_i)] = \beta' x_i$, where $logit(p) = ln[p/(1 - p)]$.

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 $\hat{P}_t$ from X_t and b, $\hat{P}_t = logit^{-1}(X_t b)]$. Similarly, assume each participant is assigned to control and redo the above steps to get X_c and $\hat{P}_c$.

Risk difference (RD) in proportions:

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

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

$d_t = (A_t' X_t)/n$

$d_c = (A_c' X_c)/n$

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

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

Log risk ratio (RR) in proportions:

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

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:

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

Consider,

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

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

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

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

The confidence interval of *log(RR)* 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 $[1 - exp(\delta_1 + Z_{(1-\alpha/2)}\, SE(\delta_1)),\ 1 - exp(\delta_1 - Z_{(1-\alpha/2)}\, SE(\delta_1))]$.

APPENDIX K. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT EVENTS

Non-DAIDS Criteria for Clinical Laboratory Tests			
Parameter	**SI Unit**	**PCS Low Limit**	**PCS High Limit**
Basophils Percent	%	—	>4.00 × ULN
Eosinophils Percent	%	—	>4.0 × ULN
Monocytes percent	%	—	>4.00 × ULN
Hematocrit	%	<0.6 × baseline	>1.3 × ULN
Blood urea nitrogen	mmol/L	—	>1.3 × ULN
Chloride	mmol/L	<0.80 × LLN	>1.1 × ULN
Protein, total	g/L	<0.8 × LLN	>1.2 × ULN

LLN=lower limit of normal (value provided by the laboratory); PCS=potentially clinically significant; SI=International System of Units; ULN=upper limit of normal (value provided by the laboratory).

Vital Sign Parameter	**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
SpO_2	Low (CL)	≤93%	Decrease of ≥3%

Note: PCS is meeting either criterion value or change from baseline.
CH=clinically high; CL=clinically low.

- For temperature decreases, the participants baseline value should be accounted for. Scenarios to account for:
  - Participants with fever (≥38°C [100.4°F]) at baseline on Day 1 will not be reported as a PCS value unless an increase of ≥1 °C is met post-baseline.
  - Participants with fever (≥38°C [100.4°F]) at baseline on Day 1 will not be reported as a PCS value for a decrease in temperature after Day 1 unless to <35 °C, as this represents clinical improvement in a participant with COVID-19.
- For respiratory rate, the participants baseline value should be accounted for. Scenarios to account for:
  - Participants with a RR >20 breaths/minute at baseline on Day 1 will not be reported as a PCS value for a decrease in RR after Day 1 unless to ≤8 breaths/minute, as this represents clinical improvement in a participant with COVID-19.
- For heart rate, the participants baseline value should be accounted for. Scenarios to account for:
  - Participants with a HR >120 bpm at baseline on Day 1 will not be reported as a PCS value for a decrease in HR after Day 1 unless ≤50 bpm, as this may represent clinical improvement in a participant with COVID-19.
- Specific values for adolescents may be considered as appropriate.

APPENDIX L. SAFETY MONITORING

Study Phase/ Parameter	Analysis Time point	Reviewer/ Data Reviewed	Criterion	Statistical Method	Purpose
Phase 2/PK	Throughout	Unblinded Pharmacology Team: • Unblinded available PK data to be reviewed • Aggregate data to Sponsor	NA	PK Analyses as detailed in PK Analysis Plan	Confirm PK in participants
Phase 2/Safety	At any time during Phase 2	iDMC: Events meeting criterion	If any of the following pausing guidelines are met, an ad hoc iDMC meeting will occur: • 2 or more participants with a study-drug-related grade 3 or higher hypersensitivity reaction • 2 or more participants with a grade 3 or higher injection site reaction • Any study-drug-related death • Any study-drug-related SAE including hypersensitivity reactions	NA	Monitor ongoing safety
Phase 2/Safety Assessment (administrative interim analysis)	Approximately N=200 participants enrolled	iDMC: Safety assessment of 300 mg IM dose	Detailed in iDMC charter	Safety analyses as detailed in SAP	Monitor ongoing safety profile and provide recommendation regarding enrollment of adolescents and pregnant and breastfeeding women in Phase 3 and post-dose monitoring duration per Section 6.4.1 of the protocol.
Phase 3/Safety	At any time during Phase 3	iDMC: Events meeting criterion	If any of the following pausing guidelines are met, an ad hoc iDMC meeting will occur: • Any study-drug-related death • Any study-drug-related SAE including hypersensitivity reactions	NA	Monitor ongoing safety

NA=not applicable.

