Protocol

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)

NCT ID: NCT04805671

IND Identifier: 152327

EudraCT Identifier: 2020-006082-11

Date of Document: 02-March-2022

CLINICAL STUDY PROTOCOL

Protocol Title:	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)
Protocol Number:	ADG20-TRMT-001
Clinical Phase:	Phase 2/3
Protocol Version and Date:	6.0, 02 March 2022
US IND Number:	152327
EudraCT Number:	2020-006082-11
Sponsor:	Adagio Therapeutics, Inc. 303 Wyman Street, Suite 300 Waltham, MA 02451
Sponsor Contact:	[redacted]

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Adagio Therapeutics, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the express written consent of Adagio Therapeutics, Inc.

The study will be conducted according to the International Council for Harmonisation guideline E6(R2): Good Clinical Practice.

DOCUMENT REVISION HISTORY

Document	Date of Issue	Overall Rationale
Version 1.0	11 January 2021	Original Protocol. No participants were enrolled under this version of the protocol.
Version 2.0	18 February 2021	Update the protocol objectives, endpoints, and study population based on US FDA feedback. No participants were enrolled under this version of the protocol.
Version 3.0	12 April 2021	Revise the study design, sample size, and inclusion criteria based on evolving data. No participants were enrolled under this version of the protocol.
Version 4.0	06 May 2021	Remove the Phase 1 lead-in and IV dosing from the study. Revise the planned total enrollment and clarify that enrollment would not pause between Phases 2 and 3 of the study. Update the SAP to reflect removal of Phase 1 and interim analysis modifications. Protocol Version 4.0 was implemented prior to enrollment of the first participant in the study.
Version 5.0	23 November 2021	Revise the planned total enrollment to 900 participants and update inclusion criteria related to conditions considered high risk for disease progression to include a larger study population. Update the SAP with regards to sample size, timing of interim analysis, and to reflect minor adjustments to objectives/endpoints. Protocol Version 5.0 was submitted to the US FDA only and was not implemented at study sites.
Version 6.0	02 March 2022	Update the study objectives and endpoints to reflect changes due to the emergence of the SARS-CoV-2 Omicron variant, including suspending enrollment in the study. Update the SAP to reflect changes to the analysis plan due to the emergence of Omicron, including analysis of data collected in participants infected with a non-Omicron variant of SARS-CoV-2. Version 5.0 of the protocol was not submitted to sites/IRBs. Enrollment in the study has been suspended (as of 11-JAN-2022) and no further participants are expected to be enrolled under Version 6.0 of the protocol; therefore, updates to the total planned sample size and updates to inclusion criteria to expand the population for the study that were included in Version 5.0 of the protocol were removed in Version 6.0.

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title	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)
Protocol Number	ADG20-TRMT-001
Protocol Date and Version	02 March 2022 6.0

Protocol accepted and approved by:

[redacted]

Adagio Therapeutics, Inc.
303 Wyman Street, Suite 300
Waltham, MA 02451

Signature **Date**

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "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)" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 6.0, dated 02 March 2022, the International Council for Harmonisation guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Adagio Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.

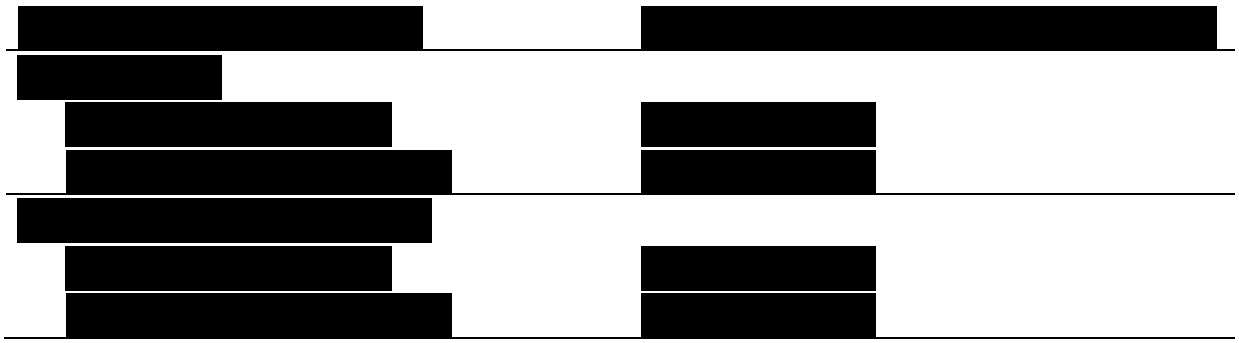
I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Adagio Therapeutics, Inc.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

CONTACT INFORMATION FOR SAE REPORTING

Any AE that meets SAE criteria (Section 6.4.6.1.2) must be reported to [redacted] Pharmacovigilance immediately (ie, within 24 hours) after site personnel first learn of the event. The following contact information is to be used for SAE reporting:



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PROTOCOL SYNOPSIS

Sponsor:	Adagio Therapeutics, Inc.
Protocol No.	ADG20-TRMT-001
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)
Study Drug:	ADG20
Study Phase:	2/3
Indication	COVID-19
US IND No.	152327
EudraCT No.	2020-006082-11
No. of Sites/Location:	Approximately 100 to 115 sites / global

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	• 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

Objectives	Endpoints
• 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	• 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
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 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 as data permit
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

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; NP=nasopharyngeal; PASC=post-acute sequelae of SARS-CoV-2 infection; 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.

Diagnosis and Main Criteria for Inclusion and Exclusion

The study population will include adults (aged ≥18 years) and adolescents (aged 12 to <18 years) in both cohorts; enrollment of adolescents will begin upon sponsor communication to the sites following iDMC review of safety data in each cohort, and only in regions permitted by health authorities and local ethics committees. Participants with laboratory confirmed mild or moderate COVID-19 who are at high risk for disease progression will be included.

Inclusion Criteria:

Each participant must meet all of the following criteria to be enrolled in this study:

1. Age: Is an adult aged 18 years and above, or is an adolescent aged 12 to 17 years (inclusive) and weighing ≥40 kg at the time of screening

   Note: Adolescent enrollment will open only upon sponsor communication to sites after iDMC review of safety data in adults, and only if permitted by the local health authority.

2. Has had a SARS-CoV-2 positive antigen test, or by RT-PCR, or other locally approved molecular diagnostic assay obtained within 5 days prior to randomization.

   Note: A historical record of a positive result from a test conducted within 5 days prior to randomization is acceptable. SARS-CoV-2 antibody testing cannot be used for study eligibility.

3. Has had initial onset of one or more of the following self-reported COVID-19-related signs or symptoms within 5 days prior to randomization:
   a. measured temperature ≥38 °C (100.4 °F)
   b. subjective fever (feeling hot or feverish)
   c. chills (shivering)
   d. cough
   e. sore throat
   f. congestion (stuffy or runny nose)
   g. shortness of breath or difficulty breathing with exertion worse than usual
   h. muscle or body aches
   i. fatigue (low energy or tiredness)
   j. headache
   k. loss of taste or smell
   l. nausea or vomiting
   m. diarrhea
4. Has mild or moderate COVID-19 (per Section 2.2.2) with one or more of the following COVID-19-related signs or symptoms on the day of randomization:
   a. measured temperature ≥38 °C (100.4 °F)

b. subjective fever (feeling hot or feverish)
c. chills (shivering)
d. cough
e. sore throat
f. congestion (stuffy or runny nose)
g. shortness of breath or difficulty breathing with exertion worse than usual
h. muscle or body aches
i. fatigue (low energy or tiredness)
j. headache
k. loss of taste or smell
l. nausea or vomiting
m. diarrhea

5. Is at high risk of disease progression defined as:
   a. Age ≥55 years
   b. Age 18 to <55 years with one or more preexisting medical conditions as follows
      i. Obesity (body mass index [BMI] ≥30 kg/m^2)
      ii. Diabetes (Type 1 or Type 2)
      iii. Chronic kidney disease (eGFR calculated by Modification of Diet in Renal Disease [MDRD] of 59 mL/min/1.73 m^2 or less, including end-stage renal disease on hemodialysis)
      iv. Chronic lung disease (emphysema/chronic obstructive pulmonary disease, chronic bronchitis, interstitial lung disease [including idiopathic pulmonary fibrosis], or cystic fibrosis)
      v. Cardiac disease (heart failure, coronary artery disease, or cardiomyopathies)
      vi. Sickle cell disease or thalassemia
      vii. Solid organ or blood stem cell transplant recipients
      viii. Other immunodeficiency due to underlying illness or immunosuppressant medication (eg, corticosteroids ≥20 mg/day prednisone or equivalent)
      ix. Down Syndrome
      x. Stroke or cerebrovascular disease, which affects blood flow to the brain
      xi. Substance use disorder
      xii. Pregnant (Enrollment of participants who are pregnant may only open upon sponsor communication to sites after iDMC review of data, and only in regions permitted by the local health authority)

c. Age 12 to 17 years (inclusive) with one or more preexisting medical conditions as follows

   i. BMI >85th percentile for age and sex based on United States Center for Disease Control (CDC) growth charts

   ii. Diabetes (Type 1 or Type 2)

   iii. Chronic kidney disease

   iv. Sickle cell disease or thalassemia

   v. Congenital or acquired heart disease

   vi. Neurodevelopmental disorders (eg, cerebral palsy, Down syndrome)

   vii. A medically-related technological dependence (eg, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19)

   viii. Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

   ix. Solid organ or blood stem cell transplant recipients

   x. Other immunodeficiency due to underlying illness or immunosuppressant medication

   xi. Substance use disorder

   xii. Pregnant (Enrollment of participants who are pregnant may only open upon sponsor communication to sites after iDMC review of data, and only in regions permitted by the local health authority)

6. Has been assigned female sex at birth and is of nonchildbearing potential. A female participant who is not of reproductive potential is eligible without requiring the use of contraception and pregnancy testing is not required. This includes female participants who have not undergone menarche or who are documented to be surgically sterile (eg, hysterectomy, or removal of both ovaries, or tubal ligation) or postmenopausal (ie, amenorrhea >1 year and FSH >40 mIU/mL). Follicle-stimulating hormone is not required in postmenopausal females with amenorrhea for >2 years

7. Has been assigned female sex at birth and is of childbearing potential and fulfills all the following criteria:

   a. Has a negative urine or serum pregnancy test at Screening

   b. Has practiced adequate contraception for or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1)

   c. Has agreed to continue adequate contraception for sexual activity that could lead to pregnancy through 6 months following study drug administration

   d. Is not currently breastfeeding

   Note: Enrollment of participants who are pregnant or breastfeeding may open only upon sponsor communication to sites after iDMC review of Phase 2 data.

Adequate contraception for participants assigned female sex at birth is defined as consistent and correct use of a highly effective locally approved contraceptive method in accordance with local regulations for contraceptive use in clinical trial participants. For example:

a. Intrauterine device (hormonal or non-hormonal)

b. Hormonal contraceptive taken or administered via oral, transdermal, intravaginal, implantable, or injectable method

c. Sterilization of a female participant's monogamous male partner prior to entry into the study

d. Sexual abstinence*

Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

*Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse starting at the time of consent to participate in the study until 6 months after dosing. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

8. Has been assigned male sex at birth with partner(s) of childbearing potential and agree to use contraception, per local regulations, through 6 months after dosing. If their partner is pregnant, males must agree to use a condom. No sperm donation is permitted through 6 months after dosing.
9. Is able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or guardian/LAR) based on the assessment of the investigator.
10. Is able and willing to provide informed consent. An LAR may be used only in cases where inclusion criterion 9 is able to be fulfilled. In the case of adolescents, informed assent must also be obtained as required by local guidelines.

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study:

1. Is currently hospitalized or, in the opinion of the investigator, requires urgent medical attention or is anticipated to require hospitalization within 48 hours of randomization.
2. Has oxygen saturation (SpO_2) ≤93% on room air at sea level or ratio of arterial oxygen partial pressure (PaO_2 in millimeters of mercury) to fractional inspired oxygen (FiO_2) <300 mmHg, respiratory rate ≥30 per minute, or heart rate ≥125 per minute.
3. Is on supplemental oxygen therapy at the time of randomization for any reason or, in the opinion of the investigator, has an anticipated impending need for mechanical ventilation.
4. Has a history of a positive SARS-CoV-2 antibody serology test. Note: serology testing is not required for study eligibility, exclusion criterion is based on known history only.

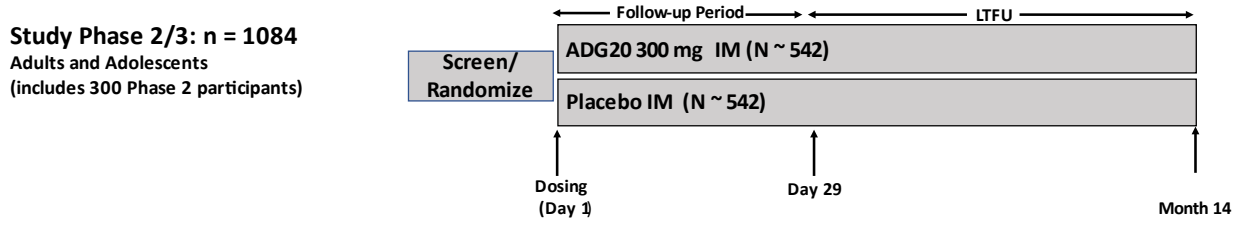
5. Has participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
6. Has known allergy/sensitivity or hypersensitivity to study drug, including excipients.
7. Has received a SARS-CoV-2 vaccine, monoclonal antibody, or plasma from a person who recovered from COVID-19 any time prior to participation in the study.
8. Has a known active co-infection (eg, influenza, urinary tract infection, etc).
9. Has any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the participant by their participation in the study including, but not limited to, any co-morbidity requiring surgery or conditions considered life-threatening within 29 days.
10. Has a clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture. Abnormal coagulation labs or use of anticoagulant medication are not exclusionary in the absence of clinical findings.
11. Is or has an immediate family member (eg, spouse, sibling, child, guardian/LAR, parent) who is an investigator or site or sponsor staff (or designee) directly involved with the study.

Study Design

This 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 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 administered by IM injection. Randomization will be stratified by age (12 to 17, 18 to 65, and >65 years) and country.

Study Design Schematic for ADG20-TRMT-001



IM=intramuscular; LTFU=long-term follow-up.
Note: Screening may be performed prior to randomization on the same day as study drug dosing.

This study will enroll approximately 1084 participants total in 2 phases:

- Phase 2: Enrolling approximately 300 adult participants to evaluate initial safety, efficacy, PK, and antiviral activity of ADG20 300 mg IM versus placebo in adults prior to enrolling additional participants in Phase 3.
- Phase 3: Enrolling an additional 784 adult and adolescent participants (to reach the total sample size of 1084 for Phase 2/3), to evaluate efficacy, safety, PK, and antiviral activity of ADG20 300 mg IM versus placebo in adults and adolescents. There is no planned enrollment pause between Phase 2 and 3.

At the recommendation of the iDMC following review at approximately n=200 and upon sponsor communication to sites, enrollment of adolescents will open only in regions permitted by health authorities and local ethics committees. Pausing guidelines triggering iDMC ad hoc reviews are described in Section 10.11.

Duration of Study

The study duration for each participant will be approximately 14 months. Each participant will receive a single dose of study drug 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 Month 6.

Efficacy and Virologic Assessments

Clinical efficacy assessments will include COVID-19-related hospitalization and all-cause death; COVID-19 severity; COVID-19-related emergency room visits and medically attended visits; and daily patient-reported symptoms.

Virologic assessments will include quantitative SARS-CoV-2 viral load, clearance and duration of viral shedding assessed on nasopharyngeal samples and/or participant collected saliva samples.

Resistance to ADG20 in viral isolates obtained from participants will be characterized using genotypic methods, with phenotypic methods deployed as appropriate. The impact of host biomarkers, such as baseline SARS-CoV-2 antibody responses, and viral load, on selected outcomes, may be evaluated.

Pharmacokinetic and Immunogenicity Assessments

Blood samples will be collected at specified time points for assessments of PK and to evaluate immunogenicity (anti-drug antibodies) to ADG20.

Safety Assessments

Safety will be assessed in an ongoing manner. Participants will receive ADG20 or placebo. As a precaution for acute worsening of disease, hypersensitivity, and injection site reactions (ISRs), participants will be observed after study drug administration as described in Section 6.4.1 of the protocol. If any hypersensitivity reactions occur, the iDMC will review available safety data and

provide a recommendation regarding the duration of monitoring. Participants will then be followed via telemedicine visits, phone calls, or in-person visits as described in the Schedule of Assessments through Day 29 for safety assessments.

Safety assessments will include monitoring of AEs, clinical laboratory testing, vital sign measurements (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure), and physical examinations. Any AESIs (hypersensitivity reactions through Day 4) will be recorded. Hypersensitivity reactions occurring after Day 4 will be recorded as AEs. Participants will record any ISRs using the Injection Site Reaction Diary starting after dosing on Day 1 through Day 4 (Appendix 12.3). Other AEs, including SAEs and medically attended adverse events (MAAEs) (including new onset chronic illnesses), will be collected through the Month 14/EOS visit.

