Protocol

Study ID: ADG20-PREV-001

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

NCT ID: NCT04859517

IND Identifier: 152327

EudraCT Identifier: 2020-005598-28

Date of Document: 05-August-2022

Adagio Therapeutics, Inc.

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 Prevention of COVID-19 (EVADE)
Protocol Number:	ADG20-PREV-001
Clinical Phase:	Phase 2/3
Protocol Version and Date:	6.0, 05 August 2022
US IND Number:	152327
EudraCT Number:	2020-005598-28
Sponsor:	Adagio Therapeutics, Inc. 303 Wyman Street, Suite 300 Waltham, MA 02451

This study will be performed in compliance with Good Clinical Practice, the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

DOCUMENT REVISION HISTORY

Document	Date of Issue	Overall Rationale
Version 1.0	01 December 2020	Original Protocol.
Version 2.0	05 March 2021	Based on US FDA feedback, update the timing of the primary endpoint for Cohort A to Day 28; add Cohort B to evaluate ADG20 for pre-exposure prophylaxis; incorporate a sentinel cohort (across Cohorts A and B) into the safety lead-in, as well as other measures to reduce risk; and make changes to the analysis plan. Protocol Version 2.0 was implemented prior to enrollment of the first participant in the study.
Version 3.0	11 June 2021	Based on US FDA feedback, update primary and key secondary objectives for Cohort A to reflect "real world" situations and make substantial changes to the analysis plan for the study.
Version 4.0	11 November 2021	Allow enrollment of pregnant and breastfeeding participants in Cohorts A and B and remove birth control requirements. Refine Cohort A to household contacts. Extend the screening window from 14 to 21 days for pre-exposure prophylaxis participants. Add Cohort C to evaluate ADG20 for pre-exposure prophylaxis in immune compromised participants at select sites. Version 4.0 of the protocol was submitted to the US FDA only and was not implemented at study sites.
Version 5.0	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 of Cohorts A and B. Update the statistical analysis section to reflect changes to the analysis plan due to the emergence of Omicron, including analysis of data collected prior to and after the emergence of Omicron. Remove in-home saliva collection during the CLI Period. Simplify procedures for participant reporting of COVID-19-like illness symptoms. Version 4.0 of the protocol was not implemented at study sites. Enrollment in Cohorts A and B of the protocol has since been suspended and no further participants are expected to be enrolled under these cohorts; therefore, updates to the inclusion/exclusion criteria to expand the population for these cohorts included in Version 4.0 of the protocol were removed in Version 5.0. Furthermore, the addition of Cohort C was removed. Version 5.0 of the protocol was submitted to the US FDA only and was not implemented at study sites.
Version 6.0	05 August 2022	Discontinue study procedures for collection of efficacy endpoint data, as analyses of efficacy endpoints of the study are complete; this includes monitoring and assessment of CLI symptoms, collection of health care resource utilization data, and pre- and post-COVID-19 vaccination visits. Update the study to remove virtual visits at Months 7, 8, 10, and 11, as these were primarily for the purpose of CLI monitoring. Update the study to remove virtual visit at Month 13, as long-term safety follow-up via in-person visits at Months 6 and 12 and virtual visits at Months 9 and 14 is considered sufficient based on the experience with ADG20 to date. Update the statistical analysis section to reflect the completed and planned analyses of efficacy and safety.

SIGNATURE PAGE

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

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol. The undersigned agree that the trial will be carried out in compliance with the clinical study protocol, Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor Approval:

Signature: _____ Date: _____

Name (print): [redacted]

Title: [redacted]

Investigator Agreement:

I have read the clinical study protocol and agree the trial will be carried out in accordance with the clinical study protocol, Good Clinical Practice, Declaration of Helsinki (with amendments) and laws and regulations of the countries in which the study takes place.

Signature: _____ Date: _____

Name (print): _____

SYNOPSIS

Sponsor:	Adagio Therapeutics, Inc.
Protocol No.	ADG20-PREV-001
Title of Study:	A Phase 2/3 Randomized, Double-blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of ADG20 in the Prevention of COVID-19 (EVADE)
Study Drug:	ADG20
Study Phase:	2/3
US IND No.	152327
EudraCT No.	2020-005598-28
No. of Sites/Location:	Approximately 75 to 120 Sites Multinational

Study Objectives and Endpoints

The objectives and their corresponding endpoints for each cohort are provided below:

Cohort A (PEP) Objectives and Endpoints

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

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

Secondary (Cohort A [PEP])	
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in each of the following populations: • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 diagnosis. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through Day 28 in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through Day 28. Supplementary: • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through Day 28.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months, in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through 3 months. Supplementary: • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in all randomized participants with prior but not current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.

To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection, in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	• Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by RT-qPCR (nasal sample) on Days 8 and 15. • Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology through Day 28.
To evaluate the impact of ADG20 compared with placebo on viral load in all randomized participants with asymptomatic SARS-CoV-2 infection detected by RT-qPCR (nasal sample) at baseline via surveillance.	• Peak post-baseline SARS-CoV-2 viral load as measured by RT-qPCR • SARS-CoV-2 viral load as assessed by RT-qPCR change from baseline to Day 8 and Day 15.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

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

Cohort B (PrEP) Objectives and Endpoints

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

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

Objectives	Endpoints
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in all randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months in all randomized participants.	Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection (based on serology) in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

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

Study Design

This is a Phase 2/3, multicenter, double-blind, placebo-controlled, randomized study of the mAb ADG20 in the prevention of symptomatic COVID-19 in adults and adolescents with no known history of SARS-CoV-2 infection but whose circumstances place them at increased risk of acquiring SARS-CoV-2 infection and developing symptomatic COVID-19. This objective will

be independently evaluated in participants with reported recent exposure to an individual diagnosed with a SARS-CoV-2 infection (Cohort A, PEP) and in a cohort of participants with no reported exposure to SARS-CoV-2 (Cohort B, PrEP). These cohorts will be enriched for participants whose advanced age (≥55 years old) or health status places them at risk for severe COVID-19 or COVID-19 complications.

This Phase 2/3 study will enroll in two parts: a Phase 2 safety lead-in consisting of 200 adult participants enrolled across Cohorts A and B and a separate Phase 3 expansion for enrolling the remainder of participants in each cohort. The first 30 participants (across both cohorts) in Phase 2 will constitute a sentinel group and will undergo extended monitoring as detailed below. After a combined number of approximately 200 adult participants (aged ≥18 years) across Cohorts A and B are enrolled in Phase 2 (inclusive of the 30 sentinel participants) and followed for 4 weeks, an interim analysis of safety will be performed and reviewed by the iDMC. Enrollment of adult participants will continue during this review and will follow Phase 2 post-injection monitoring requirements. Enrollment of adolescents in each cohort will open only upon sponsor communication to sites after iDMC review of Phase 2 data and only in regions permitted by health authorities and local ethics committees. Pausing guidelines triggering iDMC ad hoc reviews and additional details on safety monitoring are provided in Section 5.12.

The participants in Phase 2 will be combined with the corresponding Phase 3 expansion population in each cohort for the final efficacy and safety analyses.

The participant population, study procedures, and endpoints will be identical in Phase 2 and the Phase 3 expansion portions of the study with the following exceptions:

- The sentinel group will be restricted to adult participants (aged ≥18 years) and the post injection monitoring period will be 4 hours. Participants will then be assessed daily by telephone through Day 4 for hypersensitivity reactions.
- In the remainder of Phase 2, enrollment will be restricted to adult participants (aged ≥18 years) and the post-injection monitoring period may be reduced to no less than 2 hours after safety data review.
- After iDMC review of Phase 2 data, enrollment will include both adult (aged ≥18 years) and adolescent (aged 12 to <18 years) participants (only in regions permitted by health authorities and local ethics committees). The post-injection monitoring period for adult participants may be decreased to a minimum of 1 hour based on iDMC recommendation. The post-injection monitoring period will be 2 hours for the first 20 adolescent participants. If no hypersensitivity reactions are observed in this group, the post-injection monitoring period for subsequent adolescent participants may also be reduced to a minimum of 1 hour.