APPENDIX M. SCHEDULE OF EVENTS

Study Period	Screening/ Treatment		Follow-up							Long-Term Follow-Up				
	Day		Day							Day		Month		
Day/Month	-2	1[a]	3	5	7	11	14	21	29[b]	60	90	6[b]	11	14 EOS[b]
Visit Window (days)	2	0	±1	±1	±1	±2	±2	±2	+5	±7	±14	±30	±30	+60
Visit Type[c]	C/H	C	T	T	C/H	T	T	T	C/H	T	C/H	C/H	C/H	T
Assessment														
Baseline Assessments														
Informed consent/assent	X													
Demographic data	X													
Medical history **(i**ncluding risk factors & COVID-19 symptom onset)	X													
Complete physical exam (including weight, height, & COVID-19 signs/symptoms)	X													
Local urine or serum pregnancy test (for WOCBP; must be performed within 24 hours of study drug administration)	X													
Documentation of local positive SARS-CoV-2 test[d]	X													
Review of study inclusion/exclusion criteria (Day 1 re-review prior to randomization)	X	X												
Randomization		X												
Central Laboratory Assessments														
Nasopharyngeal swab(s) collection for SARS-CoV-2 RT-qPCR, SARS-CoV-2 sequencing, & respiratory panel (Day 1: 2 swabs, Day 7: 1 swab)		X			X									
Blood collections for SARS-CoV-2 antibodies		X												
Blood collection for safety laboratory (chemistry, hematology, coagulation) Day 1 & Month 6 includes serum pregnancy for females		X			X				X		X	X		
Blood collection for PK[e]		X			X				X		X	X	X	
Blood collection for ADA (immunogenicity)[e]		X							X		X	X	X	
Site Clinical Assessments														
Prior/Concomitant medications[f]	——————————————————————————X——————————————————————————													
AEs, SAEs, MAAEs[g]	——————————————————————————X——————————————————————————													

Study Period	Screening/ Treatment		Follow-up							Long-Term Follow-Up				
	Day		Day							Day		Month		
Day/Month	-2	1[a]	3	5	7	11	14	21	29[b]	60	90	6[b]	11	14 EOS[b]
Visit Window (days)	2	0	±1	±1	±1	±2	±2	±2	+5	±7	±14	±30	±30	+60
Visit Type[c]	C/H	C	T	T	C/H	T	T	T	C/H	T	C/H	C/H	C/H	T
Assessment														
Targeted review of changes in health[h]					X				X		X	X	X	
Educate participant on At-Home Assessments/ Collections (Symptom Diary, vitals, saliva collections, ISR Diary[i], recognizing emergency symptoms & hypersensitivity reactions)		X												
Study drug administration & safety monitoring (All Day 1 assessments must occur prior to study drug administration)		X [j]												
Vital signs, including SpO_2	X	X [j]			X				X		X	X	X	
Review of COVID-19 Symptom Diary, reported vitals, ISR diary, & COVID-19 severity assessment (Day 1 assessment should be completed prior to study drug administration)		X	X	X	X	X	X	X	X					
Survival assessment & Medically Attended Visits assessment[k]			X	X	X	X	X	X	X	X	X	X	X	X
Collect/update participant contacts		X			X				X	X	X	X	X	
Long-term health status assessment										X	X	X		
Household transmission questionnaire									X					
Participant At-Home Assessments/Collections														
Day 1 assessments/collections by participant will be observed by site staff prior to study drug administration; Days 1-4: ISR diary for IM injection participants.														
Saliva sample for SARS-CoV-2 RT-qPCR[l]		X	X	X	X	X	X	X	X					
Daily COVID-19 Symptom Diary & ISR Diary[i]		X	——————X——————											
Daily temperature, SpO_2, heart rate[m]		X	——————X——————											

ADA=anti-drug antibodies; EOS=end-of-study; ISR=injection site reaction; RT-qPCR=quantitative reverse transcription polymerase chain reaction; SpO_2=oxygen saturation; WOCBP=women of childbearing potential.