For the purposes of this study, 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 as these are expected endpoints. Subsequent episodes of COVID-19 in the same participant will be captured according to standard AE processes, including the standard process for expedited reporting of SAEs if the event meets the definition of an SAE.

Details of Applicable Monitoring Committee

The iDMC will provide safety oversight for all parts of the study, including monitoring for potential antibody-dependent enhancement (ADE). The iDMC will meet at designated points per Section 7.13 and the iDMC charter and on an ad hoc basis to review cumulative safety data and other clinical study data to ensure the benefit/risk remains favorable.

Details regarding iDMC membership, conduct, ongoing safety monitoring, decision making, and communication will be provided in the iDMC Charter. Pausing guidelines for iDMC ad hoc safety reviews are outlined in Section 10.11.

Study Drug, Dosage, and Route of Administration

The study drug, ADG20, is a mAb, which will be administered once on Study Day 1. Participants will receive either 300 mg IM injection or matching placebo (3 mL injection). Placebo (normal saline solution) will be administered by the same route at a matched volume.

Number of Planned Participants

Approximately 1084 participants are planned to be enrolled.

Efficacy Analyses

Enrollment in the study was suspended on 11-Jan-2022 after emergence and global spread of the Omicron variant in regions enrolling the trial, beginning in December 2021. Therefore, the primary analysis is focused on evaluating the efficacy of ADG20 300 mg IM in participants with a non-Omicron variant of SARS-CoV-2. With this analysis plan, the primary efficacy and short-term 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.

The primary analysis is the comparison of the ADG20 arm versus the placebo arm with respect to the 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 sample size was calculated based on assumptions obtained from a review of data from studies of other mAbs in participants at high risk for disease progression leading to hospitalization or death prior to widespread emergence of both the Delta and Omicron variants. 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 approximate aggregate event rate of 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 the same efficacy assumption.

The analysis of the primary estimand, incidence of COVID-19-related hospitalization or all-cause death through Day 29 in the ADG20 arm versus the placebo arm in the mFAS-non-Omicron analysis set will be analyzed using the methodology for determining a standardized estimator for a binary outcome as detailed in Ge 2011, with adjustment for the following prognostic factors: age (continuous), sex (categorical), baseline qualitative serostatus (categorical), BMI (continuous), and baseline viral load (continuous). The standard error of the standardized estimator will be estimated using the delta method based on the algorithm presented in Ge 2011. The risk difference (placebo minus ADG20) with CI (using the Miettinen-Nurminen method), standardized risk difference with CI, relative risk reduction with CI, and associated p-value for the standardized risk difference will be provided. A treatment policy strategy will be used to handle intercurrent events of interest. For example, treatment effect will be estimated regardless of baseline or emergence of coinfection with a non-SARS-CoV-2 pathogen, which is a potential intercurrent event of interest.

The key secondary endpoints will be tested in the following order in the mFAS-non-Omicron analysis set: (1) Severe/critical COVID-19 or all-cause death through Day 29, (2) COVID-19-related emergency room visits, COVID-19-related hospitalization, or all-cause death through Day 29, and (3) Time to sustained resolution of COVID-19 symptoms through Day 29.

Analyses of other secondary and exploratory efficacy endpoints will be conducted to support the findings of the primary and key secondary efficacy endpoints.

Safety Analyses

Safety summaries through Day 29 and overall will be presented.

The incidence of TEAEs (including solicited ISRs), SAEs, TEAEs related to study drug, SAEs related to study drug, TEAEs leading to study drug discontinuation, AESIs, and MAAEs will be summarized by MedDRA system organ class (SOC), preferred term (PT), and treatment group.

The incidence of study drug related TEAEs (including solicited ISRs) will also be summarized by maximum severity by SOC, PT, and treatment group.

The incidence of solicited AEs (ISRs) will be summarized by maximum severity through Day 4. The maximum duration and time from injection to report of first onset of any solicited ISR will also be summarized.

Descriptive statistics for clinical laboratory results and vital sign parameters and for the change from baseline will be presented by treatment group and time point assessed. Potentially clinically significant laboratory and vital sign parameters will be summarized by treatment group and time point assessed.

Immunogenicity Analyses

Immunogenicity data will be listed and summarized in tables using descriptive statistics.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization
ADA	anti-drug antibodies
ADE	antibody-dependent enhancement (of disease)
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BLQ	below the limit of quantification
BMI	body mass index
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CV%	coefficient of variation
DAIDS	Division of AIDS (National Institute of Allergy and Infectious Disease)
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOS	end of study
EU	European Union
EUA	emergency use authorization
FAS	full analysis set
Fc	fraction crystallizable
FDA	Food and Drug Administration
FiO_2	fractional inspired oxygen
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IA	interim analysis

Abbreviation	Definition
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	independent data monitoring committee
IEC	independent ethics committee
IgG	immunoglobulin G
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous
KM	Kaplan-Meier
LAR	legally authorized representative
LLOQ	lower limit of quantitation
LS	least squares
MAAE	medically attended adverse event
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full-analysis set
MMRM	Mixed Model for Repeated Measures
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	no observed adverse effect level
NP	nasopharyngeal
OTC	over-the-counter
PASC	post-acute sequelae of SARS-CoV-2 infection
PaO_2	oxygen partial pressure
PCR	polymerase chain reaction
PCS	potentially clinically significant
PK	pharmacokinetic
PPS	per-protocol set
PT	preferred term

Abbreviation	Definition
QSP/PBPK	quantitative systems pharmacology/whole body physiologically based pharmacokinetic
RBD	receptor-binding domain
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
SC	subcutaneous
SOC	system-organ-class
SOP	standard operating procedure
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
sVNA	serum virus neutralizing antibody
TCR	tissue cross reactivity
TEAE	treatment-emergent adverse event
UP	unanticipated problems involving risks and adverse events
US	United States
USP	US Pharmacopeia
VOC	variants of concern
VNA	virus neutralizing antibody
WGS	whole genome sequencing
WOCBP	women of childbearing potential

PHARMACOKINETIC ABBREVIATIONS

Abbreviation	Definition
AUC	area under the concentration-time curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from zero to an infinite time
$AUC_{0\text{-last}}$	area under the concentration-time curve from zero up to the last concentration ≥LLOQ
CL	clearance
C_{max}	observed maximum plasma or serum concentration after administration
$T_{1/2}$	plasma concentration half-life
T_{max}	time to reach maximum plasma or serum concentration
Vd	volume of distribution

1. INTRODUCTION

1.1. ADG20 Background

ADG20 (also known as adintrevimab) is a fully human monoclonal immunoglobulin G1 antibody targeted to the spike glycoprotein of SARS-CoV-2. ADG20 binds with high affinity to a conserved epitope in the RBD of the spike protein of SARS-CoV-2 and related Clade 1 sarbecoviruses and displays broad and potent in vitro neutralizing activity against SARS-CoV-2, SARS-CoV, SARS-CoV-2 D614G, and the bat SARS-like viruses WIV1-CoV and SHC014-CoV. In addition to potent neutralization, ADG20 displays Fc-mediated innate immune effector activity, including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent complement deposition. The Fc region of ADG20 has also been engineered to contain the Fc heavy chain modification LA (M435L, N441A), resulting in an estimated half-life of approximately 97 days in humans based on preliminary data from a Phase 1 study (ADG20-1-001) in healthy adult volunteers. No ADG20-specific off target binding to human tissues was observed in adult and fetal human tissue cross-reactivity and immunohistochemistry studies, and ADG20 was not associated with any toxicologically relevant or clinically meaningful findings during or at the end of the in-life portion in a repeat-dose rat toxicology study.

1.1.1. Nonclinical Studies of ADG20

Given the rising prevalence of SARS-CoV-2 variants, nonclinical studies evaluating the ability of ADG20 to bind to and neutralize known and emerging variants of concern are performed on an ongoing basis. ADG20 has displayed potent binding and neutralizing activity against multiple SARS-CoV-2 variants of concern, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) (Dejnirattisai 2021). In vitro activity has been demonstrated against variants that have shown relative or absolute resistance to a subset of other clinical stage SARS-CoV-2 mAb products (Dejnirattisai 2021; Liu 2021a; Liu 2021b; Planas 2021; Starr 2021; Wang 2021; Dejnirattisai 2022) and that have been associated with lower rates of vaccine efficacy (Madhi 2021; Mahase 2021; Voysey 2021). In addition, ADG20 displayed in vitro binding and/or neutralizing activity against the SARS-CoV-2 variant B.1.1.529 BA.1 (Omicron), albeit with reduced potency compared to activity against prior variants (Liu 2021b; Planas 2021; Starr 2021; Wang 2021). The nonclinical program includes in vitro studies evaluating the avid and monovalent binding by ADG20 to SARS-CoV-2 RBDs incorporating mutations present in known and emerging variants and in vitro neutralization assays using authentic virus variants and pseudovirus. A detailed review of nonclinical experience with ADG20 is provided in the IB.

1.1.2. Clinical Studies of ADG20

ADG20 is being developed for the treatment and prevention of COVID-19, the disease caused by SARS-CoV-2. This placebo-controlled study (ADG20-TRMT-001; STAMP) is intended to generate safety and efficacy data to provide treatment options for COVID-19 in patients with a high risk of disease progression based on age or co-morbid medical conditions. On 21-Dec-2021, the iDMC reviewed unblinded data from approximately 200 participants dosed with ADG20 300 mg IM or placebo in this study and recommended that the study continue.

In addition to this study, Adagio Therapeutics, Inc. is evaluating the safety, tolerability, and PK of ADG20 in 2 ongoing trials.

1.1.2.1. Study ADG20-1-001

Study ADG20-1-001 is a first-in-human, Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study conducted in the United States in healthy adult volunteers to evaluate the safety and PK of ADG20 (100 mg/mL formulation). To date, 24 participants across 3 dose levels (300 mg IM, 500 mg IV, and 600 mg IM) received ADG20 (8 per dose cohort) and 6 received placebo (2 per dose cohort). Dosing in these cohorts was initiated on 12-Feb-2021 and completed on 23-Mar-2021; follow-up is ongoing.

Preliminary findings from blinded data review with a minimum of 9 months of follow-up showed that no SAEs, AESIs (hypersensitivity reactions or infusion-related reactions), study drug-related AEs, or ISRs have been reported. The observed ADG20 PK appears to be dose proportional, with an estimated half-life of approximately 97 days based on linear regression of the Days 21, 90, and 180 PK timepoints from the 300 mg IM dose.

1.1.2.2. Study ADG20-PREV-001 (EVADE)

Study ADG20-PREV-001 (EVADE) is a Phase 2/3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ADG20 in the prevention of COVID-19. Dosing in the study was initiated on 23-Apr-2021; follow-up is ongoing. On 24-Aug-2021, the iDMC reviewed the EVADE trial Phase 2 safety data, and on 30-Nov-2021, the iDMC reviewed the cumulative Phase 2/3 data. No safety concerns were identified, and the iDMC recommended that the trial continue. As of 11-Jan-2022, approximately 2471 participants had received study drug (ADG20 or placebo) in the study and enrollment was suspended on this date due to the global spread of the Omicron variant.

1.2. Background on COVID-19

Coronaviruses are ubiquitous pathogens with high pandemic potential. In recent years, 3 pathogenic coronaviruses have crossed into the human population from zoonotic sources: SARS-CoV, MERS-CoV, and SARS-CoV-2. SARS-CoV-2, the most recent of these coronaviruses emerged in late 2019 and is the causative agent of COVID-19. As of 27-Jan-2022, over 363 million cases have been reported globally, including over 5.6 million deaths (Johns Hopkins University & Medicine 2022). In addition to this health crisis, the COVID-19 pandemic has led to steep economic recessions in many countries. The World Bank reported a 3.5% contraction in global gross domestic product in 2020, the deepest global recession since World War II (World Bank 2021). The ongoing pandemic has had a devastating effect on income growth and inequality that is expected to linger for a protracted period, with recovery largely dependent on controlling the ongoing pandemic. Although rigorous testing, contact tracing, and quarantine procedures may help to temporarily slow down the spread of COVID-19 in society, widespread immunity is required to truly halt the pandemic.

Symptoms of COVID-19 may appear from 2 to 14 days following exposure to SARS-CoV-2, with clinical manifestations ranging from mild symptoms to severe illness and death. The majority of infections result in mild to moderate symptoms and asymptomatic infections have

been estimated to account for as many as 40% to 45% of all SARS-CoV-2 infections (Oran 2020). In a report from the Chinese CDC that described 44 415 confirmed cases, an estimation of disease severity of mild, severe, and critical disease was reported in 81%, 14% and 5% of cases, respectively, with a 2.3% case fatality rate (Wu 2020). Common symptoms include fever or chills, cough, shortness of breath/difficulty breathing, fatigue, muscle/body aches, headache, new loss of sense of taste or smell, sore throat, nasal congestion, nausea/vomiting and diarrhea (CDC 2021b). A subset of individuals with initially mild to moderate symptoms may experience disease progression. Dyspnea developed after a median of 5 days after symptom onset with hospital admission occurring after a median of 7 days after symptom onset in a study of 138 patients hospitalized with COVID-19 pneumonia (Wang 2020).

Complications of COVID-19 include respiratory failure (acute respiratory distress syndrome), cardiac and cardiovascular complications (arrythmias, acute cardiac injury, shock, and cardiomyopathy), thromboembolic events (pulmonary embolism and acute stroke) and inflammatory complications (Guillain-Barré syndrome, multisystem inflammatory syndrome similar to Kawasaki disease/toxic shock syndrome in children). Time to recovery is variable and appears to be approximately 2 to 3 weeks for mild infection and 2 to 6 weeks for severe disease (WHO 2020). In a survey of 350 hospitalized patients in the US, only 39% of patients reported a return to baseline health by 14 to 21 days after diagnosis (Tenforde 2020a) and only 13% of 143 hospitalized patients in Italy reported being symptom-free 60 days after onset of disease (Carfì 2020). Recent data suggests that even individuals with mild disease may experience prolonged symptoms, with only 65% of individuals reporting return to baseline health by 14 to 21 days after diagnosis (Tenforde 2020b).

Age is the predominant risk factor for development of severe COVID-19, with older patients, particularly those with comorbid disease, displaying the highest risk of morbidity and mortality (Garg 2020). In addition to age, the following comorbidities have been identified as risk factors for the development of severe COVID-19: cancer, chronic kidney disease, chronic lung disease (COPD, moderate to severe asthma), Down syndrome, heart conditions (heart failure, coronary artery disease, cardiomyopathies, hypertension), immunocompromised state (eg, solid organ transplant), obesity (BMI ≥30 kg/m^2), pregnancy, sickle cell disease, smoking, and diabetes (CDC 2021a). The symptoms of COVID-19 are similar in adolescents and adults, although the frequency of specific symptoms may vary (Stokes 2020). Similar to adults, severe outcomes are more common in adolescents with underlying comorbidities, including chronic lung disease, obesity, cardiovascular disease, neurologic/developmental disorders and immunosuppressive conditions (Bixler 2020; Stokes 2020). Current data suggest that adolescents have similar susceptibility to infection and risk of secondary transmission as adults (Boehmer 2020; Leeb 2020; Goldstein 2021; Viner 2021) and may play an increasingly important role in ongoing community transmission of SARS-CoV-2. The incidence of confirmed infections increased 3-fold among those aged 10 to 19 years in the US from May 2020 to August 2020 (Boehmer 2020), and large outbreaks have been reported in high schools and university campuses (Salvatore 2020; Stein-Zamir 2020; Wilson 2020; Starr 2021).

To date, remdesivir is the only approved antiviral agent for the treatment of COVID-19 in the US (Gilead Sciences 2022a) and has conditional marketing authorization by the EMA (Gilead Sciences 2022b). Two other antivirals possess FDA emergency use authorization (EUA) for the treatment of patients with mild-to-moderate COVID-19 who are at high risk for progression to

severe disease: molnupiravir, which is authorized for use in adult patients only (Merck & Co 2022) and nirmatrelvir co-packaged with ritonavir (Paxlovid), which is authorized in adult and pediatric (≥12 years) patients (Pfizer 2022). Paxlovid recently received conditional marketing authorization in the EU (Pfizer Europe MA EEIG 2022) and the EMA issued advice for the use of molnupiravir to support national decision making before a marketing authorization is issued (EMA 2021). However, the availability of these antivirals is limited. Furthermore, molnupiravir is not recommended for pregnant or breastfeeding women due to the risk of embryo-fetal toxicity and Paxlovid is not recommended for patients with severe renal or hepatic impairment and is contraindicated with many drugs that are highly dependent on CYP3A for clearance.