If any hypersensitivity reactions are observed in Phase 2, subsequent participants will be monitored for 2 hours post-injection. This period may be reduced to a minimum of 1 hour based on iDMC recommendation upon review of additional safety data.

Methodology

For Cohort A (PEP), the study will consist of a Screening Period of up to 5 days, a 1-month Study Period (including dosing on Day 1), a 5-month follow-up Period, and an 8-month

long-term follow-up (LTFU) Period. For Cohort B, the study will consist of a Screening Period of up to 21 days, a 6-month Study Period (including dosing on Day 1), and an 8-month LTFU Period. Each cohort of the study will be considered completed when the last telephone visit (Month 14) or Early Termination (ET) visit for the last participant in each cohort is complete.

All participants will undergo assessments as indicated in the main SoA.

Participants will receive a single IM dose of study drug on Day 1. Participants will record any ISRs using an e-Diary (or paper back-up) daily on Day 1 postdose through Day 4. The first diary entry will be completed by the participant with assistance of study staff prior to the end of the postdose monitoring period.

As of protocol clarification letter 6, the use of an e-Diary for recording CLI qualifying symptoms and collection of saliva samples beyond CLI Day 1 were discontinued. As of protocol version 6.0, monitoring for CLI symptoms and CLI visits are discontinued. Spontaneously reported CLI symptoms will be captured as AEs as per Section 4.1.1 and Section 4.1.3 of the protocol. Safety monitoring will be performed via site phone calls or in-person visits through Month 14. **Prior to implementation of protocol clarification letter 6 and protocol version 6.0 at each clinical site, the following procedures were in place for CLI monitoring and are described here for reference only:**

> *Participants will be instructed to monitor for any CLI symptoms and report them to the site if they occur at any time during the study. Surveillance for CLI will be performed via participant completion of an e-Diary twice weekly from Day 1 up to the Month 6 Visit, then weekly up to the Month 12 Visit. Surveillance for symptomatic COVID-19 will also be performed via site phone calls to the participant weekly up to the Month 6 Visit, then monthly up to the Month 12 Visit. Participants reporting CLI symptoms will be evaluated via phone call to confirm whether their symptoms meet criteria for a CLI visit. If CLI symptoms are confirmed by the site, the participant will enter the CLI Period and have an initial CLI visit within 48 hours. Participants who enter the CLI Period will be assessed as described in the CLI SoA. Study visits described in the main SoA should not be conducted while a participant is following the CLI SoA.*
>
> *During the initial CLI Visit (CLI Day 1), an NP swab for RT-qPCR testing for SARS-CoV-2 and a saliva sample for assessing viral load will be collected for processing by a central laboratory. For the remainder of the CLI Period, vital signs and severity, duration, and outcome of CLI will be collected via daily telemedicine visits (on CLI Days 2 to 21) and at the final visit on CLI Day 28. Saliva samples will be collected by participants at home on CLI Day 3, 5, 8, 11, 14, and 21 to measure viral shedding over time. Participants will continue in the CLI Period unless a negative result on the CLI Day 1 central NP RT-PCR test is received. These participants will stop CLI assessments and will continue with the main SoA. Participants with positive or pending central NP SARS-CoV-2 results will continue in the CLI Period, regardless of symptoms. Continuation in the CLI Period will not be guided by local RT-PCR testing.*

As of protocol version 6.0, all participants in Cohort A have completed surveillance for asymptomatic SARS-CoV-2 infection and monitoring for CLI symptoms and CLI visits are

discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

In Cohort A (PEP) only, surveillance for asymptomatic SARS-CoV-2 infection will be performed via SARS-CoV-2 RT-qPCR testing of nasal swabs collected by the Clinical Site on Day 1 (predose) and Day 8 and collected by the participant on Day 15. Any participant who has a positive result on a nasal swab RT-PCR (Cohort A) or local RT-PCR test (either cohort) up to the Month 12 study visit will be instructed to monitor for onset of symptoms and to report any symptoms to the clinical site; if the participant reports qualifying symptoms within 14 days of collection of the positive RT-PCR, they will enter the CLI Period.

As of protocol version 6.0, collection of health care resource utilization data is discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

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

Sparse blood samples will be collected for PK and immunogenicity throughout the study, as indicated in the main SoA and CLI SoA.

At the time of study entry, each participant will be asked to indicate to the Clinical Site the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization, if necessary, should they get infected with SARS-CoV-2. If this information is not available, a plan for where such care could be obtained should be developed.

All necessary precautions (as per local regulations) should be taken to protect medical staff and other contacts of participants who are suspected of having COVID-19. In the event of a confirmed SARS-CoV-2 infection, the participant will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

Treatment Assignment and Randomization

Participants will be randomly assigned in a 1:1 ratio in each cohort to receive either IM ADG20 or IM placebo. The randomization will be assigned in a blinded manner using a centralized Interactive Response Technology (IRT) system, in accordance with a pre-generated randomization schedule. A participant is considered randomly assigned when a randomization transaction is recorded in the IRT. A separate randomization list will be created for each cohort. Randomization will be stratified by geography (United States/Western Europe vs Central/Eastern Europe vs Rest of the World) and age/risk for severe/critical COVID-19 (12 to <55 years and low risk for severe/critical COVID-19 vs 12 to <55 years and high risk for severe/critical COVID-19 vs aged ≥55 years).

Selection of Study Population

The study population will comprise adults (aged ≥18 years) and adolescents (aged 12 to <18 years); enrollment of adolescents will begin during the Phase 3 expansion in regions permitted by health authorities and local ethics committees. Participants whose circumstances place them at increased risk of acquiring SARS-CoV-2 infection and/or developing symptomatic COVID-19 will be included. This objective will be independently evaluated in participants with reported recent exposure to an individual diagnosed with a SARS-CoV-2 infection (Cohort A, PEP) and in participants with no reported recent exposure to SARS-CoV-2 (Cohort B, PrEP).

Approximately 20% of the study population is anticipated to be comprised of individuals at increased risk for severe COVID-19 or COVID-19 complications. Participants aged 12 to <55 years who are at an increased risk (as described in Appendix 4) will be included, and participants aged ≥55 years will be eligible for enrollment with or without underlying medical conditions that might place them at increased risk. These at-risk populations are likely to derive the greatest benefit from a preventive mAb therapy. Importantly, participants will be enrolled in the study only if they do not intend to receive a COVID-19 vaccine for 6 months after discussion of risks/benefits of study enrollment in the setting of current or potential future vaccine availability and their underlying risk for development of severe COVID-19.

Inclusion Criteria

Participants are eligible to be included in the study only if **all** the following criteria apply:

1. Adult aged ≥18 years or adolescent aged 12 to <18 years and weighs at least 40 kg at the time of Screening.

   Note: Adolescent enrollment in these cohorts will open only upon sponsor communication to sites after review of Phase 2 data, and only if permitted by the local health authority (see Appendix 7).

2. Tests negative for current or previous SARS-CoV-2 infection by RT-PCR and serology at the time of Screening.

   Note: Participants may be randomized in Cohort A without RT-PCR results, if these results are not available by Day 5 of Screening.

3. Is at high risk of SARS-CoV-2 infection as assessed by the Investigator, as follows:

   a. Cohort A (PEP): recent exposure to an individual with a diagnosis of SARS-CoV-2 infection (the index case).

      Note: Randomization must occur within 5 days (120 hours) from both exposure to and sample collection from the index case. Participants with recent exposure to a laboratory-confirmed index case must be asymptomatic at randomization. Exposure is generally defined as repeated contact lasting 15 minutes or more within a 24-hour period, where the individuals were within 2 meters (approximately 6.5 feet) of each other, and neither party was wearing a facemask of respirator.

   b. Cohort B (PrEP): occupational, housing, recreational and/or social conditions that are likely to increase risk of exposure to SARS-CoV-2 as assessed by the criteria in Appendix 3.