[a] Note that screening procedures may occur on the same day of dosing on Day 1. Study Day 1 is the calendar day that study drug is administered. On Day 1, all study procedures except ISR diary completion and collection of participant contacts are to be performed prior to study drug administration. Adverse events occurring from when the participant signs the ICF until the Month 14 (EOS) visit or withdrawal will be recorded. Any screening inclusion criteria with laboratory values associated (eg, eGFR, FSH, etc) should be based on local laboratory results or most recent medical record.

[b] If a participant/guardian/LAR requests a participant to be withdrawn at any time after randomization into the study, the investigator will make every effort to encourage the participant to complete the Day 29 assessments (if prior to Day 29), Month 6 visit assessments (if after the Day 29 visit but before Month 6), or the Month 14 EOS visit assessments (if after the Month 6 Visit completed).

[c] Visits after Day 1 may not be combined. Visit codes: C (in-clinic); C/H (in-clinic or home health); T (Telemedicine, 'T' visits may also be in-clinic or home health).

[d] A local positive SARS-CoV-2 test (antigen, RT-PCR, or other locally approved molecular test) taken within 5 days prior to randomization is required for eligibility. The day of randomization is not considered in the calculation of 5 days. Historical documentation is acceptable. Local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF. SARS-CoV-2 antibody testing is not acceptable for eligibility. Additional samples for SARS-CoV-2 testing at local laboratory for the purposes of case management may be collected per local standard of care. Clinical care should be delivered per local standards of care and not wait for results of central laboratory testing.

[e] On Day 1, one PK sample to be collected at baseline prior to study drug administration. All other visits with PK sample collection will have one sample collected. An additional PK and ADA sample should be collected from participants experiencing hypersensitivity reactions as described in protocol Section 6.8.2.

[f] Record information regarding all prior and concomitant medications taken, including OTC medications and investigational agents or supportive care taken for index COVID-19 infection under study. All concomitant medications will be recorded up to and including Day 60. Any concomitant medications related to AEs and any vaccinations received will be recorded for the entire length of the study (ie, through Month 14).

[g] Record all AEs from when the participant signs the ICF through the Month 14 Visit. On Day 1 through Day 4, record AESIs (hypersensitivity reactions, including but not limited to urticaria, edema, respiratory distress, anaphylaxis, and allergic reactions) occurring through Day 4. Hypersensitivity reactions occurring after Day 4 will be recorded as AEs. Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution. Worsening or sequelae of the index case of COVID-19 will not be recorded as AEs, unless they meet SAE criteria; these data will be captured as efficacy assessment data. Subsequent instances of COVID-19 in the same participant will be recorded as AEs.

[h] Targeted review of changes in health based on reported AEs or ongoing signs/symptoms of COVID-19.

[i] Participants will complete the daily COVID-19 Symptom Diary (includes global impression questions) Day 1 through Day 29. The Injection Site Reaction Diary will be completed Day 1 through Day 4. Site will provide a ruler along with instructions regarding completion of the Injection Site Reaction Diary (protocol Appendix 12.3). Instruct participants to record any local ISRs daily through Day 4.

[j] Perform vital signs before, during, and after study drug administration per protocol Section 6.4.1. Protocol Section 6.4.1 outlines required vital signs on Day 1, duration of monitoring post-dose, and ISR monitoring and management.

[k] Record information regarding participant survival and participant medically attended visits (telemedicine, physician office, urgent care center, emergency room, hospitalization) and relationship of medically attended visits to COVID-19. During telemedicine visits, the participant will also be reminded to complete daily COVID-19 Symptom Diary, daily temperature, blood oxygen saturation and heart rate, and saliva sample collection on the appropriate days.

[l] Participants will collect their own saliva sample using the collection materials provided on Days 3, 5, 11, 14, and 21 and return them to the study site according to provided instructions. Note: Day 7 and Day 29 are in-clinic or home health visits and the saliva sample will be collected and transported by site staff or delegate. Participants should NOT eat, drink, smoke, or chew gum for 30 minutes before sample collection. The sample will be used for SARS-CoV-2 RT-qPCR and may be used for viral sequencing. In the event of worsening COVID-19 or potential relapse or re-infection, a saliva sample for SARS-COV-2 RT-qPCR and sequencing should be collected as described in protocol Section 6.8.1.

[m] Participants will be asked to monitor temperature, blood oxygen saturation, and heart rate at approximately the same time each day. Additional measurements may be taken at other times during the day if the participant feels feverish or short of breath at rest.