Four monoclonal antibody (mAb) products, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab have been granted FDA EUA for the treatment of patients with mild-to-moderate COVID-19 at high risk for progressing to severe COVID-19 and/or hospitalization (Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022). In the EU, casirivimab/imdevimab, sotrovimab, and regdanvimab are all authorized for treatment of high-risk patients (Celltrion Healthcare Hungary 2021; GlaxoSmithKline 2021; Roche Registration GmbH 2021). However, the availability of these treatments is limited at this time. Further, mAbs are susceptible to relative or absolute resistance to emerging variants of SARS-CoV-2, as was demonstrated with the emergence of Omicron, against which bamlanivimab/etesevimab, casirivimab/imdevimab, and regdanvimab have no in vitro activity (Planas 2021; Eli Lilly and Company 2022a; Regeneron 2022). As a result, mAb products may not be authorized for use in regions where the predominant variant is non-susceptible to that product.

1.3. Study Rationale

1.3.1. Rationale for Use of a Monoclonal Antibody

Given the global magnitude of the COVID-19 pandemic, efforts to develop safe and effective treatment have taken on unprecedented urgency.

Clinical trial experience of neutralizing mAbs that target the SARS-CoV-2 spike protein supports a favorable risk-benefit profile for the evaluation of mAb therapies in recently diagnosed ambulatory patients with mild-to-moderate COVID-19 who are at high risk of disease progression (Celltrion Healthcare Hungary 2021; Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022).

The potential for ADG20 to provide broad protection against disease progression to a wide range of individuals is supported by nonclinical data, in which ADG20 displayed potent binding and neutralizing activity against all SARS-CoV-2 variants of concern identified prior to the emergence of Omicron, and retained neutralizing activity against Omicron, albeit with reduced potency (Liu 2021b; Planas 2021; Starr 2021; Wang 2021). In combination with the clinical experience with other mAbs targeting SARS-CoV-2, these data support the evaluation of ADG20 in ambulatory adult and adolescent participants with mild or moderate COVID-19 who are at high risk of disease progression. Clinical evaluation of agents such as ADG20 that possess broad activity against SARS-CoV-2 and additional coronaviruses with pandemic potential is

urgently needed to provide potential solutions for both the current and future pandemics due to sarbecoviruses.

1.3.2. Rationale for Study Design

This randomized, double-blind, placebo-controlled Phase 2/3 study is intended to generate safety and efficacy data to provide a treatment option for mild or moderate COVID-19 in patients with a high risk of disease progression based on age or co-morbid medical conditions. The patient population, placebo-control, safety monitoring, duration of follow-up, and efficacy endpoints are consistent with regulatory guidance (FDA 2020b; FDA 2021b).

Phase 2/3 design: A streamlined Phase 2/3 design is being utilized due to the critical nature of the COVID-19 pandemic and the urgent need for effective therapies. Available Phase 1 safety data in healthy volunteers from Study ADG20-1-001 identified no safety concerns for ADG20 across 3 dose levels (300 mg IM, 500 mg IV, and 600 mg IM), including no injection site or infusion-related reactions and no hypersensitivity reactions within 6 weeks following study drug administration. Additionally, healthy volunteer PK demonstrated that QSP/PBPK model predicted the observed ADG20 concentrations well and with relatively little bias across the 21-day sampling interval. The study demonstrated high sVNA titers in healthy volunteers receiving ADG20, which were consistent with those associated with efficacy in nonhuman primate adoptive transfer studies (McMahan 2021). The absence of safety and tolerability signals, PK results that confirm prior model predictions, and high sVNA titers supported the initiation of ADG20-TRMT-001. Refer to the IB for additional detailed Phase 1 data from study ADG20-1-001.

Participant Population: Mild or moderate COVID-19 in adults and adolescents can typically be managed in the outpatient/ambulatory setting. Data from other SARS-CoV-2 mAb programs suggest that populations at high risk for progression of COVID-19 are likely to benefit from treatment with a mAb (see Section 1.4.1). In order to ensure similar risk of COVID-19 disease progression across the two treatment groups, enrollment will be stratified based on age. Data from several regions have consistently shown that age is the most critical factor for risk of severe COVID-19 including hospitalization, ICU stay, and death (Docherty 2020; Grasselli 2020; Ko 2020; Wu 2020; Kim 2021). Of the risk factors identified, age appears to have the most profound impact on outcomes, with significant increase in risk clearly evident around age 65 and a greater magnitude in risk than that associated with any individual co-morbidity (Kim 2021). In a cohort of more than 1.3 million patients diagnosed with COVID-19, of patients with no reported underlying health conditions, 9.6%, 15.5%, and 27.9% of patients 50-59, 60-69, and 70-79 years of age required hospitalization, respectively (Stokes 2020).

Symptom Onset Within 5 Days: Symptoms of COVID-19 generally appear from 2 to 14 days following exposure to SARS-CoV-2. A subset of individuals with initially mild or moderate symptoms may experience disease progression. For example, in a study of 138 hospitalized patients with COVID-19 pneumonia, dyspnea, and hospitalization developed after a median of 5 and 8 days, respectively, from symptom onset (Wang 2020). These data suggest a window for intervention of <7 days from onset of symptoms with a potently neutralizing antiviral mAb like ADG20 to prevent disease progression. Consistent with this hypothesis, experience with other highly potent mAbs (casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab,

regdanvimab, and bebtelovimab) suggests that administration early in the course of infection (eg, within 5 to 7 days or less of onset of symptoms) is associated with faster resolution of symptoms and a reduction in the need for medically attended visits, including emergency room visits and hospitalizations (Celltrion Healthcare Hungary 2021; Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022).

Adolescent Population: Evidence supporting the efficacy and safety of potential therapeutic agents are urgently needed for the treatment of COVID-19 children and adolescents (Gotzinger 2020). Overall, the symptoms of COVID-19 are similar in adolescents and adults, although the frequency of specific symptoms may vary, and disease is generally less severe in adolescents (Stokes 2020). Although COVID-19 in children is generally mild and the case fatality rate is low, some children progress to severe disease requiring intensive care admission (Gotzinger 2020). Similar to adults, severe outcomes are more common in adolescents with underlying co-morbidities including chronic lung disease, obesity, cardiovascular disease, neurologic/developmental disorders and immunosuppressive conditions (Bixler 2020; Stokes 2020). FDA EUA for SARS-CoV-2 mAbs (bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab) and EMA marketing authorization of casirivimab/imdevimab include adolescent populations at high risk for progressing to severe COVID-19 despite limited clinical data generated for these products in adolescents, underscoring the high unmet need for treatment options for adolescents at risk of severe outcomes (Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022).

The dose regimens of ADG20 under evaluation in this study are expected to result in comparable serum exposures of ADG20 in patients 12 years of age and older and weighing at least 40 kg as observed in adults. For these reasons, adolescents with mild or moderate COVID-19 who are at increased risk for severe COVID-19 will be included in Phase 3 of the study upon sponsor communication to sites after iDMC review of safety data in adults, and only if permitted by the local health authority.

Pregnant and Breastfeeding Women: Pregnant individuals are at an increased risk for severe illness from COVID-19 when compared to non-pregnant individuals and may also be at increased risk for other poor outcomes, such as preterm birth (CDC 2021a). As with other COVID-19 monoclonal antibody products (FDA 2020a; FDA 2021a), no specific risks to pregnant or lactating individuals have been identified based on ADG20 non-clinical safety data. Specifically, in a tissue cross reactivity study using human fetal tissues, no binding of clinical concern was detected for ADG20 (refer to the IB for details). Based on the increased risk for poor COVID-19 outcomes for pregnant individuals and the low assessed risk associated with SARS-CoV-2 mAb administration, pregnant or breastfeeding individuals may be included in the trial upon sponsor communication to sites after iDMC review of safety data, and only in regions permitted by the local health authority. No dosage adjustment of ADG20 is recommended during pregnancy or while lactating.

Use of Placebo Control: In the absence of globally approved and widely available therapies defining a clear standard of care for the treatment of ambulatory patients with COVID-19 at high risk of disease progression, a placebo-controlled trial is appropriate. Despite FDA and/or EMA marketing authorization of bamlanivimab/etesevimab, casirivimab/imdevimab, regdanvimab, sotrovimab, and bebtelovimab for treatment of high-risk patients, the continued emergence of

variants resistant to some available monoclonal antibodies remains a concern, limiting the utility of these agents (see Section 1.2). Additionally, the availability of these treatments in the US and EU remains limited at this time. Similarly, while the antivirals Paxlovid, molnupiravir, and remdesivir have FDA EUA and/or EMA conditional marketing authorization, the availability of these treatments remains limited at this time. Potential study participants will be made aware if these treatments are available in their region, how to access these therapies, and the anticipated activity these treatments may offer against variants of SARS-CoV-2 known to be circulating in their region.

Furthermore, specific designated standard of care may be provided to patients in this study, as appropriate, as described in Section 5.6.2.3 and the *ADG20-TRMT-001 Designated Background Standard of Care* document, which outlines prohibited and allowed concomitant medications. For participants who become hospitalized due to COVID-19, treatment of COVID-19 as deemed appropriate is acceptable.

Safety assessment and duration of follow-up: As a precaution for acute worsening of disease, hypersensitivity, and ISRs, participants will be observed after study drug administration as described in Section 6.4.1. In-clinic monitoring post-dosing will include frequent assessment of vital signs and is considered appropriate for IM injection of a fully human mAb targeted to the spike glycoprotein of SARS-CoV-2. Study drug will only be administered in settings in which health care providers have immediate access to medications to treat a severe injection reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary. AESIs will include hypersensitivity reactions occurring through Day 4. Solicited AEs (ISRs) will be monitored through Day 4 via patient-reported diary. Long term safety follow-up will continue through 14 months postdose (or approximately 5 half-lives). This timeframe is considered appropriate due to the preliminary estimate of an extended half-life of ADG20 of approximately 97 days.

Efficacy Endpoints: The primary efficacy endpoint is COVID-19-related hospitalization or all-cause death through Day 29. This endpoint evaluates clinically relevant measures for mild and moderate COVID-19 over a relevant duration of time. Development of severe or critical COVID-19, a key secondary endpoint, will be evaluated using pre-specified disease severity definitions and will provide a systematic estimate of disease progression from mild or moderate COVID-19 (required for study entry) to a worse severity. A secondary endpoint is the time to sustained resolution of COVID-19 symptoms through Day 29. Although recovery from COVID-19 is variable, Day 29 is an appropriate time period for assessment of resolution of COVID-19 based on published findings suggesting that resolution of mild infection occurs over a period of approximately 2 to 3 weeks (WHO 2020). Data from SARS-CoV-2 mAb trials enrolling a similar population further support the Day 29 assessment period, with the majority of patients experiencing symptom resolution in <14 days (Celltrion Healthcare Hungary 2021; Eli Lilly and Company 2022a; GlaxoSmithKline 2022; Regeneron 2022).

1.3.2.1. Rationale for Dose Selection

ADG20 will be administered IM at a dose of 300 mg in this study. This dose was selected upon consideration of the ADG20 target and mechanism of action, in vitro/in vivo toxicology data, the no observed adverse-effect level observed in the pivotal toxicology study, and estimations of

human PK projected using a QSP whole-body PBPK model. Human PK projections were used to determine safety margins based on exposures anticipated from the proposed dose.

The QSP/PBPK model was used to support dose selection. Preliminary early PK data from the healthy volunteer study (Phase 1; ADG20-1-001) described in Section 1.1.2 indicate ADG20 pharmacokinetics following IM administration of a single 300 mg dose are consistent with the QSP/PBPK model predictions, providing support for use of the model for dose selection.

Three complementary modeling approaches were used to support the dose selected for study: 1) the ability of ADG20 to attain rapid, near complete (>90%), and durable (28 days) SARS-CoV-2 occupancy in the lung upper airway ELF; 2) the ability of ADG20 to maintain serum neutralizing antibody titer >500, a value associated with therapeutic efficacy in a non-human primate (NHP) treatment study (McMahan 2021), and 3) the ability of ADG20 to maintain ELF in concentrations relative to a concentration associated with 100% viral growth suppression in a post-infection assay.

Following a 300 mg IM ADG20 dose, greater than 90% of simulated patient exposures are predicted to result in near complete SARS-CoV-2 receptor occupancy within approximately 5 hours of ADG20 administration. High receptor occupancy is associated with efficacy for viral receptor antagonists, such as ADG20 (Demarest 2008; Muller 2009; Emu 2018). Moreover, with the 300 mg IM ADG20 dose regimen, greater than 90% of simulated patients are predicted to maintain serum neutralizing antibody titers >500-fold the in vitro IC_{50} (as a proxy for neutralizing antibody titers >500) for a minimum of 28 days, a target associated with efficacy in a nonhuman primate treatment adoptive transfer model (McMahan 2021). Finally, following a 300 mg IM dose, over 90% of simulated patients are to maintain ADG20 concentrations exceeding that required for 100% viral growth suppression in a post-infection assay. For details regarding the modeling and simulation, refer to the IB.

Preliminary analysis of sVNA titers from healthy volunteers receiving a single 300 mg IM dose of ADG20 in Study ADG20-1-001 further supports selection of this dose. Geometric mean (CV%) serum 80% (MN80) and 50% (MN50) neutralization titers of 130 (177%) and 346 (122%), respectively, were achieved within 24 hours of ADG20 administration and were 569 (43.8%) and 1382 (32.7%), respectively, at Day 13 post-injection. These data confirm the ability of ADG20 to rapidly attain potentially efficacious sVNA titers and to maintain them above the target threshold for at least 13 days post administration.

ADG20 dose selection for treatment of ambulatory patients with mild to moderate COVID-19 was also guided by results from Phase 2 dose ranging studies evaluating the safety and efficacy of casirivimab/imdevimab, a SARS-CoV-2 spike targeting mAb product with similar potency as ADG20, in a similar patient population (Weinreich 2021). Clinical data from this product suggest a favorable benefit/risk profile if administered early in the course of illness. Based on these data, casirivimab/imdevimab was granted EUA at a dose level of 2400 mg (1200/1200 mg) (Regeneron 2022). A more recent study evaluating lower dose regimens of casirivimab/imdevimab demonstrated similar clinical efficacy between 2400 mg (1200/1200 mg) and 1200 mg (600/600 mg) IV dose levels. In a separate study, the antiviral effect of several different casirivimab/imdevimab regimens (IV: 2400 mg, 1200 mg, 600 mg and 300 mg; SC: 1200 mg and 600 mg) was evaluated (Roche 2021). All tested doses met the primary endpoint, rapidly and significantly reducing patients' viral load (log_{10} copies/mL) compared to placebo

(p<0.001) with each dose demonstrating similar efficacy, including the lowest doses tested (IV: 300 mg; SC: 600 mg). Similar to the modelled ADG20 300 mg IM dose regimen in simulated patients, the modelled imdevimab 600 mg SC regimen (as a proxy for casirivimab/imdevimab 300/300 mg SC given similar PK and spike protein affinity of these two mAbs) maintained serum neutralizing antibody concentrations >500 for greater than 28 days in >90% of simulated patients.

Preliminary safety and PK data from the Phase 1 Study ADG20-1-001 further supports the appropriateness of the 300 mg IM dose regimen (see Section 1.1.2). Given the safety profile described in healthy volunteers and the prospect for benefit in the setting of acute treatment, the potential benefit of the 300 mg IM dose regimen outweighs the potential risk to patients.

The dose level is fixed, with no dose adjustment recommended for body weight, renal impairment, or mild to moderate hepatic impairment. Similarly, no ADG20 dose adjustment is warranted in adolescents (12 to <18 years of age) weighing at least 40 kg.

In conclusion, based on this analysis, a single dose level of 300 mg ADG20 administered IM will be evaluated in ADG20-TRMT-001. The 300 mg IM dose is supported by: 1) ability to rapidly achieve antibody concentrations in the respiratory compartments to result in near complete and durable SARS-CoV-2 spike protein receptor occupancy; 2) ability to maintain serum neutralizing antibody titers associated with efficacy in a NHP treatment adoptive transfer model for 28 days; 3) ability to maintain concentrations in the respiratory compartments that are associated with 100% viral growth suppression in vitro; 4) the ability to be safely administered as a single injection; and 5) the potential advantages to patients, healthcare providers and healthcare systems of an IM dosing formulation for outpatient therapy. For additional details regarding dose selection, refer to the IB.

1.4. Risks and Benefits

1.4.1. Target Study Population and Risk/Benefit Assessment

The target populations for this study are ambulatory adults and adolescents with mild or moderate COVID-19 and at high risk of disease progression based on age (≥55 years) and/or preexisting medical conditions (eg, obesity, type 2 diabetes, chronic kidney or lung disease, immunocompromised, pregnancy, etc.) as defined in Section 4.1.1 (CDC 2021a). Enrollment of participants who are pregnant or breastfeeding may only open upon sponsor communication to sites after iDMC review of safety data, and only in regions permitted by the local health authority.

These populations that are at high risk for progression of COVID-19 are likely to benefit from treatment with a mAb. It is notable that clinical experience with other mAbs against the SARS-CoV-2 spike protein suggests potential clinical benefit in ambulatory patients with mild or moderate COVID-19 (Celltrion Healthcare Hungary 2021; Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022).