4. Agrees to defer receipt of COVID-19 vaccination for a minimum of 180 days (6 months) after dosing.
5. Provides written documentation of informed consent by signing a current IEC/IRB approved ICF at the time of screening. A legally authorized representative may be used in cases where inclusion criterion 9 is able to be fulfilled. In the case of adolescents, informed consent/assent must also be obtained as required by local guidelines.
6. Participants assigned female sex at birth who are not of reproductive potential are eligible without requiring the use of contraception and do not require a pregnancy test. This includes female participants who have not undergone menarche or who are documented to be surgically sterile (eg, hysterectomy, removal of both ovaries, or tubal ligation) or postmenopausal (ie, amenorrhea >1 year and follicle stimulating hormone >40 mIU/mL). Follicle stimulating hormone is not required in postmenopausal females with amenorrhea for >2 years.
7. Participants assigned female sex at birth and who are of childbearing potential may be enrolled in the study if the participant has practiced adequate contraception or has abstained from all sexual activities that could result in pregnancy for at least 28 days before the day of dosing (Day 1) and has agreed to continue adequate contraception for sexual activity that could lead to pregnancy through 6 months following dosing.

   Adequate contraception for participants assigned female sex at birth is defined as consistent and correct use of a contraceptive approved by the local Health Authority and used in accordance with the product label. For example:

   a. Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide.
   b. Intrauterine device.
   c. Hormonal contraceptive taken or administered via oral (pill), transdermal (patch), intravaginal, implantable, or injectable method.
   d. Sterilization of a female participant's male partner before entry into the study.
   e. Sexual abstinence.

      Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception. Sexual abstinence is considered an effective method only if defined as refraining from heterosexual intercourse from providing consent 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. Participants assigned male sex at birth with partner(s) of childbearing potential who agree to use adequate contraception through 6 months after dosing. If their partner is pregnant, males

must agree to use a condom. Male participants must also refrain from sperm donation through 6 months after dosing.

9. Able to understand and comply with study requirements/procedures (if applicable, with assistance by a caregiver, surrogate, or legally authorized representative) based on the assessment of the Investigator.

Exclusion Criteria

A potential participant who meets **any** of the following exclusion criteria must be excluded from the study.

1. Prior receipt of a COVID-19 vaccine, convalescent plasma, or mAb, including in the setting of a clinical trial.

   Note: immune compromised participants (eg, due to hematological malignancy, anti-CD20 medication use, etc.) who have completed a COVID-19 vaccine series and who have a documented negative SARS-CoV-2 Spike ("S") protein serum antibody test drawn a minimum of four weeks after completion of the recommended dosing series may be screened and subsequently enrolled if other criteria are met, including a confirmatory negative "S" protein antibody test at the time of screening. This test must be confirmed negative prior to enrollment in either Cohort A or Cohort B.

2. Receipt of any investigational product within 30 days or 5 half-lives (whichever is longer) before the day of enrollment.

3. Is acutely ill or has any of the following symptoms:

Fever ≥38 °C (≥100.4 °F)	Loss of taste
Shortness of breath/difficulty breathing	Loss of smell
Chills (shivering)	Sore throat
Cough	Congestion (stuffy or runny nose)
Fatigue (low energy or tiredness)	Nausea
Muscle or body aches	Vomiting
Headache	Diarrhea

   Note: Participants meeting this criterion may be scheduled for rescreening within the relevant window periods.

4. Has received or plans to receive a non-COVID-19 vaccine within 28 days before or after dosing (except for seasonal influenza vaccine, which is not permitted within 14 days before or after dosing).

5. Known allergy/sensitivity or hypersensitivity to the study drug, including excipients.

6. Is pregnant, as confirmed with a positive pregnancy test at Screening or on the day of dosing (Day 1), or breastfeeding.

7. Known 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.

8. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, autoimmune disease or immune compromise, or neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed; see Appendix 4).
9. Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the Investigator, might confound the results of the study or confer an additional risk to the participant by their participation in the study.

Details of Study Treatments

ADG20 is a fully human monoclonal immunoglobulin G1 antibody targeted to an epitope in the receptor binding domain of the spike glycoprotein of SARS-CoV-2. All participants will receive either ADG20 300 mg administered as a single 2 mL or 3 mL IM injection or placebo (normal saline) in a volume matched to the active treatment.

Criteria for Evaluation

Efficacy:

Efficacy assessments will include SARS-CoV-2 testing, evaluation of signs and symptoms of COVID-19, and determination of health care resource utilization.

Safety:

Safety will be assessed in an ongoing manner throughout the study. Safety assessments will include the following: complete physical examinations, vital signs, clinical laboratory assessments, injection-site reactions, hypersensitivity reactions, and adverse events (AEs, including serious AEs, medically attended AEs, AEs of special interest, and solicited AEs for injection site reactions).

Pharmacokinetics/Immunogenicity:

Blood samples will be collected at specified time points for PK and anti-drug antibody (ADA) assessment. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of ADG20. Antibodies may be further characterized for their ability to neutralize the activity of ADG20.

Statistical Analysis

Each cohort will be treated independently under this master protocol. Cohorts A and B will each have a separate randomization list. Efficacy and safety analyses will be performed separately for each cohort, with each cohort allocated a 2-sided alpha of .05.

Enrollment in Cohort A (PEP) and in Cohort B (PrEP) was suspended on 11-Jan-2022 after emergence and global spread of the Omicron variant in regions enrolling the trial, beginning in December 2021, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. Therefore, the primary analysis is focused on evaluating

ADG20 300 mg IM treatment in the population randomized prior to the emergence of the Omicron variant.

A preliminary efficacy and safety analysis was conducted with a data cutoff of 02-Mar-2022. The primary efficacy objective was to assess efficacy of ADG20 in the setting of susceptible variants (pre-emergence of Omicron); thus, the primary efficacy population included participants randomized on or prior to 30-Nov-2021 and followed for at least 2 weeks (up to 15-Dec-2021) when Omicron became the predominant variant in the US. The efficacy of ADG20 after the emergence of the Omicron variant was evaluated independently as an exploratory analysis in participants randomized after 30-Nov-2021. A full analysis of efficacy following a database soft lock (data cutoff: 11-Apr-2022) was carried out when all enrolled participants had a minimum of 3 months follow-up or had discontinued. A 6-month safety analysis will be carried out following a database soft lock when all enrolled participants have a minimum of 6 months follow-up or have discontinued. A final safety analysis will occur after all enrolled participants have been followed through 14 months/EOS or have discontinued.

The population for the primary efficacy analyses in each cohort are:

- Cohort A: RT-PCR-negative participants pre-emergence of Omicron (mFAS-1 pre-Omicron)
- Cohort B: RT-PCR-negative and seronegative participants pre-emergence of Omicron (mFAS pre-Omicron)

These analysis sets are defined as follows:

Pre-Emergence of Omicron Analysis Set	Includes all participants randomized on or prior to 30-Nov-2021, allowing participants to be followed a minimum of 2 weeks through 15-Dec-2021 when Omicron became the predominant variant.
Modified Full Analysis Set – RT-PCR-negative and seronegative (mFAS)	Includes all randomized participants without prior or current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative and seronegative). If either central RT-PCR or central serology is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.
Modified Full Analysis Set – RT-PCR-negative (mFAS-1)	Includes all randomized participants without current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative regardless of serology status). If central RT-PCR is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.

In the efficacy analysis, participants will be analyzed based on the treatment they are randomized to, irrespective of what they actually might have received.

Safety analyses will be performed in the Safety Set, defined as all participants who receive study drug. In the safety analysis, participants will be analyzed based on the study drug received.

Cohort A (PEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 28 days after randomization. The original sample size of 1078 participants was planned with 90% power, 2-sided α=.05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 5% per 28 days in the placebo group and 1.5% in the ADG20 group. A sample size of 1270 participants

was planned to account for 15% participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort A on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort A only included events through 28 days after randomization or the emergence of Omicron, whichever was earlier. Prior to suspension of enrollment, 487 participants were randomized in Cohort A, of which approximately 377 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 351 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative pre-Omicron). The primary efficacy population yielded approximately 14 events through 28 days or emergence of Omicron, whichever was earlier, for the analysis. With 14 events, any observed efficacy >68% would be statistically significant at 2-sided α=.05.

Cohort B (PrEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 3 months. The original sample size of 4628 participants was planned with 84% power, 2-sided α=.05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 1% per 3 months in the placebo group and 0.3% in the ADG20 group. A sample size of 5142 participants was planned to account for 10% participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort B on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort B only included events through 3 months after randomization or the emergence of Omicron, whichever was earlier. Prior to suspension of enrollment, 2094 participants were randomized in Cohort B, of which approximately 1639 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 1477 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative and seronegative pre-Omicron). A higher than expected aggregate attack rate resulted in a sufficient number of cases to enable this cohort to be a fully powered study to detect clinically meaningful and statistically significant treatment differences. Based on a 3.6% aggregate attack rate, 974 participants in a 1:1 randomization ratio provides 90% power to detect a statistically significant treatment effect when the true RR is 0.3 with 2-sided α=.05. Therefore, the current sample size of 1477 provided sufficient statistical power to carry out the primary efficacy analysis, as well as preliminary evaluation of safety.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACIP	Advisory Committee on Immunization
ADA	anti-drug antibody
ADE	antibody-dependent enhancement
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CLI	COVID-19-like illness
CoV	coronavirus
DAIDS	Division of AIDS
eCRF	electronic case report form
EDC	electronic data capture
e-Diary	electronic diary
EOS	end of study
ET	early termination
EUA	emergency use authorization
FAS	full analysis set
Fc	fraction crystallizable
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICE	intercurrent event
ICF	informed consent form
ICU	intensive care unit
iDMC	independent data monitoring committee
IEC	independent ethics committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IM	intramuscular(ly)
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction
LTFU	long-term follow-up
MAAE	medically attended adverse event

Abbreviation	Definition
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
NP	nasopharyngeal
ODM	operational data mode
PBPK	physiologically based pharmacokinetic
PCS	potentially clinically significant
PEP	post-exposure prophylaxis
PK	pharmacokinetics
POC	point of care
PP	per-protocol
PrEP	pre-exposure prophylaxis
PT	preferred term
QSP	quantitative systems pharmacology
RBD	receptor binding domain
RR	risk ratio
RSV	respiratory syncytial virus
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
SoA	schedule of assessments
SOC	system organ class
SOP	standard operating procedures
SOT	solid organ transplant
SpO_2	oxygen saturation
sVNA	serum virus neutralizing antibody
TEAE	treatment-emergent adverse event
UP	unanticipated problem
US	United States
USP	United States Pharmacopeia
β-hCG	beta human chorionic gonadotropin

PHARMACOKINETIC ABBREVIATIONS

AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve extrapolated to infinite time
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from zero up to the last concentration above the lower limit of quantification
CL	Clearance
C_{max}	Maximum plasma concentration
$t_{½}$	Plasma concentration half-life
T_{max}	Time to reach C_{max}
V_{ss}	Apparent volume of distribution at steady state

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 heathy 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

Dosing in the EVADE study was initiated in April 2021; follow-up is ongoing. As of 11-Jan-2022, 487 participants were randomized in Cohort A and 2101 participants were randomized in Cohort B; enrollment was suspended on this date due to the global spread of the Omicron variant. Pre-specified analyses in the pre-Omicron population demonstrated that adintrevimab provided a statistically significant and clinically meaningful reduction in the risk of developing symptomatic COVID-19 compared with placebo through Day 28 in adults with no

current SARS-CoV-2 infection who were recently exposed to SARS-CoV-2 and through 3 months in adults with no current or prior SARS-CoV-2 infection who were at high risk for acquiring SARS-CoV-2. Further details are provided in the IB.

In addition to this study, Adagio Therapeutics, Inc. (hereafter referred to as Adagio) 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, 48 participants across 6 dose levels (300 mg IM, 500 mg IV, 600 mg IM, 1200 mg IM, 1200 mg IV, and 4500 mg IV) received ADG20 (8 per dose cohort) and 12 received placebo (2 per dose cohort). All participants in Cohorts 1-3 have completed the study; safety follow-up is ongoing in Cohorts 4-6. Findings from the unblinded analysis of Cohorts 1-3 and preliminary findings from blinded data review with a minimum of 4 months of follow-up in Cohorts 3-6 are as follows:

- No SAEs, AESIs (hypersensitivity reactions or infusion-related reactions), drug-related AEs, or ISRs have been reported as of 01-Aug-2022.
- The observed ADG20 PK appears to be dose proportional, with a median observed half-life of approximately 91 days for the 300 mg IM dose.
- In an exploratory research analysis, 50% sVNA titers following a single 300 mg IM dose of ADG20 were compared to peak titers induced 7 to 30 days following 2 doses of the AZD1222 (Vaxzevria) or mRNA-1273 (Spikevax) vaccines given according to current on-label or EUA dosing:
  - By Day 2, 50% sVNA titers against an authentic SARS-CoV-2 D614G variant in ADG20-treated participants were similar to peak titers generated following the mRNA-1273 vaccine series and significantly exceeded peak titers generated after the AZD1222 vaccine series.
  - By Day 7, 50% sVNA titers were significantly higher than peak titers generated by the mRNA-123 vaccine series and remained above mRNA-1273-elicited titers for at least 3 months.
  - By 6 months, 50% sVNA titers in ADG20-treated participants declined to levels similar to or exceeding peak responses following the mRNA-1273 or AZD1222 vaccine series, respectively.

1.1.2.2. Study ADG20-TRMT-001 (STAMP)

Study ADG20-TRMT-001 (STAMP) is a randomized, double-blind, placebo-controlled, multicenter Phase 2/3 study to evaluate the safety, efficacy, and PK of ADG20 (300 mg IM) versus placebo in the treatment of mild to moderate COVID-19 in adult and adolescent participants at high risk of disease progression. Dosing in the study was initiated on 18-Aug-2021; follow-up is ongoing. As of 11-Jan-2022, 399 participants were randomized in the study and enrollment was suspended on this date due to the global spread of the Omicron variant.

Pre-specified analyses in the population of participants with non-Omicron COVID-19 demonstrated that treatment with adintrevimab provided a statistically significant and clinically meaningful reduction in the risk of COVID-19–related hospitalization or all-cause death through Day 29 compared with placebo. Further details on the study are provided in the IB.

1.2. Background on the Disease/Condition

Coronaviruses are ubiquitous pathogens with high pandemic potential. In recent years, 3 pathogenic CoVs have crossed into the human population from zoonotic sources: SARS-CoV, Middle East respiratory syndrome CoV, and SARS-CoV-2. SARS-CoV-2, the most recent of these CoVs, 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. Approximately 20% (~73 million) of reported cases have occurred in the US alone with >876 000 deaths to date (Johns Hopkins University & Medicine 2022a). 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 the Second World War (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.

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 2022d). A subset of individuals with initially mild or moderate symptoms may experience disease progression. Dyspnea developed after a median of 5 days of symptom onset with hospital admission occurring after a median of 7 days of 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 and 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 patients with mild disease may experience prolonged symptoms, with only 65% of patients 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, Down syndrome, heart conditions (heart failure, coronary artery disease, cardiomyopathies, and hypertension), immunocompromised state (eg, SOT), obesity (BMI of ≥30 kg/m^2), pregnancy, sickle cell disease, smoking, and diabetes (CDC 2021b). 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).

There are currently over 20 COVID-19 vaccines spanning several platforms (eg, mRNA, adenovirus, inactivated) that are approved or available under emergency use across various regions globally, with over 50 in Phase 3 development. However, vaccine roll-out has been persistently slow worldwide, with only ~53% of the population fully vaccinated as of 27-Jan-2022 (Johns Hopkins University & Medicine 2022b), at least in part due to unequal vaccine distribution and high rates of vaccine hesitancy in some countries (Solís Arce 2021). Furthermore, available data suggest that vaccine efficacy wanes over time, leading to the recommendation for booster doses in some regions at 6 months for all adults and some adolescents (CDC 2022b). Recent studies have also demonstrated that certain immune compromised individuals (eg, those with hematologic malignancies, hematopoietic stem cell, or SOT recipients, and people actively receiving chemotherapy for cancer or using immunosuppressive medications) mount poor neutralizing antibody responses to currently available vaccines (Agha 2021; Boyarsky 2021). In some cases, even a third dose of vaccine fails to induce significant antibody responses in SOT recipients (Kamar 2021).