1.4.2. Risks from Study Participation

Because ADG20 targets an exogenous epitope (spike protein) that is not present in humans, significant safety issues due to off-target effects are not expected. No safety concerns for ADG20

have been identified in data generated across the ADG20 clinical development program to date (see Section 1.1.2). The anticipated safety risks are those common to the mAb therapeutic class and include ISRs and, rarely, hypersensitivity reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia. Most mAb administration-related reactions occur within the first 24 hours after administration. Severe reactions are rare and are more often associated with mAbs targeting human proteins rather than exogenous targets. As a precaution for acute injection reactions, study drug will only be administered in settings in which health care providers have immediate access to medications to treat severe injection reactions, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary. Refer to the IB for further clinical safety information.

Risks associated with large-volume IM injections include but are not limited to bleeding, nerve damage, hematoma, and infection. These risks will be mitigated by clear instructions regarding the injection site and technique as detailed in the Pharmacy Manual.

Experience with mAbs directed against cell surface targets, particularly on lymphocytes, has been associated with cytokine release syndrome (Bugelski 2009). Cytokine release syndrome reactions have been attributed to lysis of the target cells and generally present within the first few hours following the first administration as the target cell burden is greatest under these conditions. Therefore, as a precaution for acute worsening of disease, hypersensitivity, and ISRs, participants will be observed after study drug administration as described in Section 6.4.1.

There is a risk that receipt of a SARS-CoV-2 mAb such as ADG20 may result in a decreased immune response (ie, effectiveness) to COVID-19 vaccines during the period when ADG20 remains at significant concentrations in the body. The Advisory Committee on Immunization Practices (ACIP) originally recommended delaying COVID-19 vaccination for 90 days (approximately 2.5 half-lives based on authorized mAbs) after receipt of a SARS-CoV-2 mAb product. On 11-Feb-2022, ACIP updated its guidance based on recent data (Benschop 2021) and no longer recommends a delay in vaccination after the receipt of a SARS-CoV-2 mAb (CDC 2022).

There is a theoretical risk that receipt of a mAb against SARS-CoV-2 may cause a paradoxical increase in disease severity. This phenomenon, known as ADE of disease, is based on the rare occurrence of vaccine-associated disease enhancement, which was first seen in the 1960s with two formalin-inactivated whole virus vaccines designed to protect children against infection with respiratory syncytial virus (Chin 1969) or measles (Fulginiti 1967). Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas 2019; WHO 2019). ADE is thought to be the consequence of low affinity or cross-reactive antibodies that bind to viral entry proteins but have limited or no neutralizing activity or suboptimal titers of otherwise potentially neutralizing antibodies.

Available data suggests a low risk of ADE with the use of ADG20 in the treatment of acute COVID-19. Nonclinical studies of ADG20 demonstrated no increased viral uptake by FcγR-expressing cells across a range of ADG20 concentrations, including sub-neutralizing concentrations. Clinical experience with other highly potent mAbs against the SARS-CoV-2 spike protein suggests a favorable benefit/risk profile in ambulatory patients with early COVID-19 (Celltrion Healthcare Hungary 2021; Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022). Of note, a warning has been

provided within the EUA fact sheets for bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and bebtelovimab regarding potential clinical worsening of COVID-19 after administration, which may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (eg, atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. It is not known if these events were related to use of the mAbs or were due to progression of COVID-19 (Eli Lilly and Company 2022a; Eli Lilly and Company 2022b; GlaxoSmithKline 2022; Regeneron 2022). These data suggest that ADE-mediated immune complex deposition or release of pathogenic cytokines upon antibody administration in the presence of high viral load is low with ADG20. To monitor the risk of enhanced disease in this study, the incidence and severity of COVID-19 cases will be monitored and reviewed by the iDMC.

1.4.3. Overall Benefit-Risk Conclusion

The participants in this study will be included based on a diagnosis of mild or moderate COVID-19 and the presence of clinical factors that indicate a high risk of disease progression. Based on currently available data, this population is likely to derive the greatest benefit from early therapy designed to reduce the risk of disease progression.

Considering the paucity of approved therapies for the treatment of COVID-19, the limited availability of these treatments in many regions, the widespread emergence of SARS-CoV-2 variants resistant to some antibody-based therapies, and the safety profile of ADG20 across the clinical development program to date, the overall benefit-risk assessment for this study is considered favorable for treatment of disease due to variants for which a dose of 300 mg IM is anticipated to provide adequate tissue exposure. Notably, ADG20 has been shown to bind to and neutralize multiple SARS-CoV-2 variants, as detailed in the IB.

2. STUDY OBJECTIVES, ENDPOINTS, AND DEFINITIONS

2.1. Objectives and Endpoints

The objectives and endpoints are presented in Table 2-1.

Table 2-1: 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 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 as data permit
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; NP=nasopharyngeal; PASC=post-acute sequelae of SARS-CoV-2 infection; 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.

2.2. Definitions

2.2.1. SARS-CoV-2 Variant Determination

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, as detailed in the SAP. A final clinical and virological review (adjudication as needed) may be performed.

2.2.2. COVID-19 Severity Categorization

The following COVID-19 severity categorizations are adapted from the FDA COVID-19 Developing Drugs and Biological Products for Prevention or treatment Guidance for Industry (FDA 2021b). Only participants with mild and moderate disease severity are eligible for study participation. Progression to severe or critical disease will be evaluated as a secondary endpoint.

Mild COVID-19 is defined as having a positive test by standard RT-PCR assay or equivalent test plus the following:

- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, or gastrointestinal symptoms, **without shortness of breath or dyspnea.**

- Respiratory rate <20 breaths per minute and heart rate <90 beats per minute.
- No clinical signs indicative of moderate, severe, or critical illness severity.

Moderate COVID-19 is defined as having a positive test by standard RT-PCR assay or equivalent test plus the following:

- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or **shortness of breath <u>with exertion</u> worse than usual**.
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, with SpO_2 >93% on room air at sea level, or heart rate ≥90 beats per minute.
- No clinical signs indicative of severe or critical illness severity.

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 <u>at rest</u>**, 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 the following:

- 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.
  - Multi-organ 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.

2.2.3. COVID-19-Related Medically Attended Visits

COVID-19-related medically attended visits include in-person or telemedicine visits not specified by the protocol. These include unscheduled in-person or telemedicine visits conducted by the investigator for the purposes of evaluating worsening signs or symptoms attributed to COVID-19 or emergency room, urgent care center or physician office visits, or hospitalization for attention to worsening signs or symptoms attributed to COVID-19, in the opinion of the investigator.

2.2.4. COVID-19-Related Hospitalization

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).

2.2.5. COVID-19-Related Mortality

COVID-19-related mortality is defined as death directly due to COVID-19 or any death in which COVID-19 or COVID-19 complications contributed to the death, as determined by the investigator, a formal autopsy report or death certificate.

2.2.6. Time to Sustained Resolution of COVID-19 Symptoms

The following assessed COVID-19 symptoms will be included in the time to event analysis: fever, chills, cough, sore throat, congestion, shortness of breath/difficulty breathing at rest, shortness of breath/difficulty breathing with exertion, muscle or body aches, fatigue, headache, nausea, vomiting, and diarrhea. Loss of taste/smell is not considered in this analysis.

Time to sustained resolution of COVID-19 symptoms is 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.

3. INVESTIGATIONAL PLAN FOR ADG20-TRMT-001 PROTOCOL

3.1. Study Design

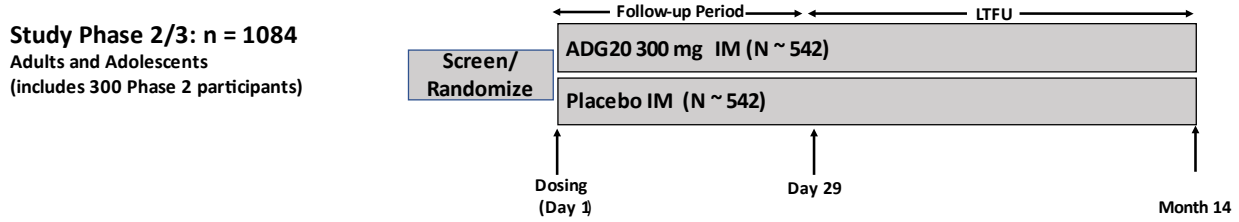
This is a randomized, double-blind, placebo-controlled, multi-center adaptive study of the mAb ADG20 in the treatment of ambulatory participants with mild or moderate COVID-19. The study will evaluate the safety, efficacy, PK, and antiviral activity of ADG20 versus placebo. A total of approximately 1084 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 administered by IM injection. Randomization will be stratified by 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 Section 6.4.1. The iDMC will review available safety data as described in Section 6.4.1 and will provide recommendations regarding the duration of monitoring, which will be formally communicated to sites without a protocol amendment. After Day 1, participants will be followed via telemedicine visits, phone calls, or in-person visits through Month 14 as indicated in the Schedule of Assessments (Table 12-1). See Section 6 for details on the assessments and procedures for this study.

Figure 3-1: Study Design Schematic for ADG20-TRMT-001



IM=intramuscular; LTFU=long-term follow-up
Note: Screening may be performed prior to randomization on the same day as study drug dosing. Randomization is stratified by age and country. The Schedule of Assessments is presented in Table 12-1.

This study will enroll approximately 1084 participants total in 2 phases (Figure 3-1).

- Phase 2: Enrolling approximately 300 adult participants to evaluate initial safety, efficacy, PK, and antiviral activity of ADG20 300 mg IM versus placebo in adults prior to enrolling additional participants in Phase 3.
- Phase 3: Enrolling an additional 784 adult and adolescent participants (to reach the total sample size of 1084 for Phase 2/3), to evaluate efficacy, safety, PK, and antiviral activity of ADG20 300 mg IM versus placebo in adults and adolescents. There is no planned enrollment pause between Phase 2 and 3.

At the recommendation of the iDMC following review at approximately n=200 and upon sponsor communication to sites, enrollment of adolescents will open only in regions permitted by health authorities and local ethics committees. Pausing guidelines triggering iDMC ad hoc reviews are described in Section 10.11.

Database locks and interim analyses will occur as described in Section 5.5 and Section 7.13.

3.1.1. Study Duration

The study duration for each participant will be approximately 14 months. Each participant will receive a single dose of study drug 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 Month 6.

4. PARTICIPANT SELECTION AND WITHDRAWAL CRITERIA

4.1. Selection of Study Participants

The study population will include adults (aged ≥18 years) and adolescents (aged 12 to <18 years) in both cohorts; enrollment of adolescents will begin upon sponsor communication to the sites following iDMC review of safety data in each cohort, and only in regions permitted by health authorities and local ethics committees. Participants with laboratory confirmed mild or moderate COVID-19 who are at high risk for disease progression will be included.

Participants will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because of their potential to jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the eligibility criteria as specified in the protocol is required.

4.1.1. Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Age: Is an adult aged 18 years and above, or is an adolescent aged 12 to 17 years (inclusive) and weighing ≥40 kg at the time of screening

   Note: Adolescent enrollment will open only upon sponsor communication to sites after iDMC review of safety data in adults, and only if permitted by the local health authority.

2. Has had a SARS-CoV-2 positive antigen test, or by RT-PCR, or other locally approved molecular diagnostic assay obtained within 5 days prior to randomization.

   Note: A historical record of a positive result from a test conducted within 5 days prior to randomization is acceptable. SARS-CoV-2 antibody testing cannot be used for study eligibility.

3. Has had initial onset of one or more of the following self-reported COVID-19-related signs or symptoms within 5 days prior to randomization:
   a. measured temperature ≥38 °C (100.4 °F)
   b. subjective fever (feeling hot or feverish)
   c. chills (shivering)
   d. cough
   e. sore throat
   f. congestion (stuffy or runny nose)
   g. shortness of breath or difficulty breathing with exertion worse than usual
   h. muscle or body aches
   i. fatigue (low energy or tiredness)
   j. headache

k. loss of taste or smell
l. nausea or vomiting
m. diarrhea

4. Has mild or moderate COVID-19 (per Section 2.2.2) with one or more of the following COVID-19-related signs or symptoms on the day of randomization:
   a. measured temperature ≥38 °C (100.4 °F)
   b. subjective fever (feeling hot or feverish)
   c. chills (shivering)
   d. cough
   e. sore throat
   f. congestion (stuffy or runny nose)
   g. shortness of breath or difficulty breathing with exertion worse than usual
   h. muscle or body aches
   i. fatigue (low energy or tiredness)
   j. headache
   k. loss of taste or smell
   l. nausea or vomiting
   m. diarrhea
5. Is at high risk of disease progression defined as:
   a. Age ≥55 years
   b. Age 18 to <55 years with one or more preexisting medical conditions as follows
      i. Obesity (body mass index [BMI] ≥30 kg/m^2)
      ii. Diabetes (Type 1 or Type 2)
      iii. Chronic kidney disease (eGFR calculated by Modification of Diet in Renal Disease [MDRD] of 59 mL/min/1.73 m^2 or less, including end-stage renal disease on hemodialysis)
      iv. Chronic lung disease (emphysema/chronic obstructive pulmonary disease, chronic bronchitis, interstitial lung disease [including idiopathic pulmonary fibrosis], or cystic fibrosis)
      v. Cardiac disease (heart failure, coronary artery disease, or cardiomyopathies)
      vi. Sickle cell disease or thalassemia
      vii. Solid organ or blood stem cell transplant recipients

viii. Other immunodeficiency due to underlying illness or immunosuppressant medication (eg, corticosteroids ≥20 mg/day prednisone or equivalent)

ix. Down Syndrome

x. Stroke or cerebrovascular disease, which affects blood flow to the brain

xi. Substance use disorder

xii. Pregnant (Enrollment of participants who are pregnant may only open upon sponsor communication to sites after iDMC review of data, and only in regions permitted by the local health authority)

c. Age 12 to 17 years (inclusive) with one or more preexisting medical conditions as follows

i. BMI >85th percentile for age and sex based on United States Center for Disease Control (CDC) growth charts

ii. Diabetes (Type 1 or Type 2)

iii. Chronic kidney disease

iv. Sickle cell disease or thalassemia

v. Congenital or acquired heart disease

vi. Neurodevelopmental disorders (eg, cerebral palsy, Down syndrome)

vii. A medically-related technological dependence (eg, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19)

viii. Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

ix. Solid organ or blood stem cell transplant recipients

x. Other immunodeficiency due to underlying illness or immunosuppressant medication

xi. Substance use disorder

xii. Pregnant (Enrollment of participants who are pregnant may only open upon sponsor communication to sites after iDMC review of data, and only in regions permitted by the local health authority)

6. Has been assigned female sex at birth and is of nonchildbearing potential. A female participant who is not of reproductive potential is eligible without requiring the use of contraception and pregnancy testing is not required. This includes female participants who have not undergone menarche or who are documented to be surgically sterile (eg, hysterectomy, or removal of both ovaries, or tubal ligation) or postmenopausal (ie, amenorrhea >1 year and FSH >40 mIU/mL). Follicle-stimulating hormone is not required in postmenopausal females with amenorrhea for >2 years

7. Has been assigned female sex at birth and is of childbearing potential and fulfills all the following criteria:

a. Has a negative urine or serum pregnancy test at Screening

b. Has practiced adequate contraception for or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1)

c. Has agreed to continue adequate contraception for sexual activity that could lead to pregnancy through 6 months following study drug administration

d. Is not currently breastfeeding

Note: Enrollment of participants who are pregnant or breastfeeding may open only upon sponsor communication to sites after iDMC review of Phase 2 data.

Adequate contraception for participants assigned female sex at birth is defined as consistent and correct use of a highly effective locally approved contraceptive method in accordance with local regulations for contraceptive use in clinical trial participants. For example:

a. Intrauterine device (hormonal or non-hormonal)

b. Hormonal contraceptive taken or administered via oral, transdermal, intravaginal, implantable, or injectable method

c. Sterilization of a female participant's monogamous male partner prior to entry into the study

d. Sexual abstinence*

Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

*Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse starting at the time of consent to participate in the study until 6 months after dosing. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

8. Has been assigned male sex at birth with partner(s) of childbearing potential and agree to use contraception, per local regulations, through 6 months after dosing. If their partner is pregnant, males must agree to use a condom. No sperm donation is permitted through 6 months after dosing.
9. Is able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or guardian/LAR) based on the assessment of the investigator.
10. Is able and willing to provide informed consent. An LAR may be used only in cases where inclusion criterion 9 is able to be fulfilled. In the case of adolescents, informed assent must also be obtained as required by local guidelines.

4.1.2. Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Is currently hospitalized or, in the opinion of the investigator, requires urgent medical attention or is anticipated to require hospitalization within 48 hours of randomization.