As the COVID-19 pandemic has persisted over time and the number of vaccinated individuals or those with natural infection continues to rise, SARS-CoV-2 breakthrough infections in fully vaccinated individuals and re-infections in those who have recovered from prior infection have become more common due to emerging variants that are relatively resistant to vaccine-induced immunity or natural immunity from prior infection, as well as waning natural/vaccine-induced immunity over time (CDC 2021c; Levin 2021; Lipsitch 2022; UKHSA 2022). In particular, vaccine efficacy has been shown to be decreased against the Delta variant and even more so against the Omicron variant, especially for the endpoint of symptomatic infection (Collie 2021; Li 2021; Lopez Bernal 2021). Though breakthrough infections may be less severe, severe COVID-19 (CDC 2021a; Wang 2022) and post-acute sequalae of COVID-19 (Bergwerk 2021) following breakthrough infections have been reported.

In conclusion, novel approaches are urgently needed to ensure the availability of safe and effective options for the broader population to curtail the current COVID-19 pandemic and potentially address future emergent CoVs with pandemic potential.

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 prophylaxis have taken on unprecedented urgency, with a primary focus on vaccines. However, there are still several unanswered questions regarding the available vaccines. Chief among these are the duration of protection, long-term safety profile, effectiveness against emerging viral variants, the ability to prevent transmission, and effectiveness in pediatric and immunocompromised populations.

The therapeutic use of passive polyclonal antibodies to prevent viral infections, including hepatitis B, varicella, cytomegalovirus, rabies, and RSV, is well established. More recently, mAbs have been approved for the prevention or treatment of viral infections, including palivizumab for the prevention of RSV infection, ibalizumab for the treatment of HIV-1 infection in heavily treatment-experienced adults, atoltivimab/maftivimab/odesivimab combination and ansuvimab for treatment of Zaire ebolavirus infection, and SII RMab for post-exposure prophylaxis of rabies in India. Notably, mAb prophylaxis is the only currently licensed therapy for RSV.

The unique properties of mAbs address several limitations of vaccines in disease prevention. While vaccines require several weeks, and in some cases, multiple doses, to induce a protective immune response, the protection provided by mAbs is nearly immediate, making them well-suited for post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).

In support of the use of mAbs in PEP, results from two SARS-CoV-2 mAb programs demonstrate the ability to protect non-immune (seronegative) and non-infected (RT-PCR negative), recently exposed individuals from symptomatic COVID-19 across a variety of exposure settings, including households and nursing homes (Eli Lilly and Company 2022; Regeneron 2022). These data led to emergency use authorizations for casirivimab/imdevimab and bamlanivimab/etesevimab in individuals with suboptimal immunity and known recent exposure to an active case. However, the authorizations for these mAbs were revised in January 2022 based on the finding that neither product retains in vitro activity against the Omicron variant, which is currently the predominant variant circulating in the United States. As such, both products are currently not authorized for use in any region of the US at this time (FDA 2022).

The use of mAbs in PrEP is supported by data from the tixagevimab/cilgavimab program, which demonstrated the ability of this combination mAb product to provide durable protection due to the extended half-life through a median of 3 months of follow-up in the primary analysis and 6.5 months of follow-up in a post-hoc analysis (AstraZeneca 2022). These data led to emergency use authorization for tixagevimab co-packaged with cilgavimab for PrEP in individuals who are not currently infected with and have not had a known recent exposure to an individual infected with SARS-CoV-2 who have moderate to severe immune compromise and either may not mount an

adequate immune response to COVID-19 vaccination or for whom vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components.

Monoclonal antibodies do not rely on an intact immune system for efficacy, and thus may confer protection in those with impaired immune function, such as the immune compromised and patients on immunosuppressive therapy. Another potential limitation of vaccines is variable initial antibody responses coupled with waning of immunity over time. Extended half-life mAbs address this limitation by providing more predictable antibody levels and duration of protection. As they do not alter the immunologic repertoire, mAbs may also act additively with vaccines, providing a bridge of protection until the vaccine reaches maximal efficacy or augmenting the immunological response triggered by the vaccine.

Given these potential advantages of mAbs in the prevention of respiratory virus infection and disease, several mAbs are currently in clinical development for prevention of respiratory virus infection and/or disease, including agents for influenza virus, RSV, and SARS-CoV-2 (Corti 2017; Walker 2018).

The potential for ADG20 to provide broad immediate and longer-term protection to a wide range of individuals is supported by nonclinical data (see Section 1.1.1), in which ADG20 displayed binding and/or neutralizing activity against multiple SARS-CoV-2 variants, and preliminary clinical data (see Section 1.1.2.1) that demonstrate the extended half-life of ADG20 (97 days) and robust sVNA titers against the D614G variant through 6 months following a single 300 mg IM injection of ADG20. Considering this potential, Adagio is developing ADG20 for PEP for individuals with documented, recent exposure to SARS-CoV-2 and for PrEP for individuals with high ongoing risk of exposure to SARS-CoV-2 due to their occupation, housing situation, or other activities.

The study will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements.

1.3.2. Rationale for Use of Placebo-Control

Despite the availability of COVID-19 vaccines for pre-exposure prophylaxis for adults and, in some regions, adolescents and children 5 years of age and older, a placebo-controlled study is acceptable as these vaccines may not be widely available for use globally and a sizeable portion of the global population remains resistant to vaccination. Only those participants who intend to delay vaccination for 6 months after discussion of the risks/benefits of trial enrollment in the setting of current or potential future vaccine availability and their underlying risk for development of severe COVID-19 are eligible for enrollment in the trial. Participants who receive vaccine within the first 6 months of enrollment into the study may undergo additional assessments to evaluate the potential impact of ADG20 on vaccine-induced immunity.

Prior to protocol version 6.0, if a participant wished to receive a vaccine during the study, they could request unblinding to support informed decision making; as of protocol version 6.0, unblinding is no longer necessary.

Similarly, despite availability of SARS-CoV-2 mAbs for PEP or PrEP for certain individuals under emergency use authorization in some regions, a placebo-controlled study is acceptable as

these mAbs are not widely available for use globally. Potential participants under consideration for enrollment in the study and who are eligible for mAbs offered under EUA or similar authorization outside the US will be advised of their availability and provided information regarding how to obtain them as part of the informed consent process.

1.3.3. Pregnant and Breastfeeding Individuals

Pregnant individuals are at increased risk for severe illness from COVID-19 when compared to nonpregnant individuals and may also be at increased risk for other poor outcomes, such as preterm birth (CDC 2022a). The risks of ADG20 treatment for pregnancy and the developing fetus are unknown. As with other COVID-19 mAb products (FDA 2021b; FDA 2021a), no specific risks to pregnant individuals and their fetuses or to breastfeeding individuals and their infants have been identified based on ADG20 nonclinical safety data. Because ADG20 is directed against an exogenous antigen, administration is not anticipated to impact endogenous pathways.

Human IgG1 antibodies are known to cross the placental barrier; therefore, ADG20 has the potential to be transferred from the mother to the developing fetus. Similarly, maternal IgG is known to be present in breastmilk. Robust secretion of SARS-CoV-2-specific IgA and IgG antibodies was observed in breastmilk for 6 weeks after vaccination (Low 2021; Perl 2021). However, because of the large size of ADG20, it is unlikely to be absorbed from the infant gut in large quantities. Additionally, no effect on infant health from possible absorption of ADG20 is anticipated given the antibody targets an exogenous protein not present in the human body.

Addition of pregnant women is also supported by the results of nonclinical studies. Specifically, in a tissue cross-reactivity study using human fetal tissues, no specific binding of ADG20 was observed. For additional details regarding the fetal tissue cross-reactivity study, please refer to the IB. Further, based on unblinded review of Phase 2 safety data in the first 200 participants enrolled across Cohorts A and B of this study (EVADE), the iDMC endorsed opening of enrollment in these cohorts to pregnant and breastfeeding women. Based on the increased risk for poor COVID-19 outcomes for pregnant individuals, the low assessed risk associated with ADG20 administration, and the iDMC recommendation, enrollment of pregnant or breastfeeding individuals may be opened in the Phase 3 portion of this trial in regions permitted by health authorities and local ethics committees.

All women of childbearing potential will undergo pregnancy testing prior to dosing and at the end of study. Participants who become pregnant during the study will be followed for the outcome of their pregnancy for the duration of the study.

Information regarding pregnancies occurring in female partners of male study participants will not be solicited as the risk of exposure is negligible in this scenario.

1.3.4. Rationale for Dose Selection

ADG20 will be administered IM at a dose of 300 mg. This dose was selected based on 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 projects that the 300 mg IM dose is expected to maintain serum ADG20 concentrations ~500-fold greater than the in vitro IC_{50} (0.001 µg/mL) against authentic SARS-CoV-2 (USA-WA1/2020) in Vero E6 cells for a minimum of 6 months in ≥90% of simulated patients. This threshold is similar to the 50% SARS-CoV-2 geometric mean titer observed on Day 35 (7 days after a second vaccine dose) with the COVID-19 vaccine BNT62b1 (Mulligan 2020), which has been shown to confer 95% protection against COVID-19 through 2 months after the second dose (Polack 2020).

Further, in the context of a prevention study, it is also likely that a small subset of participants, particularly in the subgroup with known recent exposure, will have very early asymptomatic SARS-CoV-2 infection and low or undetectable viral load at baseline. At the 300 mg IM dose, the QSP/PBPK model forecasted ADG20 lung interstitial concentrations range from approximately 100 to 275-times the ADG20 IC_{90} against authentic virus (USA-WA1/2020) at 28 days postdose. These ADG20 lung interstitial exposures indexed to IC_{90} exceed those projected for bamlanivimab, a SARS-CoV-2-specific mAb that has shown clinical benefit and reductions in viral load in ambulatory patients with symptomatic, mild to moderate COVID-19 and high viral load (Chen 2021). Thus, ADG20 has the potential to provide adequate exposure to prevent progression of early SARS-CoV-2 infection in participants infected with SARS-CoV-2 variants for which a dose of 300 mg IM is anticipated to provide adequate tissue exposure, such as Alpha, Beta, Delta, and Gamma. These findings suggest that the 300 mg IM dose is appropriate for both prevention of infection in individuals without prior exposure to SARS-CoV-2, as well as for prevention of disease progression in individuals with very early asymptomatic or pre-symptomatic infection associated with relatively low or undetectable viral load.

The dose level is fixed, with no dose adjustment required for body weight, renal impairment, or moderate hepatic impairment. Similarly, no dose adjustment is required for adolescents weighing at least 40 kg.

Preliminary safety, PK, and sVNA titer data from the 300 mg IM cohort of the Phase 1 Study ADG20-1-001 further support the appropriateness of the 300 mg IM dose chosen for study (see Section 1.1.2.1).

Further details on dose selection are provided in the IB.

1.4. Risks and Benefits

1.4.1. Benefits to the Target Study Population

Two target populations are included in this trial and will be enrolled in separate cohorts. Cohort A (PEP) will enroll adults and adolescents with no known history of SARS-CoV-2 infection and who are at risk of SARS-CoV-2 infection and COVID-19 due to reported recent exposure (within 5 days) to an individual with a laboratory-confirmed diagnosis of SARS-CoV-2 infection (index case).

Cohort B (PrEP) will enroll adults and adolescents with no known history of SARS-CoV-2 infection who are at risk of SARS-CoV-2 infection and COVID-19 due to risk of ongoing SARS-CoV-2 exposure based on occupation, housing situation, social activities, and/or religious activities. Examples of high-risk occupations may include health care workers and staff of nursing homes or correctional facilities. High-risk housing situations may include long-term care facilities or student housing. Participants (including adolescents) may also be considered at risk due to participation in sports or recreation requiring close contact. A worksheet designed to facilitate assessment of risk factors for SARS-CoV-2 exposure is presented in Appendix 3.

Additionally, the study will allow enrollment of participants with risk factors associated with severe complications from COVID-19 in the event they acquire a SARS-CoV-2 infection, including older adults (≥55 years of age), and those with underlying conditions such as chronic cardiopulmonary disease, diabetes, obesity, or an immune compromised state, and may include pregnant/breastfeeding women (allowed following the iDMC review of the Phase 2 safety data in regions permitted by health authorities and local ethics committees). A detailed list of risk factors associated with severe complications from COVID-19 is presented in Appendix 4.

These populations that are at high risk of SARS-CoV-2 acquisition, including the subset with elevated risk of severe COVID-19 disease, are likely to derive the greatest benefit from a preventive mAb.

1.4.2. Risks from Study Participation

Because ADG20 targets an exogenous epitope (spike protein) that is not present in humans, significant safety issues are not expected. No safety concerns for ADG20 have been identified in data generated across the ADG20 pre-clinical and clinical development program to date (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 administration-related reactions occur within the first 24 hours after administration. Severe reactions are rare (see Section 1.1.2 and the IB) and are more often associated with mAbs targeting human proteins rather than exogenous targets.

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 infusion as the target cell burden is greatest under these conditions.

As a further precaution for acute injection reactions, study drug administration will occur in a setting where 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. Participants will be monitored at the administration site for up to 4 hours postdose, depending on enrollment group.

There is a risk that receipt of ADG20 may lead to false positive serology testing results using commercially available assays that detect antibodies to the SARS-CoV-2 spike protein. For this reason, participants will be encouraged not to seek testing outside the study. If a participant requires testing outside of the protocol-mandated testing schedule, the Sponsor will provide

guidance to the Clinical Site regarding an appropriate assay that identifies antibodies to the viral nucleocapsid protein (and not the spike protein).

There is a risk that receipt of a SARS-CoV-2 monoclonal antibody 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; CDC 2022c) 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 and enrolled participants were advised of the potential risk of receiving a vaccine while participating in this trial. Participants were also made aware of the risk involved in delaying vaccination during an active pandemic as part of the informed consent process. 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 2022c). Participants dosed with study drug (ADG20 or placebo) were notified of this change in ACIP recommendation. Participants who receive a vaccine during study conduct may undergo additional assessments as detailed in Section 3.5.2.7.

There is a theoretical risk that receipt of a mAb against SARS-CoV-2 may cause a paradoxical increase in the risk of disease acquisition or/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 RSV (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 sub-optimal 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 antibody 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 mild to moderate COVID-19 (Eli Lilly and Company 2022; 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

All participants included in this study will have no known history of prior or current SARS-CoV-2 infection and will be at risk of SARS-CoV-2 acquisition either due to reported recent exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case) or a high risk of ongoing SARS-CoV-2 exposure based on occupation, housing situation, or other activities. The study will be enriched for participants at increased risk of complications from COVID-19 based on age or underlying comorbidities, as these at-risk populations are likely to

derive the greatest benefit from a preventive mAb therapy. Importantly, only individuals who agree to delay vaccination for at least 6 months after discussion of potential risks/benefits and alternative available options for prophylaxis of COVID-19, will be enrolled in the study.