2. Has oxygen saturation (SpO_2) ≤93% on room air at sea level or ratio of arterial oxygen partial pressure (PaO_2 in millimeters of mercury) to fractional inspired oxygen (FiO_2) <300 mmHg, respiratory rate ≥30 per minute, or heart rate ≥125 per minute.
3. Is on supplemental oxygen therapy at the time of randomization for any reason or, in the opinion of the investigator, has an anticipated impending need for mechanical ventilation.
4. Has a history of a positive SARS-CoV-2 antibody serology test. Note: serology testing is not required for study eligibility, exclusion criterion is based on known history only.
5. Has participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
6. Has known allergy/sensitivity or hypersensitivity to study drug, including excipients.
7. Has received a SARS-CoV-2 vaccine, monoclonal antibody, or plasma from a person who recovered from COVID-19 any time prior to participation in the study.
8. Has a known active co-infection (eg, influenza, urinary tract infection, etc).
9. Has any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the participant by their participation in the study including, but not limited to, any co-morbidity requiring surgery or conditions considered life-threatening within 29 days.
10. Has a clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture. Abnormal coagulation labs or use of anticoagulant medication are not exclusionary in the absence of clinical findings.
11. Is or has an immediate family member (eg, spouse, sibling, child, guardian/LAR, parent) who is an investigator or site or sponsor staff (or designee) directly involved with the study.

4.1.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomly assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information 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.

4.2. Discontinuation of Study Drug or Withdrawal from the Study

4.2.1. Premature Discontinuation from Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue study drug. Premature discontinuation does not require or represent discontinuation from the study.

In the event of study drug discontinuation for safety reasons or participant refusal, the participant should remain in the study until all protocol-specified procedures and assessments are completed through the EOS Visit at Month 14. If a participant was randomized but did not receive study drug, these assessments are not required; however, the participant must be followed for efficacy endpoints through Day 29, unless the participant has withdrawn from the study. The estimated dose of study drug received prior to discontinuation will be documented.

Reasons for premature discontinuation from study drug administration must be recorded in the eCRF and may include, but are not limited to, the following:

- Occurrence of an AE that, in the opinion of the investigator, warrants the participant's permanent discontinuation from study drug administration.
- Participant refusal to continue study drug administration.

4.2.2. Premature Withdrawal from the Study

Participants may withdraw from the study at any time and for any reason, without prejudice to their future medical care, by the investigator or at the study site. Every effort should be made to keep participants in the study.

A participant will be considered to have completed the study when the Month 14 Follow-up Visit is completed. If a participant/guardian/LAR/sponsor 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 visit 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 is completed) as shown in Table 12-1.

As permitted by local guidelines, survival status should be reported through Month 14 for participants who received study drug but withdrew from study participation, including survival status or death available via public records (eg, death certificates or public registers), medical records, participant, or participant contacts, unless the participant has expressly withdrawn consent for survival follow up.

If a participant/guardian/LAR/sponsor chooses to withdraw a participant from the study prior to completion, the investigator must be informed immediately and the reason for withdrawal is to be recorded in the eCRF. The primary reason for premature withdrawal from the study should be selected from the following standard categories:

Death: The participant died.

Participant's Request: The participant is unable to continue to participate in the study but does not withdraw consent. If the participant gives a reason, this reason must be recorded in the eCRF.

Withdrawal of Consent: The participant desired to withdraw from further participation in the study absence an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it must be recorded in the eCRF.

Note: If the participant withdraws consent for disclosure of future information, the sponsor may retain, and continue to use, any data collected before such a withdrawal of consent. If a

participant withdraws from the study, they may request destruction of any samples taken that were not tested, and the investigator must document this in the site study records.

Lost to Follow-up: The participant stopped coming for visits and study personnel were unable to contact the participant.

Note: This reason for withdrawal should not be selected until the last scheduled visit for the participant has been missed. In the event the site is unable to contact the participant for telemedicine visit, or the participant fails to have an in-clinic or home health visit, site personnel must attempt to reschedule the visit. Site personnel must make efforts to contact the participant for each scheduled visit. Attempts to contact the participant must be documented and may include, but are not limited to, telephone calls or letters to the last known telephone number or address.

Other: The participant was withdrawn from the study for a reason other than those listed above, such as termination of study by the sponsor.

4.2.3. Replacements

Participants who prematurely discontinue from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Method of Assigning Participants to Treatment Groups

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

- ADG20 300 mg administered IM
- Placebo administered IM

Randomization will be assigned in a blinded manner using an 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 (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.

5.2. Treatments Administered

An unblinded pharmacist (or locally qualified designee) will prepare the study drug or placebo for administration. After randomization, participants will receive either a single 300 mg dose (up to 3 mL) of ADG20 or matching placebo administered via IM injection.

Refer to the instructions provided in the Pharmacy Manual for preparing and administering ADG20 and placebo dosing solutions.

5.3. Identity of Study Drug

ADG20 is a fully human IgG1 targeted to an epitope in the RBD of the spike glycoprotein of SARS-CoV-2. Details for the study drug and placebo are shown in Table 5-1.

Table 5-1: Details for Study Drug

	Preparations to be Administered	
	Study Drug	**Placebo**
Study Drug Name	ADG20	Normal saline
Manufacturer	WuXi Biologics	Commercially available
Sourcing	Provided centrally by the sponsor	Sourced locally or provided by sponsor depending on regional requirements
Packaging and Labeling	Provided in glass vials within a carton. Each carton and vial will be labeled per country requirement.	Not applicable
Formulation	ADG20, 20 mM L-histidine, 150 mM sodium chloride, 0.01% polysorbate 80, pH 6.5	0.9% (weight/volume) sodium chloride (normal saline)
Dosage Form	Solution for Injection 100 mg/mL	Solution for Injection
Route of Administration	IM	IM
Dose and Frequency	300 mg IM once	Matched volume and route

5.4. Management of Clinical Supplies

5.4.1. Study Drug Packaging and Labeling

ADG20 drug product will be supplied in glass vials as a sterile, preservative-free solution. ADG20 drug product vials are supplied to the study site in a tamper-evident sealed and labeled carton. Each carton and vial will be labeled per country requirement.

The placebo is commercially available 0.9% sodium chloride (normal saline) injection, which meets the criteria of the USP.

Prepared doses of study drug and placebo will be labeled by study site staff according to the Pharmacy Manual.

5.4.2. Storage and Handling Instructions

Study drug must be stored in a secure, environmentally controlled, and monitored area in accordance with the storage conditions described in the Pharmacy Manual, with access limited to the unblinded pharmacist (or locally qualified designee) and authorized site staff.

ADG20 will be shipped to the study site; temperature will be monitored throughout the transit period, and temperature tracings will be available for review upon receipt. The investigator or designee must confirm the appropriate temperature conditions have been maintained during transit for all study drug received per the Pharmacy Manual, and any discrepancies must be

reported and resolved before use of the study drug. ADG20 must be stored according to the Pharmacy Manual.

Placebo (normal saline) will be stored and handled at the study site under conditions specified by the manufacturer.

Refer to the Pharmacy Manual for preparing and administering ADG20 and placebo dosing solutions and any special handling instructions.

5.4.3. Study Drug Accountability

Participants will be dosed at the study site and will receive the study drug directly from the investigator or locally qualified designee. The date and time of each dose administered at the study site will be recorded in the source documents and recorded in the eCRF.

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept by unblinded site personnel, including when, and how much, study drug is prepared and administered to each participant in the study. Only participants enrolled in the study may receive study drug and only authorized site personnel may supply or administer study drug. Reasons for departure from the expected preparation and administration of study drug must also be recorded. Upon completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

5.5. Blinding

The study will be double-blind. The investigator, participant, all clinical site staff, and sponsor personnel or delegates (except as detailed below) involved in study drug administration and evaluation will be blinded to study drug assignments on the participant level. Investigators and participants will remain blinded to each participant's assigned study drug throughout the study. Sponsor personnel (or designees) will become unblinded as described below. An iDMC will review data in an unblinded manner as described in Section 10.11 and in the iDMC Charter.

The efficacy and short-term safety analyses will be performed at the time of the database soft lock. Participants will be followed through the Month 14 visit or discontinuation from study. After the soft lock, all participants, site staff, and sponsor personnel (or designees) working directly with the site will remain blinded to the individual study drug assignment until the final database lock. The final database lock will occur after all participants have been followed through Month 14/EOS (or if it is known that the Month 14 visit will not occur). Subsequently, unblinded analysis of data through Month 14/EOS will be performed. Plans for additional data locks or analyses may be revised during the study to adapt to unexpected issues in study execution and/or data that affect planned analyses and/or to address regulatory authority request, and/or to address protocol amendments.

Vials of ADG20 and normal saline (0.9% sodium chloride injection, USP) will be unblinded to the study pharmacist (or locally qualified designee), who will prepare the study drug and placebo. All other site staff, sponsor personnel (or designee) working directly with the site staff,

and participants will remain blinded to each participant's assigned study treatment throughout the study.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel, including blinded sponsor personnel.

In the event of a quality assurance audit, the auditor(s) may be permitted access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately. However, any findings will be reported in a blinded manner.

Further details will be included in the study's unblinding plan.

5.5.1. Breaking the Blind

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

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. To the extent possible before unblinding, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that participant. The treatment assignment will be unblinded through IRT. Reasons for treatment unblinding must be clearly explained and justified in the source documentation. The date on which the code was broken together with the identity of the person responsible must also be documented. If a participant's study treatment assignment is unblinded, the sponsor or designee must be notified within 24 hours after breaking the blind without revealing the study treatment.

The study specific IRT Manual will provide contact information and additional details on the use of the IRT system.

5.6. Prior and Concomitant Medications and Treatments

5.6.1. Prior Therapy

Information about prior medications, (including any prescription or OTC medications, vaccines, or blood products), taken by the participant within the 30 days before dosing (Day 1) must be recorded at Screening and predose on Day 1. Refer to exclusion criteria (Section 4.1.2) for prohibited prior therapies.

5.6.2. Concomitant Therapy

All concomitant medications and treatments, defined as those taken after dosing with study drug, will be recorded in the participant's eCRF.

As a minimum requirement, drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications.

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). See the Schedule of Assessments (Table 12-1). Any changes in concomitant medications also will be recorded in the participant's eCRF.

5.6.2.1. Prohibited Concomitant Therapy

If a participant receives a prohibited concomitant medication, such as those listed below, the investigator, in consultation with the sponsor or designee, will evaluate any potential impact on receipt of study drug based on time the medication was administered, the medication's pharmacology and PK, and whether the medication will compromise the participant's safety or interpretation of the data.

The following medications are prohibited concomitant therapy. The use of prohibited concomitant medications and/or vaccines will not require withdrawal of the participant from the study.

The following agents are prohibited from randomization to Day 29:

- Investigational agents or off-label use of marketed products for the treatment of SARS-CoV-2 or COVID-19 (eg, convalescent plasma, direct acting antivirals, etc)

  Note: Please refer to the *ADG20-TRMT-001 Designated Background Standard of Care* document for all prohibited therapies. This document will be updated in an ongoing manner to address changes in standard of care as additional information becomes available, such as from randomized controlled trials.

- Monoclonal antibodies to SARS-CoV-2
- Direct-acting antivirals for SARS-CoV-2 (eg, molnupiravir, nirmatrelvir/ritonavir, remdesivir)

  Note: For participants who become hospitalized due to COVID-19, products for the treatment of SARS-CoV-2 or COVID-19 and/or participation in investigational treatment studies is permitted. This includes other monoclonal antibody products and direct-acting antiviral agents. 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). Rescue therapy for participants who are not hospitalized may be used at the discretion of the investigator if felt to be in the best interest of the participant.

- Receipt of any SARS-CoV-2 or COVID-19 vaccine prior to randomization and through Day 29 is prohibited.
- Any investigational agent or device is prohibited through 90 days after study drug administration (see note above for participants who become hospitalized).

The sponsor or designee must be notified as soon as possible of any instances in which prohibited therapies are administered.

5.6.2.2. COVID-19 Vaccination

Receipt of any SARS-CoV-2 or COVID-19 vaccine prior to randomization and through Day 29 is prohibited.

Adagio and its investigators have the responsibility to inform potential participants (or LAR/guardian) that mAb treatment may interfere with vaccine effectiveness. The ACIP originally recommended that COVID-19 vaccination be delayed for 90 days post-dosing of mAb products. However, based on recent data (Benschop 2021), the ACIP no longer recommends delaying COVID-19 vaccination after receipt of a SARS-CoV-2 mAb product (CDC 2022).

Participants should be made aware of the following:

1. Participants are encouraged to remain in the study for the full duration even after receipt of a COVID-19 vaccination (regardless of blinding status).
2. Participants will be encouraged to follow local or national guidelines regarding if and when they should receive a COVID-19 vaccine.
3. Participants should notify study staff if they plan to receive a COVID-19 vaccine. The study staff will discuss the potential risks and benefits of vaccination after receiving ADG20.

5.6.2.3. Allowed Concomitant Therapy

The following are allowed concomitant therapies:

- Supportive care for the management of COVID-19 signs and/or symptoms (such as anti-inflammatory and antipyretic agents).
- Only specific Designated Background Standard of Care therapeutics for the management of COVID-19 may be maintained in all treatment arms. Please refer to the *ADG20-TRMT-001 Designated Background Standard of Care* document, which will be updated in an ongoing manner to address changes in standard of care as additional information becomes available, such as from randomized controlled trials.
  - If the standard of care per regional or site written guidelines or policies (that is, not just an individual clinician's decision) conflict with the study Designated Background Standard of Care, sites should consult with the sponsor or designee.
  - See note in Section 5.6.2.1 regarding participants who become hospitalized due to COVID-19 or have a COVID-19-related medically attended visit.
- Participants may take concomitant medications for the treatment of adverse events.
- Participants may take concomitant medications prescribed by their primary care or other provider for management of chronic medical conditions and/or for health maintenance. Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.

It is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

6. STUDY ASSESSMENTS AND PROCEDURES

Before any study procedures are performed, the participant/guardian/LAR must provide written informed consent. In the case of adolescents, informed assent must also be obtained as required by local guidelines. Additional procedural details related to the ICF are provided in Section 9.3. The amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be no more than approximately 200 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participants will be dosed and monitored in clinic on Day 1 as described in Section 6.4.1.

During the Follow-Up Period, participants will be followed via telemedicine visits or in-person visits (in-clinic or home health) through Day 29 as outlined in the Schedule of Assessments (Table 12-1) for safety, PK, virology, and efficacy assessments. In the event that a participant is hospitalized during the Follow-Up Period, all procedures and assessments described in Table 12-1 should be continued if feasible. Visits or assessments that are not performed or are performed late due to hospitalization will not be considered protocol deviations.

The Schedule of Assessments is provided in Table 12-1. Sections 6.1 and 6.2 describe Screening and Day 1 procedures. The remainder of Section 6 describes requirements related to each of the activities outlined in the Schedule of Assessments that are common across several visits.

6.1. Screening Procedures

Participants may be randomized on the same day as Screening. After the completion of the screening assessments, eligible participants will be randomized.

Additional requirements for screening procedures are provided below.

- **Review of participant eligibility** based on study inclusion/exclusion criteria (Section 4.1.1 and Section 4.1.2) will be completed during screening. All screening assessments must be reviewed to confirm participant eligibility. Any inclusion criteria with laboratory values associated (eg, eGFR, FSH, etc) should be based on local laboratory results or most recent medical record.
  - **Confirmation of eligibility** should be conducted on the day of randomization in case participant eligibility changes, eg, disease severity worsens to meet exclusion criteria. Site personnel will document details of all reasons for screen failures.
- **Medical history** documentation will include all medical conditions, surgeries, or drug allergies within the prior year. Participant risk factors meeting inclusion criterion 5 and the date of COVID-19 self-reported symptom onset will also be documented.
- **Demographic data** collection will include age, sex, and race where locally permitted.
- **Complete physical exam and vital signs**, including SpO_2, are to be completed per Section 6.4.3 and Section 6.4.5.
- **A urine or serum pregnancy test** (for women of childbearing potential) must be performed within 24 hours prior to study drug administration.

- **Documentation of positive SARS-CoV-2 local testing result**, specimen type, assay type, and date of the test will be recorded in the eCRF. SARS-CoV-2 positive antigen, RT-PCR, or other locally approved molecular diagnostic assay must have been obtained within 5 days prior to the date of randomization (the day of randomization is not considered in the calculation of 5 days). A historical record of a positive result from a test conducted within 5 days prior to randomization is acceptable. SARS-CoV-2 antibody testing cannot be used for study eligibility.

6.2. Day 1 Procedures

Perform all Day 1 procedures as outlined in the Schedule of Assessments (Table 12-1). This section describes details regarding only the participant education and participant activities performed under observation on Day 1.

On Day 1, prior to study drug dosing site staff will provide participant study supplies and education to participants (guardians/LARs) regarding the following procedures to be completed by the participants at home and information about seeking medical care:

- Saliva collection and packaging for transport to site
- Daily measurement and documentation of body temperature, SpO_2, and heart rate using provided thermometer and pulse oximeter
- Daily COVID-19 Symptom Diary (Appendix 12.2)
- Injection Site Reaction Diary, including showing participants how to use the measuring device (Appendix 12.3)
- Educate participants (guardians/LARs) to seek emergency medical care if emergency warning signs for COVID-19, such as trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, bluish lips or face, should develop.
- Educate participants (guardians/LARs) regarding recognizing and reporting potential hypersensitivity reactions to site staff after study drug administration, including but not limited to urticaria, edema, respiratory distress, anaphylaxis, and allergic reactions.

On Day 1, under observation by site staff, participants will:

- Provide a saliva sample for SARS-CoV-2 testing *prior to study drug dosing*
- Complete the daily COVID-19 Symptom Diary *prior to study drug dosing*
- Measure and document body temperature, SpO_2, and heart rate prior to study drug dosing using the thermometer and pulse oximeter provided for at-home use
- Demonstrate understanding of how to use measuring device and how to document IM Injection Site Reaction Diary (Appendix 12.3). At the end of the postdose monitoring period at the site, participants will complete the Day 1 ISR prior to departing the clinical site.

6.3. Efficacy Assessments

6.3.1. Participant At-Home Assessments/Collections

6.3.1.1. Daily COVID-19 Symptom Diary

Participants will be asked to complete the COVID-19 Symptom Diary (includes global impression questions) daily from Day 1 to Day 29 (Appendix 12.2). Site staff will educate the participant on the use of the COVID-19 Symptom Diary and will observe the participant completing the COVID-19 Symptom Diary on Day 1 prior to study drug administration.

The diary should be completed around the same time each day documenting each symptom at its worst in the prior 24 hours. Targeted symptoms and overall health status questions included in the diary are outlined in Appendix 12.2. If a participant is unable to complete the COVID-19 Symptom Diary on their own, a parent/guardian/LAR/family member/other caregiver may assist in completion of the diary and should be educated on diary completion. When asking the participant the Diary questions, the exact language provided in the Diary should be used and the person assisting should not lead the participant or elaborate. Proxy reporting by an observer (eg, parent) on behalf of the participant should not be used. Only participant reported symptoms should be captured in the diary.

Additionally, site staff may interview the participant via telemedicine visit or in-person visit for diary completion and document on the paper back-up diary for entry into the eCRF. In this situation, when asking the participant the Diary questions, the exact language provided in the Diary should be used and site staff should not lead the participant or elaborate.

Regular reminders at each visit will be provided by site staff (or delegate) to participants for completion of the COVID-19 Symptom Diary. The COVID-19 Symptom Diary will be reviewed at all telemedicine and in-person visits (Days 3, 5, 7, 11, 14, 21, and 29) and the investigator (or medically qualified designee) will assess the participant's COVID-19 severity.

In the event that a participant is hospitalized during the Follow-Up Period, the diary should be completed if feasible. A parent/guardian/LAR/family member/other caregiver may assist in completion of the Diary or site staff or local home health care provider may interview the participant via telemedicine visit or in-person visit for diary completion as described above per local regulations. Upon discharge, the participant should resume diary completion through Day 29.

6.3.1.2. Saliva Collection for SARS-CoV-2 Quantitative RT-PCR

Participants will be provided with saliva sample test kits and transport packaging materials for use on Days 3, 5, 11, 14, and 21. Site staff will educate the participant on the proper collection and transport procedures. Saliva samples on Day 7 and Day 29 will be collected and transported by site staff at the in-person visits (in-clinic or home health).

On Day 1 prior to study drug administration, site staff will observe the participant collecting and packaging the saliva sample. Participants should NOT eat, drink, smoke, or chew gum for 30 minutes before all saliva sample collections.

Saliva samples will be analyzed for quantitative RT-PCR for determination of viral load, viral clearance, and duration of viral shedding and may be used for viral sequencing.

In the event that a participant is hospitalized during the Follow-Up Period, saliva collection should be continued if feasible. If access to a participant by parent/guardian/LAR/family member/other or site staff is not possible, engagement of a local home health care visit can be considered per local regulations.

6.3.1.3. Daily Temperature, Blood Oxygen Saturation, and Heart Rate

On Day 1, participants will be provided with a thermometer and a pulse oximeter. Site staff will educate the participant (or guardian/LAR) on the measurement of temperature, SpO_2, and heart rate and proper documentation in the daily diary. The participant (or guardian/LAR) will be observed completing the measurement and documentation of temperature, SpO_2, and heart rate on Day 1 prior to study drug administration.

Participants (or guardians/LARs) will be asked to monitor temperature, SpO_2, 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. In the event that a participant is unable to complete the measurements and documentation on their own, a parent/guardian/LAR/family member/other caregiver may assist in measuring and documenting the temperature, SpO_2, and heart rate.

In the event that a participant is hospitalized, information regarding temperature, SpO_2, and heart rate should be collected if feasible. If access to a participant by parent/guardian/LAR/family member/other caregiver or site staff is not possible, engagement of a local home health care visit can be considered per local regulations.

6.3.2. Site Clinical Assessments

6.3.2.1. COVID-19 Symptom Diary, Reported Vitals Review, and Injection Site Reaction Diary Review

Site staff will review the COVID-19 Symptom Diary, vitals (temperature, SpO_2, and heart rate), and ISRs reported in the diary as outlined in the Schedule of Assessments (Table 12-1). In the event of participant use of paper diary, the participant will provide information at telemedicine visits to the site staff about their diary entries to allow for monitoring and documenting participant COVID-19 severity (Section 6.3.2.2), and paper diaries will be collected from participants at all in-person visits.

Based on investigator judgment, participants reporting worsening of signs or symptoms related to COVID-19 during the study may be referred to have an unscheduled study visit with site personnel or home health care provider. Participants will be referred to seek emergency medical care if emergency warning signs for COVID-19 should develop (trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, bluish lips or face).

During the telemedicine visit, the site staff will review the body temperature, SpO_2, and heart rate documented in the diary. The participant (or guardians/LARs) will report any medications taken to treat current illness/symptoms, any new onset AEs, and the investigator or medically

qualified designee will determine if medical attention is required due to worsening of COVID-19. At all visits, the participant will be reminded to complete daily COVID-19 Symptom Diary; daily temperature, SpO_2, and heart rate; ISR diary; and saliva sample collection on the appropriate days. Participants will be reminded at these visits regarding the importance of completion of the diary. See the Schedule of Assessments (Table 12-1) for additional details.

6.3.2.2. COVID-19 Severity Assessment

The investigator (or medically qualified designee) will assign an overall COVID-19 severity grade for each visit through Day 29 as determined according to the severity definitions provided in Section 2.2.2. The Day 1 assessment should occur prior to the first dose of study drug based on signs/symptoms present on Day 1.

6.3.2.3. Survival Assessment

The participant's survival status (known to be alive or dead) will be determined at the planned time for any missed visit through Month 14 or at any time that the participant is thought to be lost to follow up. In the event that the participant is not able to be reached, site staff should utilize primary and secondary contacts including personal contacts, health care provider, and local hospitals as outlined in the ICF (Section 9.3). As described in Section 6.9.3, every effort should be made by site staff to ascertain survival status. If survival status is not known, the date last known to be alive will be recorded.

As required for SAE reporting, a death must be reported in the eCRF within 24 hours of the site becoming aware of the death. As permitted by local guidelines, survival status should be reported for participants who have withdrawn from study participation (including survival status or death available via public records [eg, death certificates or public registers]).

6.3.2.4. Medically Attended Visits Assessment

Medically attended visits will be solicited from participants (or guardians/LARs) as outlined in the Schedule of Assessments (Table 12-1). In the event that the participant is not able to be reached, site staff should utilize primary and secondary contacts including personal contacts, health care provider, and local hospitals as outlined in the ICF (Section 9.3).

COVID-19-related medically attended visits include telemedicine visits not specified by the protocol, emergency rooms or urgent care center visits, hospitalization, or visits to a physician's office for attention to worsening signs or symptoms attributed to COVID-19, in the opinion of the investigator.

Every effort will be made to capture medical information from any medical visits (eg, visits to the primary care provider(s), emergency department/urgent care clinic visits, hospitalizations, etc) related to COVID-19 or its complications using the appropriate eCRFs. Any data relevant for assessment of the efficacy endpoints and ADE will also be collected. These are likely to include, but are not limited to, type and duration of visit(s), reason for visit(s), information on ICU admissions; clinical parameters, such as SpO_2, respiratory rates, and vital signs; need for oxygen therapy; need for ventilatory support; imaging; blood tests results; and overall outcome (survival or death).

In the event that a participant is hospitalized during the Follow-Up Period, all procedures and assessments described in the Schedule of Assessments (Table 12-1) should be continued if feasible. If access to a participant by site staff is not possible, engagement of a local home health care visit can be considered per local regulations. If the hospital institution does not permit in-person visits, telemedicine visits can be performed to collect all feasible assessments in Table 12-1. Visits or assessments that are not performed or are performed late due to hospitalization will not be considered protocol deviations. Upon discharge, every effort should be made to ensure continued study visits occur.

6.3.2.5. Long-Term Health Status Assessment

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.

6.3.2.6. Household Transmission Questionnaire

At the Day 29 visit, participants will be asked about household transmission of SARS-CoV-2 and symptomatic COVID-19. Participants will be asked if any household contacts had a documented asymptomatic SARS-CoV-2 infection or symptomatic COVID-19 after the participant's receipt of study drug. If so, participants will be asked to report the number of household contacts that had SARS-CoV-2 asymptomatic infection and the number of household contacts that had symptomatic COVID-19.

6.4. Safety Assessments

Safety will be assessed in an ongoing manner. Participants will receive a single dose of ADG20 or placebo at the study site and will be monitored after dosing for acute worsening of disease, hypersensitivity, and ISRs. During Phase 2, the first 10 participants will be monitored for at least 4 hours after dosing. If no significant hypersensitivity reactions or ISRs are identified, the monitoring period may be reduced as described in Section 6.4.1. If any hypersensitivity reactions occur, the iDMC will review available safety data and provide a recommendation regarding the duration of monitoring, which will be formally communicated to sites without a protocol amendment and included in ICF/assents. Participants will then be followed via telemedicine visits, phone call, or in-person visits as indicated in the Schedule of Assessments (Table 12-1) through Month 14.

Safety assessments will include monitoring of AEs, clinical laboratory testing, vital sign measurements (body temperature, heart rate, respiration rate, and systolic and diastolic blood pressure), and physical examinations. AESI (hypersensitivity reactions) will be recorded through Day 4. Hypersensitivity reactions occurring after Day 4 will be recorded as AEs. Participants will record any ISRs using the Injection Site Reaction Diary starting after dosing on Day 1 through Day 4 (Appendix 12.3). Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution. Only ISRs that qualify as an SAE or that worsen or begin after Day 4 should be recorded in the eCRF AE form; all other ISRs are only to be recorded in the eDiary. Other AEs, including SAEs and MAAEs (including new onset chronic illnesses), will be collected through 14 months.

See Table 12-1 for the Schedule of Assessments.

6.4.1. Safety Monitoring After Study Drug Administration

Participants will be observed at the study site after study drug administration according to Table 6-1.

Table 6-1: Safety Monitoring After Study Drug Administration

Post-dose monitoring duration	• The first 10 participants enrolled require post-dose monitoring at site for 4 hours. • If no hypersensitivity reactions are seen in the first 10 participants, monitoring will be reduced to 2 hours[a] • If no hypersensitivity reactions are seen during the administrative interim analysis when 200 participants have been enrolled in Phase 2, monitoring will be reduced to 1 hour for the remaining participants. • If hypersensitivity reactions are observed, the iDMC will make a recommendation for monitoring. Note: Changes to post-dose monitoring required at site will be formally communicated to sites without a protocol amendment.
Vital signs	Required vital sign measurements (temperature, heart rate, respiratory rate, blood pressure, and SpO_2). • 15 minutes (±15 minutes) prior to injection • 30 minutes (±5 minutes) after the injection is completed • Any additional monitoring as determined by the iDMC will be communicated to sites without a protocol amendment

[a] As of 21 Dec 2021, evaluation of safety data revealed no hypersensitivity reactions or adverse events of concern reported through Day 4 in the first 200 participants. Therefore, the post-dose monitoring period was reduced from 2 hours to 1 hour. Previously, as 07 Oct 2021, evaluation of safety data revealed no hypersensitivity reactions or adverse events of concern reported through Day 4 in the first 10 participants. Therefore, the post-dose monitoring period was reduced from 4 hours to 2 hours.

6.4.1.1. Injection Site Reaction Monitoring and Management

Monitor all participants closely during and after study drug administration as outlined above as there is a risk of injection site reaction and hypersensitivity (including anaphylaxis) with any biological agent.

Study drug will only be administered in settings in which health care providers have immediate access to medications to treat a severe injection or hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary. The clinical site should have necessary equipment and medications for the management of any reactions, which may include but is not limited to oxygen, IV fluid, epinephrine, acetaminophen, and antihistamines.

Symptoms and signs that may occur include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Investigators should manage reactions based on standard of care and their clinical judgment. If a hypersensitivity or injection reaction occurs, then supportive care should be used in accordance with the signs and symptoms. Hypersensitivity reaction severity will be assessed and reported

using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Table 6-2). In the case of mild to moderate ISRs, acetaminophen, topical steroids, cold compress and/or antihistamines may be provided. Participants experiencing more severe reactions will be referred for appropriate care (eg, dermatology evaluation or emergency care, depending on the severity of the reaction).

Hypersensitivity reactions after study drug administration will be collected as AESI through telephone/telemedicine visits during the follow-up period per the Schedule of Assessments (Table 12-1). On Day 1 through Day 4, hypersensitivity reactions including but not limited to urticaria, edema, respiratory distress, anaphylaxis, and allergic reactions will be recorded as AESIs. Hypersensitivity reactions occurring after Day 4 will be recorded as AEs. Participants reporting a hypersensitivity reaction outside of a regularly scheduled in-person visit should have an unscheduled visit as described in Section 6.8.2 for evaluation of such reaction (including collection of PK and ADA samples). Site staff will educate participants (guardians/LARs) on Day 1 regarding recognizing and reporting potential hypersensitivity reactions to site staff.

Participants will be queried regarding any ISRs (see Section 6.4.6.2.1) and the injection sites examined at least 1 hour following injection. Solicited ISRs will be collected in the diary from Day 1 through Day 4 as described in Section 6.4.1.2. Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution.

6.4.1.2. Injection Site Reaction Diary

Solicited ISRs will be collected in the Injection Site Reaction (ISR) Diary from Day 1 through Day 4. Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution. Each day, participants should document the worst pain, tenderness, redness, or swelling that was experienced in the last 24 hours. Participants will be provided a ruler by the site study team to measure redness or swelling at the injection sites. For irregular shapes, the widest part of the area (how much of the skin the redness or swelling covers) should be measured. Redness or swelling should be measured each day that it is visible. Severity will be assessed for solicited AEs (ISRs) by the participant (or, if applicable, with help from their caregiver, surrogate, or guardian/LAR) as described in Appendix 12.3.

At the Day 1 visit, study site staff will provide information to the participant (or guardian/LAR) about the questions that will be asked in the diary and how to complete the ISR Diary and use the measuring device. At the end of the post-dose monitoring period at the site, participants will complete the Day 1 ISR prior to departing the clinical site. Site staff will observe the participants completing the diary on Day 1 and will answer any questions participants may have about the diary.

Only ISRs that qualify as an SAE or that worsen or begin after Day 4 should be recorded in the eCRF AE form, all other ISRs are only to be recorded in the eDiary.

6.4.2. Clinical Safety Laboratory Assessments

Blood samples for safety laboratory assessments (hematology, serum chemistry, and coagulation; see Appendix 12.4) will be collected on the days specified in the Schedule of Assessments (Table 12-1).

6.4.3. Physical Examinations

A complete physical examination during screening will include general/appearance; head, eyes, ears, nose, throat, and oropharynx; pulmonary; cardiovascular; gastrointestinal; screening neurologic exam (mental status, cranial nerves, motor, sensory, coordination, reflexes, and gait); extremities; and skin evaluations. Height and weight will also be measured and recorded. On Day 1, the complete physical exam will include review and documentation of all COVID-19-related signs/symptoms. Investigators should pay special attention to clinical signs related to previous serious illnesses. Any clinically significant abnormalities should be documented as medical history.

6.4.4. Targeted Review of Changes in Health

A targeted, symptom-directed review of changes in health based on reported AEs or ongoing signs/symptoms of COVID-19 will be conducted at the visits specified in the Schedule of Assessments (Table 12-1). Any clinically significant abnormalities should be documented as AEs by site staff.

6.4.5. Vital Signs

Vital signs, including temperature, heart rate, respiratory rate, seated blood pressure, and SpO_2 will be assessed by site staff at the specified timepoints in the Schedule of Assessments (Table 12-1) and recorded in the eCRF. At the Day 1 Visit, vital signs will be performed as described in Section 6.4.1. Daily measurement of temperature, SpO_2, and heart rate by participants is described in Section 6.3.1.3.

6.4.6. Adverse Events

Adverse events occurring from when the participant signs the ICF until the Month 14 (EOS) visit or withdrawal will be recorded. Only study procedure-related AEs occurring before randomization will be recorded. All AEs will be followed and recorded up to the Month 14 (EOS) Visit.

6.4.6.1. Definitions

6.4.6.1.1. Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study drug or their clinical significance.

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. Participants will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

For the purposes of this study, 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 as these are expected endpoints. Subsequent episodes of COVID-19 in the same

participant will be captured according to standard AE processes, including the standard process for expedited reporting of SAEs if the event meets the definition of an SAE.

Anticipated day-to-day fluctuations of preexisting diseases or conditions present or detected at the start of the study that do not worsen would not be considered AEs. Laboratory results of disease/disorders being studied and medical/surgical procedures are not considered AEs but rather the condition/event that leads to it are defined as an AE.

6.4.6.1.2. 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

Immediately life-threatening: report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the medical product might have resulted in the death of the patient.

Inpatient hospitalization: report as an SAE if admission to the hospital or prolongation of hospitalization was a result of an adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (eg, life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.4.6.1.3. Suspected Unexpected Adverse Events

A SUSAR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product).

6.4.6.1.4. Adverse Events of Special Interest

An AESI (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 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

6.4.6.1.5. Medically Attended Adverse Events

MAAEs are defined as AEs leading to medically attended visits that were 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.

6.4.6.2. Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the participant signs the ICF until exit from the study.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor or designee.

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being.

In addition to participant observations, AEs identified from any study data (eg, clinically meaningful laboratory values, physical examination findings) or identified from review of other documents (eg, participant diaries) that are relevant to participant safety will be documented on the AE page in the eCRF.

6.4.6.2.1. Assessment of Severity

Adverse Event 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 AEs **(with the exception of solicited AEs of ISRs)** will be graded 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.)

Hypersensitivity Reactions

All participants will be monitored closely for signs/symptoms of local or systemic hypersensitivity reactions.

The site should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving dosing. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

Hypersensitivity reaction severity will be assessed and reported using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Table 6-2).

Table 6-2 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events – Systemic

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Severe and Potentially Life-threatening
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Cytokine Release Syndrome[a]	Mild signs and symptoms AND Therapy interruption not indicated	Therapy interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (for example, requiring pressor or ventilator support)

[a] A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

Source: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (NIAID 2017).

Intramuscular Injection Site Reaction Severity

Intramuscular ISRs will be graded using the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007b). The Injection Site Reaction Diary is in Appendix 12.3. Because solicited AEs are expected to occur after injections, ISRs will not be assessed for relationship to study drug.

6.4.6.2.2. Assessment of Causality

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. 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.

When assessing the relationship to the study drug, the following criteria will be considered:

- Known class effect
- Biological plausibility
- Lack of alternative explanation, ie, concomitant drug, or disease

6.4.6.3. Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF from the time of dosing until the EOS Visit. If a study procedure-related AE occurs after the execution of informed consent (and assent where applicable for adolescents) but prior to randomization, it will also be recorded. Information to be collected includes the following:

- Event term
- Date and time of onset
- Investigator-specified assessment of severity and relationship to the study drug
- Date and time of resolution of the event
- Seriousness
- Any required treatment or evaluations
- Outcome

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 Section 6.4.6.1.1. All AEs will be followed to adequate resolution. MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.4.6.3.1. Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Each AE will be assessed to determine whether it meets seriousness criteria (Section 6.4.6.1.2). All SAEs (related and unrelated) will be recorded from the time of dosing until the EOS Visit. If a study procedure-related SAE occurs after the execution of informed consent (and assent where applicable for adolescents) but prior to randomization, it will also be recorded. Any SAEs considered related to the study drug and discovered by the investigator at any time after the study should be reported. The investigator will report any SAE to the sponsor or designee as outlined below and to the IRB/IEC according to its SOPs.

If the investigator detects an SAE in a study participant after the last scheduled Follow-up Visit, and considers the SAE related or possibly related to prior study treatment, the investigator should report it to the sponsor or designee. If this occurs after the electronic data capture (EDC) closure, this will only be captured in the Safety Database.

Any AE that meets SAE criteria (Section 6.4.6.1.2) must be reported to [redacted] Pharmacovigilance immediately (ie, within 24 hours) after site personnel first learn of the event.
See Contact Information for Reporting SAEs.

At a minimum, the initial report should include the following information:

- Event
- Study code
- Participant number
- Study drug (in situations where the blind had to be broken [Section 5.5.1])
- Reporter name and contact information

In the case of a “minimum report” (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed until resolution or stabilization and for reported deaths, the investigator should supply the sponsor or designee and the IRB/IEC with any additional requested information (eg, autopsy reports, and terminal medical reports). The investigator will be responsible for reviewing and signing each SAE report that is submitted.

The original SAE report should be kept at the study site. Additional SAE follow-up information, if required or available, should be submitted to the sponsor or designee within 1 business day of receipt following the procedure described above. All supplemental documentation regarding the SAE shall be maintained in the investigator’s study files. The sponsor or designee will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs that are ongoing at the Month 14 (EOS) Visit should be followed until resolved.

An SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a SUSAR (Section 6.4.6.1.3). The sponsor or designee is responsible for submitting expedited safety reports to the appropriate regulatory agency for all confirmed SUSARs. These reports will comply with the applicable regulatory requirements and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). In the case of a fatal or life-threatening SUSAR, the sponsor or designee will notify the appropriate regulatory agency as soon as possible but in no case later than 7 calendar days after the sponsor or designee first receives the information. For a non-life-threatening SUSAR, the report will be submitted no later than 15 days after the sponsor or designee is made aware of the event.

Investigators will also be notified of all unexpected, serious, drug-related events (7- or 15-Day Safety Reports) that occur during the clinical trial. Each investigational site is responsible for notifying its IRB or IEC of these additional SAEs.

6.4.6.3.2. Exceptions

For the purposes of this study, 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 as these are expected endpoints. Subsequent episodes of COVID-19 in the same participant will be captured according to standard AE processes, including the standard process for expedited reporting of SAEs if the event meets the definition of an SAE.

6.4.6.3.3. Unanticipated Problems Involving Risks and Adverse Events

Investigators will report all unanticipated problems involving risk to human subjects promptly to the IRB and Sponsor if required by local country regulations. This includes AEs that are considered unanticipated problems (21 CFR 56.108[b][1], 21 CFR 312.53[c][1][vii], and 21 CFR 312.66).

Definition of Unanticipated Problems

An AE observed during the conduct of a study should be considered an Unanticipated Problem (UP) involving risk to human subjects, and be reported to the IRB, only if it meets all the following three conditions: it is unexpected, serious, and has implications for the conduct of the study (eg, requiring a significant, and usually safety-related, change in the protocol, such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or IB). The occurrence of such an event would suggest that the research may place study participants or others at a greater risk of harm.

Some examples of AEs that should be considered UPs and must be reported to the IRB are:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (eg, tendon rupture, progressive multifocal leukoencephalopathy)

- An AE that is described or addressed in the IB, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations
- An SAE that is described or addressed in the IB, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison)
- Any other AE or safety finding (eg, based on animal or epidemiological data) that would cause the sponsor to modify the IB, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure to ensure the protection of human subjects

Reporting of Unanticipated Problem

The investigators will report the UPs to their IRB and to the Sponsor if required by the local country regulations.

Include the following information in the UP report: protocol title and number, Investigator's name, and the IRB project number; a detailed description of the event, incident, experience, or outcome; and an explanation of the basis for determining that the event, incident, experience, or outcome represents an UP. For any additional details regarding reporting of UPs refer to the *FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection* (https://www.fda.gov/media/72267/download).

6.4.6.4. Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the participant is lost to follow-up.

6.4.7. Pregnancy

If a female participant becomes pregnant during the study, the investigator will notify the sponsor or designee within 72 hours following pregnancy confirmation (via urine pregnancy test, or serum pregnancy test if required by local regulations) using the Pregnancy Report Form; the form should be sent to [redacted] Pharmacovigilance (see Contact Information for Reporting SAEs). For participants who become pregnant and have received study drug, study discontinuation is not required. These participants are encouraged to continue with all follow-up visits. Pregnancy outcomes for all participants should be followed by the site through the Month 14/EOS visit or at early termination from the study. The investigator will also notify the participant's physician that the participant may have been treated with ADG20 and request that any pregnancy outcomes occurring after the participant has completed the study be reported to the clinical site. All pregnancy outcome information should be recorded on the Pregnancy Report Form and forwarded to the sponsor or designee when available.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Pregnancies will not be reported as an SAE. Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs. Any SAE

occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to the sponsor or designee.

Any spontaneously reported information from a pregnant partner of a participant assigned male at birth will similarly be captured on the Pregnancy Report Form or Newborn Form as appropriate.

6.4.8. Treatment of Overdose

The definition of overdose for this study is receipt of any dose greater than the dose the participant was randomized to receive.

Treatment of overdose with ADG20 or matching placebo should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose.

The occurrence of an overdose with no associated abnormal laboratory assessments or clinical symptoms should be reported as an overdose without adverse effect. If an overdose is associated with an AE, the AE term should describe the clinical symptoms or test result that was abnormal.

6.5. Blood Collection and Nasopharyngeal Swabs

Blood will be collected as outlined in the Schedule of Assessments (Table 12-1) for exploratory analyses. The impact of host and viral biomarkers, such as baseline SARS-CoV-2 antibody responses, and viral load, on selected outcomes may be evaluated.

Nasopharyngeal swabs will be collected as outlined in the Schedule of Assessments (Table 12-1) for quantitative SARS-CoV-2 RT-PCR and for genotypic and phenotypic characterization as appropriate of the SARS-CoV-2 isolate for evaluation of viral resistance. The presence of additional pathogens on Day 1 will be assessed through a respiratory pathogen panel assay on a nasopharyngeal swab.

6.6. Pharmacokinetics

Blood samples to provide serum for the analysis of ADG20 concentrations will be collected as outlined in the Schedule of Assessments (Table 12-1). The PK sampling schedule may be modified based on emerging PK data.

On Day 1, one PK sample is to be collected at baseline prior to study drug administration in all participants. All other visits with PK sample collection will have one sample collected during the visit.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from participants experiencing hypersensitivity reactions as described in Section 6.8.2. The date and time of sample collection should be documented.

All efforts will be made to obtain PK samples at the scheduled nominal time relative to dosing. However, samples not obtained within the protocol-specified time windows will not be captured as a protocol deviation, as long as the exact time of the sample collection is documented. If a

scheduled blood sample collection cannot be completed for any reason, the missed sample time may be rescheduled with agreement of the clinical investigator, patient, and sponsor or designee.

Samples for PK analysis will be assayed for ADG20 using a validated analytical method. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the laboratory manual.

6.7. Immunogenicity

Blood samples to provide serum for detection of ADA (and neutralizing antibody) against ADG20 will be collected at timepoints specified in the Schedule of Assessments (Table 12-1). In addition to samples collected at scheduled visits, an additional blood sample should be collected from participants experiencing hypersensitivity reactions as described in Section 6.8.2. Additional instructions for sample collection, processing, storage, and shipping will be provided in the laboratory manual.

Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of ADG20 at a laboratory approved by the sponsor or designee. Antibodies may be further characterized for their ability to neutralize the activity of ADG20. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination.

6.8. Unscheduled Visits

6.8.1. COVID-19 Unscheduled Visits (Worsening, Relapse, or Recurrence)

Based on investigator's judgment, participants reporting worsening of signs or symptoms related to COVID-19 during the study may be referred to have an unscheduled study visit with site personnel or home health care provider. Participants will be referred to seek emergency medical care if emergency warning signs for COVID-19 should develop (trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, bluish lips or face). In the case of worsening COVID-19 not warranting emergency medical care, the site should perform an unscheduled visit, including saliva sample collection for RT-PCR testing and sequencing for SARS-CoV-2, collection of local and/or central safety laboratory samples per investigator discretion, vital signs, targeted review of changes in health, review of concomitant medications and adverse events, and medically attended visits assessment.

If at any time a participant reports a recurrence of COVID-19-like symptoms after having met the sustained recovery in the investigator's judgement or in the case of suspected re-infection, the site should perform an unscheduled visit, including saliva sample collection for RT-PCR testing and sequencing for SARS-CoV-2, collection of local and/or central safety laboratory samples per investigator discretion, vital signs, targeted review of changes in health, review of concomitant medications and adverse events, and medically attended visits assessment. This recurrence of symptoms will be treated as an AE (or SAE, if meeting criteria).

6.8.2. Hypersensitivity Reaction Assessment Unscheduled Visit

In the event that a participant reports a hypersensitivity reaction after Day 4 and outside of a regularly scheduled in-person visit, an unscheduled visit for evaluation of the reaction should be performed. This visit should include collection of samples for PK and ADA and collection of

local and/or central safety laboratory samples per investigator (or qualified designee) discretion using the unscheduled extra tube supply. Additionally, the following assessments should be performed: vital signs, a targeted review of changes in health, review of concomitant medications and adverse events, and medically attended visits collection.

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.

6.8.3. Other Unscheduled Visits

An unscheduled visit may be necessary per investigator (or medically qualified designee) judgment for assessment of an AE or SAE or an abnormal lab or procedural findings. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples using the unscheduled extra supply kits.

6.9. Administrative Procedures

6.9.1. Visit Type Requirements

As outlined in the Schedule of Assessments, several visit types (in-clinic, home health, or telemedicine) will be utilized throughout the study.

In-person visits may be conducted in-clinic or as home health visits (where allowed by local regulations and as outlined in the Schedule of Assessments [Table 12-1]). Home health provider visits may also be combined with telemedicine contact with the site personnel, investigator, or medically qualified designee as needed. Home health visits will be at the location of the participant and may include a home health vendor to visit to a location other than the participants home such as a hospital or other location.

At all in-person visits (in-clinic or home health), site personnel or home health providers will follow institutional or local standards to prevent transmission of SARS-CoV-2. This may include procedures such as use of personal protective equipment for participants (and guardians/LARs), site staff, and home health providers and providing designated entry locations for study participants/guardians/LARs for visits.

Telemedicine visits may be conducted by various secure virtual means (eg, telephone, telehealth, videoconference, etc). At each visit, the identity of the participant must be confirmed based on local requirements and/or institutional procedures.

6.9.2. Use of eDiary

At the time of consent, the participants must confirm they will be willing to complete an eDiary (once daily through Day 29). The eDiary will be provided either through a device or an application downloaded to their mobile smart device (smartphone, tablet, etc) or a provided device (at site discretion/availability) at the time of enrollment.

- Before dosing on Day 1, the participant will be instructed how to access the eDiary on their personal mobile smart device or provided device.
- This study will preferably use the eDiary (via device or application) for the collection of COVID-19 symptoms; daily temperature, SpO_2, and heart rate; and ISRs.
- Participants or sites unwilling or unable to utilize an eDiary may be provided paper diaries for use (at site discretion/availability). Paper diaries may be used as back-up in the event eDiary is unavailable due to technological or other issues. Paper diaries should be collected from participants at all in-person visits.

6.9.3. Collection and Update of Contacts

In order to reduce lost to follow-up and ensure appropriate collection of medically attended visits for COVID-19, participants will be asked to provide primary and secondary contacts to the site staff. This data will not be entered into the eCRF.

The site will capture contact information for a primary and a secondary personal contact (eg, family member, friend, neighbor, etc). Additionally, sites will capture contact information for the participant's primary health care provider and the hospital/emergency care centers with closest proximity to the participant's home.

Primary and secondary personal contacts, health care provider contact and hospitals will be reviewed with the participant (or guardian/LAR) and updated at the visits outlined in the Schedule of Assessments (Table 12-1).

7. STATISTICAL CONSIDERATIONS

This section briefly describes the statistical and analytical methods to be used. An SAP will provide details of the statistical methods and definitions for the analysis of efficacy and safety data.

Enrollment in the study was suspended on 11-Jan-2022 after emergence and global spread of the Omicron variant in regions enrolling the trial, beginning in December 2021. Therefore, the primary analysis is focused on evaluating the efficacy of ADG20 300 mg IM in participants with a non-Omicron variant of SARS-CoV-2. With this analysis plan, the primary efficacy and short-term 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, have discontinued, or if it is known that the Month 14 visit will not occur.

7.1. Sample Size Determination

The primary analysis is the comparison of the ADG20 arm versus the placebo arm with respect to the 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 sample size was calculated based on assumptions obtained from a review of data from studies of other mAbs in participants at 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 2022a; GlaxoSmithKline 2022; 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 approximate aggregate event rate of 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 the same efficacy assumption.

7.2. Analysis Sets

The analysis sets that will be used for statistical analyses are defined in Table 7-1. In the efficacy analyses, participants will be analyzed based on the treatment they are randomized to, irrespective of which treatment was actually received. In the safety analysis, participants will be analyzed based on the study drug received.

Table 7-1: Defined Analysis Sets and Descriptions

Defined Analysis Data Sets	Description
Full Analysis Set (FAS)	Includes all randomized participants regardless of whether the participant received study drug.
Modified Full Analysis Set with non-Omicron SARS-CoV-2 Variant (mFAS-non-Omicron)	Includes 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):	Includes 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.
Modified Full Analysis Set-PCR (mFAS-PCR):	Includes 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. Two sub-populations will be defined: • mFAS-NP: utilizes the baseline NP swab to determine a positive SARS-CoV-2 PCR • mFAS-S: utilizes the baseline saliva sample to determine a positive SARS-CoV-2 PCR.
mFAS-non-Omicron-PCR	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	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.

Defined Analysis Data Sets	Description
Per-Protocol Set (PPS)	All mFAS-non-Omicron participants included who had no significant protocol deviations as defined in the SAP that affect the efficacy assessments and received treatment.
Safety Set	All participants who received any amount of study drug. All safety analyses will be conducted in this analysis set.
Immunogenicity Set	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.
PK Analysis Set	All participants in the Safety Set who had at least one measurable ADG20 concentration post-administration of study drug.

7.3. Subgroups of Interest

The primary and key secondary analyses in the mFAS-non-Omicron population will be repeated within subgroups of interest as defined in the SAP.

7.4. Statistical Analyses

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, standard deviation, median, first and the third quartiles, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed.

The objectives and endpoints for all study phases are shown in Table 2-1.

Unless otherwise specified, estimations involving the primary and secondary endpoints will follow a treatment policy strategy for the handling of intercurrent events, which uses and analyzes all data for the endpoints after the intercurrent event has occurred. When a hypothetical strategy is used, data may be censored in the case of a time to event endpoint or imputed in the case of continuous or binary endpoints.

Estimand attributes, intercurrent events of interest, and rationales for intercurrent event handling strategies for the primary and key secondary estimands will be fully described in the SAP. The main estimation for the primary efficacy and key secondary efficacy endpoints is described in Section 7.6 and Section 7.7. Definitions of censoring and details of imputation methodology will be provided in the SAP.

7.5. Multiplicity Adjustments

To control the overall type 1 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 efficacy 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.

7.6. Main Estimation Utilizing the Primary Efficacy Endpoint

The analysis of the primary estimand, incidence of COVID-19-related hospitalization or all-cause death through Day 29 in the ADG20 arm versus the placebo arm in the mFAS-non-Omicron analysis set will be analyzed using the methodology for determining a standardized estimator for a binary outcome as detailed in Ge 2011, with adjustment for the following prognostic factors: age (continuous), sex (categorical), baseline qualitative serostatus (categorical), BMI (continuous), and baseline viral load (continuous). The standard error of the standardized estimator will be estimated using the delta method based on the algorithm presented in Ge 2011. The risk difference (placebo minus ADG20) with CI (using the Miettinen-Nurminen method), standardized risk difference with CI, relative risk reduction with CI, and associated p-value for the standardized risk difference will be provided. A treatment policy strategy will be used to handle intercurrent events of interest. For example, treatment effect will be estimated regardless of baseline or emergence of coinfection with a non-SARS-CoV-2 pathogen, which is a potential intercurrent event of interest.

Supportive estimands for the primary efficacy objective will be fully described in the SAP.

7.7. Main Estimation Utilizing Key Secondary Efficacy Endpoints

The key secondary endpoints will be tested in the following order in the mFAS-non-Omicron analysis set:

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

Treatment differences in the proportion of participants with severe/critical COVID-19 or all-cause death through Day 29 will be presented with 95% CIs and tested using the analysis procedure outlined for the primary efficacy outcome.

Treatment differences 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 with 95% CIs and tested using the analysis procedure outlined for the primary outcome.

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. Estimand attributes for the key secondary objective and supportive estimands will be fully described in the SAP.

7.8. Analyses of Other Secondary Efficacy Endpoints

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. Analysis approaches for the other secondary endpoints (ie, non-key) are summarized in Table 7-2 .

Table 7-2: Analyses of Other Secondary Efficacy Endpoints

Endpoint	Statistical Analysis Methods
COVID-19-related medically attended visits or all-cause death through Day 29	Same as primary efficacy analysis (see Section 7.6).
Time to sustained recovery in COVID-19 symptoms through Day 29	Same as the analysis of time to sustained resolution of COVID-19 symptoms through Day 29.
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 the Cox model.
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 analyses as covariates will be performed. The LS mean for the point estimate in each group and 95% CIs will be presented. The difference in LS means between each 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	Same as primary efficacy analysis (see Section 7.6). Analysis will be performed in 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).

Endpoint	Statistical Analysis Methods
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 by SARS-CoV-2 RNA 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. KM curves will be compared between ADG20 and Placebo using a log-rank test stratified by age (categorical). 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 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. Deaths occurring prior to achieving cessation of viral shedding 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	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 will be performed. 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 assess 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 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 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. Deaths before achieving viral clearance will be considered to have no viral clearance.
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).

ANCOVA=Analysis of Covariance; BLQ=below limit of quantitation; CI=confidence interval; FAS=full analysis set; KM=Kaplan-Meier; LOD=limit of detection; mFAS=modified full analysis set; LS=least squares; RT-qPCR=quantitative reverse transcription polymerase chain reaction.

7.9. Analyses of Exploratory Endpoints

Exploratory endpoint analyses, including analyses performed on the mFAS-Omicron analysis set, will be detailed in the SAP. Additional covariate adjusted analyses may be performed.

7.10. Pharmacokinetic Analyses

Pharmacokinetic endpoint analyses will be detailed in an SAP.

7.11. Safety Analyses

All AEs will be coded using the latest version of MedDRA. Safety summaries will be presented through Day 29 and overall.

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 are expected to occur after the administration of study drug all solicited AEs will be considered TEAEs.

The incidence of TEAEs (including solicited ISRs), SAEs, TEAEs related to study drug, SAEs related to study drug, TEAEs leading to study drug discontinuation, AESIs, and MAAEs will be summarized by MedDRA SOC, PT, and treatment group. The incidence of study drug related TEAEs (including solicited ISRs) will also be summarized by maximum severity by SOC, PT, and treatment group.

The incidence of solicited AEs (ISRs) will be summarized by maximum severity through Day 4. The maximum duration and time from injection to report of first onset of any solicited ISR will also be summarized.

For all analyses of AEs, if the same AE (based on PT) is reported for the same participant more than once, the AE is counted only once for the PT and at the highest severity and most-related relationship to study drug.

Descriptive statistics for clinical laboratory test results (hematology. serum chemistry, and coagulation) and vital signs 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 and vital sign parameters will be summarized by treatment group. In addition, treatment-emergent potentially clinically significant (PCS) laboratory parameters will be summarized in shift tables from baseline to each post-baseline time point assessed. The number and percentage of participants with a PCS vital sign will be summarized by treatment group for each time point assessed. PCS values will be defined in the SAP.

7.12. Immunogenicity

Immunogenicity data will be listed, and summarized in tables using descriptive statistics, including rates, titers, and neutralization data, as appropriate. Associations between immunogenicity data and PK as well as safety and efficacy data will be explored. Details of immunogenicity analysis will be provided in the SAP.

7.13. Safety Monitoring and Interim Analyses

The safety and interim analysis monitoring are described in Table 7-2. Additional iDMC ad hoc reviews may be conducted as outlined in the DMC Charter.

Table 7-3: Safety Monitoring and Interim Analyses

Study Phase/ Parameter	Analysis Time point	Reviewer: Data Reviewed	Criterion	Statistical Method	Purpose
Phase 2/PK	Throughout	Unblinded Pharmacology Team: • Unblinded available PK data • 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 pausing guidelines are met (Section 10.11), an ad hoc iDMC meeting will occur.	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.
Phase 3/Safety	At any time during Phase 3	iDMC: Events meeting criterion	If any of the pausing guidelines are met (Section 10.11), an ad hoc iDMC meeting will occur.	NA	Monitor ongoing safety

iDMC=independent data monitoring committee; IM=intramuscular; NA=not applicable; PK=pharmacokinetics; SAP=statistical analysis plan.

If pausing guidelines are met at any point in the study, an ad hoc iDMC meeting will occur (Section 10.11).

To evaluate the safety profile of ADG20 and make recommendations regarding enrollment of adolescents and pregnant and breastfeeding women in Phase 3 and post-dose monitoring duration, an administrative interim analysis will be reviewed by the iDMC after approximately 200 participants are enrolled in Phase 2. Enrollment into Phase 3 will continue while the administrative analysis is taking place.

8. DATA QUALITY ASSURANCE

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

8.1. Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diary cards, laboratory reports, etc.

All eCRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

Investigative site personnel will enter participant data into RAVE, via a secure network. A complete electronic audit trail will be maintained. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event and medical history terms will be coded using MedDRA; prior and concomitant medications will be coded using a standard dictionary (eg, WHODrug).

9. ETHICS

9.1. Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before human subjects participate in research studies. Before study onset, the protocol, informed consent (and assent where applicable for adolescents), advertisements to be used for the recruitment of study participants, and other written information regarding this study to be provided to the participant or the participant's guardian/LAR must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH guideline

E6(R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

9.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3. Participant Information and Consent/Assent

A documented informed consent (and assent where applicable for adolescents) in compliance with regulatory authority regulations shall be obtained from each participant (or their guardian/LAR) before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An LAR may be used in Phase 2 and 3 only in cases where inclusion criterion 9 is able to be fulfilled. An informed consent and/or assent template may be provided by the sponsor or designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent and/or assent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent and/or assent will be submitted by the investigator to their IRB/IEC for review and approval before the start of the study. If the consent and/or assent is revised during the course of the study, sites will receive notification defining the participants who are required to reconsent/re-assent.

Before recruitment and enrollment, each prospective participant or their guardian/LAR will be given a full explanation of the study, be allowed to read the approved ICF/assent, and have any questions answered. Once the investigator is assured that the participant/guardian/LAR understands the implications of participating in the study, the participant/guardian/LAR will be asked to give consent to participate in the study by executing the ICF/assent. The authorized person obtaining the informed consent (and assent where applicable for adolescents) also executes the ICF/assent.

Participant medical records need to state that documented informed consent was obtained.

The investigator shall retain the executed original ICF(s)/assent(s) and give a copy of the executed original form to the participant, guardian/LAR.

10. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant's guardian/LAR), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2. Data Protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the sponsor's databases, shall be treated in accordance with local data protection law.

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

10.3. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor or designee to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor or designee a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the participant's disease.

10.4. Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR by providing all essential documents.

10.5. Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers as required under the terms of the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC (European Commission 2001) and 2007 FDAAA (FDA 2007a).

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6. Adverse Events and Study Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor or designee and/or IRB/IEC according to the timeline and method outlined in the protocol (see Section 6.4.6.3.1). In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8. Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.9. Publication Policy

The results of this study may be published or presented at scientific meetings. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10.10. Study Management

The study administrative structure will include the iDMC, CRO, third party vendors, and laboratories.

10.11. Independent Data Monitoring Committee

The iDMC will provide safety oversight for all parts of the study, including monitoring for potential ADE. The iDMC will meet at designated points per Section 7.13 and the iDMC charter and on an ad hoc basis to review cumulative safety data and other clinical study data to ensure the benefit/risk remains favorable. The iDMC will make recommendations to the sponsor as outlined Section 7.13 and the iDMC charter.

Details regarding iDMC membership, conduct, ongoing safety monitoring, decision making and communication will be provided in the iDMC Charter. Thresholds for calling ad hoc meetings for events of special interest such as potential ADE will be provided in the iDMC Charter.

Study enrollment will pause and an ad hoc iDMC meeting will be called based on any of the Pausing Guidelines being met in the ADG20 arm as presented in Table 10-1.

Table 10-1: Pausing Guidelines

Phase	Pausing Guideline
Phase 2	• 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 serious adverse event including hypersensitivity reactions
Phase 3	• Any study drug-related death • Any study drug-related serious adverse event including hypersensitivity reactions

10.12. Monitoring

10.12.1. Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. Site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on sponsor or its designee's standards, ICH E6, and all applicable, regulatory guidelines.

When on-site monitoring visits are to be conducted, the investigator is to ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit.

During the COVID-19 pandemic, planned on-site monitoring visits may not be possible due to restricted access making it necessary for sponsors of clinical trials to adjust how studies are managed.

In situations where on-site monitoring visits are not possible (eg, the COVID-19 pandemic), remote monitoring will be considered as a risk-based approach to monitor the study. Guidance regarding the conduct of clinical trials during the COVID-19 pandemic is available from the FDA (FDA 2021c) and EMA (EMA 2022) and local guidance may also be available. The

sponsor or its designee will work with study site personnel to put in place appropriate remote monitoring strategies.

10.12.2. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor or designee.

10.13. Management of Protocol Amendments and Deviations

10.13.1. Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before participants can be enrolled into an amended protocol. During emergent situations, a pandemic or other natural disaster(s), modifications may be necessary to protocol-specified procedures. Central to any decision should be ensuring that the safety of clinical trial participants can be maintained.

10.13.2. Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor or designee for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of study conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training may also be performed throughout the study during routine site monitoring activities.

10.14. Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (includes Follow-up Visit).

If the study is prematurely terminated or suspended, the sponsor or designee or investigator shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.15. Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the final data are summarized and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications (as applicable) meet the standards of the ICH guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the final report, the sponsor or designee will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

11. REFERENCES

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12. APPENDICES

12.1. Appendix: Schedule of Assessments

Table 12-1: Schedule of Assessments

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 (including 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 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 (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 Section 6.4.1. 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 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.

12.2. Appendix: COVID-19 Symptom Diary

Information about COVID-19-associated symptoms (listed below [FDA 2020b]) will be collected in a daily COVID-19 Symptom Diary as described in protocol Section 6.3.1.1.

Assessment of Common COVID-19-Related Symptoms and Global Impression Items: Items and Response Options and Scoring

*"What was the severity of your **[insert symptom]** at its worst over the last 24 hours?"*	**Response Options and Scoring**
1) Fever (feeling hot or feverish)	None Mild Moderate Severe
2) Chills (shivering)	
3) Cough	
4) Sore throat	
5) Congestion (stuffy or runny nose)	
6) Shortness of breath or difficulty breathing **at rest**	
7) Shortness of breath or difficulty breathing **with exertion** worse than usual prior to diagnosis of COVID-19	
8) Muscle or body aches	
9) Fatigue (low energy or tiredness)	
10) Headache	
11) Nausea (feeling like you want to throw up)	
12) Rate your sense of taste in the last 24 hours	My sense of taste is THE SAME AS usual My sense of taste is LESS THAN usual I have NO sense of taste
13) Rate your sense of smell in the last 24 hours	My sense of smell is THE SAME AS usual My sense of smell is LESS THAN usual I have NO sense of smell
14) How many times did you vomit (throw up) in the last 24 hours?	I did not vomit at all 1–2 times 3–4 times 5 or more times
15) How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all 1–2 times 3–4 times 5 or more times
16) In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?	Yes or No
17) In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?	Yes or No
18) In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst?	None, Mild, Moderate, or Severe

12.3. Appendix: Injection Site Reaction Diary

At the Day 1 study visit, participants will be given a ruler and instructed on use of the ruler and the Injection Site Reaction Diary along with an emergency 24-hour telephone number, if needed.

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

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

Severity will be assessed for solicited AEs (injection site reactions) by the participant (or, if applicable, with help from their caregiver, surrogate, or guardian/LAR) according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007b).

Because solicited AEs are expected to occur after injections, they will not be assessed for relationship to study drug. Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution.

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.

12.4. Appendix: Clinical Laboratory Tests

Hematology (CBC with differential):	**Chemistry Panel (Serum):**
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	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
Coagulation Tests	**ADG20 Pharmacokinetics and Immunology**
Prothrombin time (PT)/International Normalized Ratio (INR) Partial thromboplastin (PTT)	ADG20 Serum PK Anti-Drug Antibodies (ADA, immunogenicity)
SARS-CoV-2 and COVID-19-Related Tests	
SARS-CoV-2 RT-qPCR SARS-CoV-2 Genomic sequencing SARS-CoV-2 Antibodies Respiratory Pathogen Panel (co-infections)	

12.5. Appendix: Country-Specific Requirements

12.5.1. Germany-Specific Requirements

No adolescents, pregnant women, or breastfeeding women will be enrolled in Germany. All content in the protocol specific to enrollment of adolescents or pregnant/breastfeeding women is not applicable to sites in Germany. Specific changes related to the exclusion of adolescents and pregnant/breastfeeding women from the study in Germany and other changes to the protocol specific to clinical sites enrolling participants in Germany are outlined in the sections below.

Throughout the protocol:

To be eligible to participate in the study in Germany, a participant must be capable of signing the informed consent. All references to a participant's legally authorized representative (LAR) in the protocol are not applicable for participants in Germany.

Section 4.1.1 Inclusion Criterion

Inclusion Criterion 1:

Is an adult aged 18 years and above.

Inclusion Criterion 2:

Has had SARS-CoV-2 positive RT-PCR test obtained within 5 days prior to randomization.

Note: In the event the National Testing Strategy is updated to include additional testing methods, those methods will also be allowed for use in this study without a protocol amendment. A historical record of a positive result from a test conducted within 5 days prior to randomization is acceptable. SARS-CoV-2 antibody testing cannot be used for study eligibility.

Inclusion Criterion 5b xii:

Does not apply to participants enrolled in Germany.

Inclusion Criterion 5c:

Does not apply to participants enrolled in Germany.

Inclusion Criterion 9:

Is able to understand and comply with study requirements/procedures based on the assessment of the investigator.

Inclusion Criterion 10:

Is able and willing to provide informed consent.