Considering the persistent lack of universal adoption of COVID-19 vaccines, the ongoing emergence of SARS-CoV-2 variants, the need for vaccine alternatives for immune compromised individuals and the low assessed risk of safety concerns with a mAb targeting an exogenous non-host epitope, the overall benefit-risk assessment for this study is considered favorable for prevention 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 Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

For Cohort A (PEP), in participants with no known history of SARS-CoV-2 infection and reported recent exposure to SARS-CoV-2 (as defined by the criteria in Section 3.3.1), the following objectives and endpoints apply (Table 2.1):

Table 2.1 Objectives and Endpoints: Cohort A (PEP)

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

Objectives	Endpoints
Secondary (Cohort A [PEP])	
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in each of the following populations: • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 diagnosis. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.
Key Secondary Objective: To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through Day 28 in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through Day 28. Supplementary: • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through Day 28.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months, in each of the following populations: • All randomized participants without current SARS-CoV-2 infection at baseline. • All randomized participants without prior or current SARS-CoV-2 infection at baseline. • All randomized participants.	Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) as determined by positive RT-PCR or serology through 3 months. Supplementary: • Time from randomization to first SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19). • Probability of SARS-CoV-2 infection (asymptomatic or symptomatic COVID-19) through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through Day 28 in all randomized participants with prior but not current SARS-CoV-2 infection at baseline.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28. Supplementary: • Time from randomization to first RT-PCR-confirmed symptomatic COVID-19. • Probability of RT-PCR-confirmed symptomatic COVID-19 through Day 28.

Objectives	Endpoints
To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection, in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	• Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by RT-qPCR (nasal sample) on Days 8 and 15. • Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology through Day 28.
To evaluate the impact of ADG20 compared with placebo on viral load in all randomized participants with asymptomatic SARS-CoV-2 infection detected by RT-qPCR (nasal sample) at baseline via surveillance.	• Peak post-baseline SARS-CoV-2 viral load as measured by RT-qPCR • SARS-CoV-2 viral load as assessed by RT-qPCR change from baseline to Day 8 and Day 15.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

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

For Cohort B (PrEP), in participants with no known history of SARS-CoV-2 infection and no known recent exposure to SARS-CoV-2, but whose circumstances put them at increased risk of exposure to SARS-CoV-2 and symptomatic COVID-19, the following objectives and endpoints apply (Table 2.2).

Table 2.2 Objectives and Endpoints: Cohort B (PrEP)

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

Objectives	Endpoints
To evaluate the efficacy of ADG20 compared with placebo in the prevention of RT-PCR-confirmed symptomatic COVID-19 through 3 months in all randomized participants.	Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of SARS-CoV-2 infection (based on RT-PCR or serology) regardless of symptoms through 3 months in all randomized participants.	Proportion of participants with SARS-CoV-2 infection regardless of symptoms through 3 months.
To evaluate the efficacy of ADG20 compared with placebo in the prevention of asymptomatic SARS-CoV-2 infection (based on serology) in all randomized participants without prior or current SARS-CoV-2 infection at baseline.	Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6.
To evaluate the effect of ADG20 on the following clinical and virologic parameters in all randomized participants with laboratory confirmed symptomatic COVID-19 through CLI Day 28:	
Severity of COVID-19.	Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28.
Duration of COVID-19.	Time to sustained resolution of COVID-19 symptoms through CLI Day 28.
COVID-19-related medically attended outpatient visits.	Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28.
COVID-19-related hospitalization.	Proportion of participants with a COVID-19-related hospitalization through CLI Day 28.
COVID-19-related mortality.	COVID-19-related mortality through CLI Day 28.
All-cause mortality.	All-cause mortality through CLI Day 28.
SARS-CoV-2 viral load.	Viral load from CLI Day 1 sample assessed by RT-qPCR.
To evaluate the pharmacokinetics of ADG20 in serum.	PK parameters of ADG20 including but not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, T_{max}, CL, $t_{1/2}$, and V_{ss}.
To evaluate the immunogenicity of ADG20.	Incidence of ADAs against ADG20.

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

Exploratory endpoints for Cohort A (PEP) and Cohort B (PrEP) are provided in Table 2.3.

Table 2.3 Exploratory Objectives and Endpoints: Cohorts A and B

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

ICU=intensive care unit; RT-PCR=reverse transcription-polymerase chain reaction.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2/3, multicenter, double-blind, placebo-controlled, randomized study of the mAb ADG20 in the prevention of symptomatic COVID-19 in adults and adolescents with no known history of SARS-CoV-2 infection but whose circumstances place them at increased risk of acquiring SARS-CoV-2 infection and developing symptomatic COVID-19. This objective will be independently evaluated in participants with reported recent exposure to an individual diagnosed with a SARS-CoV-2 infection (Cohort A, PEP) and in a cohort of participants with no reported exposure to SARS-CoV-2 (Cohort B, PrEP). These cohorts will be enriched for participants whose advanced age (≥55 years old) or health status places them at risk for severe COVID-19 or COVID-19 complications.

This Phase 2/3 study will enroll in two parts: a Phase 2 safety lead-in consisting of 200 adult participants enrolled across Cohorts A and B and a separate Phase 3 expansion for enrolling the remainder of participants in each cohort. The first 30 participants (across both cohorts) in Phase 2 will constitute a sentinel group and will undergo extended monitoring as detailed below. After a combined number of approximately 200 adult participants (aged ≥18 years) across Cohorts A and B are enrolled in Phase 2 (inclusive of the 30 sentinel participants) and followed for 4 weeks, an interim analysis of safety will be performed and reviewed by the iDMC. Enrollment of adult participants will continue during this review and will follow Phase 2 post-injection monitoring requirements. Enrollment of adolescents in each cohort will open only upon sponsor communication to sites after iDMC review of Phase 2 data and only in regions permitted by

health authorities and local ethics committees. Pausing guidelines triggering iDMC ad hoc reviews and additional details on safety monitoring are provided in Section 5.12.

The participants in Phase 2 will be combined with the corresponding Phase 3 expansion population in each cohort for the final efficacy and safety analyses.

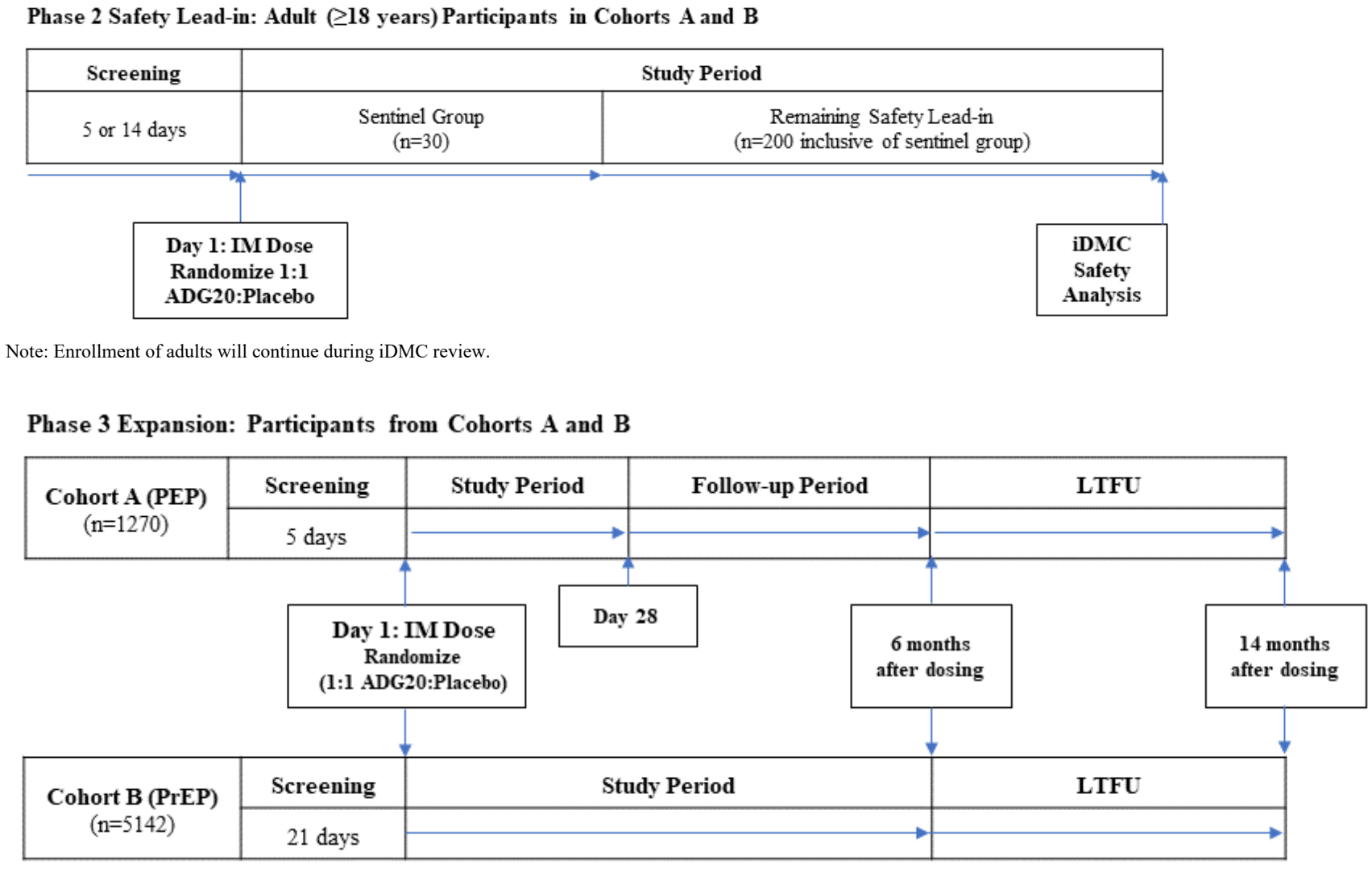
The participant population, study procedures, and endpoints will be identical in Phase 2 and the Phase 3 expansion portions of the study with the following exceptions:

- The sentinel group will be restricted to adult participants (aged ≥18 years) and the post-injection monitoring period will be 4 hours. Participants will then be assessed daily by telephone through Day 4 for hypersensitivity reactions.
- In the remainder of Phase 2, enrollment will be restricted to adult participants (aged ≥18 years) and the post-injection monitoring period may be reduced to no less than 2 hours after safety data review.
- After iDMC review of Phase 2 data, enrollment will include both adult (aged ≥18 years) and adolescent (aged 12 to <18 years) participants (only in regions permitted by health authorities and local ethics committees). The post-injection monitoring period for adult participants may be decreased to a minimum of 1 hour based on iDMC recommendation. The post-injection monitoring period will be 2 hours for the first 20 adolescent participants. If no hypersensitivity reactions are observed in this group, the post-injection monitoring period for subsequent adolescent participants may also be reduced to a minimum of 1 hour.

If any hypersensitivity reactions are observed in Phase 2, subsequent participants will be monitored for 2 hours post-injection. This period may be reduced to a minimum of 1 hour based on iDMC recommendation upon review of additional safety data.

The study design is shown in Figure 3.1.

Figure 3.1 Study Design Schematic



Note: Enrollment of adults will continue during iDMC review.

IM=intramuscular; iDMC=independent data monitoring committee; LTFU=long-term follow-up; PEP=post-exposure prophylaxis; PrEP=pre-exposure prophylaxis

3.1.1. Study Definitions

3.1.1.1. COVID-19-Like Illness

As of protocol version 6, monitoring for CLI symptoms (Table 3.1) **is discontinued.** Spontaneously reported CLI symptoms will be captured as AEs as per Section 4.1.1 and Section 4.1.3 of the protocol.

Table 3.1 Guidelines for COVID-19-Like Illness Qualifying Symptoms

Duration	Symptom
Any duration	Fever
	Shortness of breath/difficulty breathing
	Loss of taste or smell
Present for ≥2 days	Chills (shivering)
	Cough
	Fatigue (low energy or tiredness)
	Muscle or body aches
	Headache
	Sore throat
	Congestion (stuffy or runny nose)
	Nausea
	Vomiting
	Diarrhea

3.1.1.2. Symptomatic COVID-19

Symptomatic COVID-19 will be defined as having laboratory confirmed (RT-PCR) SARS-CoV-2 infection and an onset of symptoms as defined below occurring no more than 14 days from the date of positive RT-PCR test sample collection:

At least ONE of the following respiratory signs/symptoms:

- Clinical evidence of pneumonia (eg, SpO_2 ≤94% on room air, requiring new initiation of supplemental oxygen or radiographic evidence of pneumonia).
- New or worsening dyspnea/shortness of breath, OR

At least TWO of the following systemic symptoms:

- Fever ≥38 °C (≥100.4 °F)
- Cough
- Myalgia/muscle pain.
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhea (only one finding to be counted toward endpoint definition)

- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)
- Headache
- Sore throat

Severe/critical COVID-19 is defined as having laboratory confirmed (RT-PCR) SARS-CoV-2 infection plus any of the following:

- Clinical signs indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO_2 ≤93% on room air at sea level or partial pressure of oxygen to fraction of inspired oxygen ratio <300)
- Evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors)
- Respiratory distress (defined as needing oxygen therapy, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation)
- Significant acute renal, hepatic, cardiovascular, or neurologic dysfunction
- Admission to an ICU
- Death

See Appendix 5 for severity categorization as adapted from the FDA Guidance for Industry "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention" (FDA 2021a).

3.1.1.3. COVID-19 Time to Sustained Resolution

In participants with laboratory confirmed symptomatic COVID-19, time from the reported symptom onset to sustained resolution of symptoms from CLI Day 1 through CLI Day 28 will be defined in the SAP.

3.1.1.4. 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, ICUs, acute care facilities created for COVID-19 pandemic hospitalization needs, or other acute care facilities).

3.1.1.5. COVID-19-Related Medically Attended Outpatient Visits

COVID-19-related medically attended visits include in-person or telemedicine visits not specified by the protocol and lasting <24 hours. These include unscheduled in-person or telemedicine visits conducted by the investigator for the purposes of evaluating worsening signs or symptoms attributed to COVID-19 or emergency room, urgent care center, or physician office visits, for attention to worsening signs or symptoms attributed to COVID-19, in the opinion of the investigator.

3.1.2. Methodology

For Cohort A (PEP), the study will consist of a Screening Period of up to 5 days, a 1-month Study Period (including dosing on Day 1), a 5-month follow-up Period, and an 8-month long-term follow-up (LTFU) Period. For Cohort B, the study will consist of a Screening Period of up to 21 days, a 6-month Study Period (including dosing on Day 1), and an 8-month LTFU Period. Each cohort of the study will be considered completed when the last telephone visit (Month 14) or Early Termination (ET) visit for the last participant in each cohort is complete.

All participants will undergo assessments as indicated in the main SoA (Table 3.3) and described in Section 3.5.2.

Participants will receive a single IM dose of study drug on Day 1. Participants will record any ISRs using an e-Diary (or paper back-up) daily on Day 1 postdose through Day 4. The first diary entry will be completed by the participant with assistance of study staff prior to the end of the postdose monitoring period.

As of protocol clarification letter 6, the use of an e-Diary for recording CLI qualifying symptoms and collection of saliva samples beyond CLI Day 1 were discontinued. As of protocol version 6.0, monitoring for CLI symptoms (Table 3.1) and CLI visits are discontinued. Spontaneously reported CLI symptoms will be captured as AEs as per Section 4.1.1 and Section 4.1.3 of the protocol. Safety monitoring will be performed via site phone calls or in-person visits through Month 14. **Prior to implementation of protocol clarification letter 6 and protocol version 6.0 at each clinical site, the following procedures were in place for CLI monitoring and are described here for reference only:**

> *Participants will be instructed to monitor for any CLI symptoms (according to the guidelines in Table 3.1) and report them to the site if they occur at any time during the study. Surveillance for CLI will be performed via participant completion of an e-Diary twice weekly from Day 1 up to the Month 6 Visit, then weekly up to the Month 12 Visit. Surveillance for symptomatic COVID-19 will also be performed via site phone calls to the participant weekly up to the Month 6 Visit, then monthly up to the Month 12 Visit. See Section 3.5.4.1 for further details. Participants reporting CLI symptoms will be evaluated via phone call to confirm whether their symptoms meet criteria for a CLI visit. If CLI symptoms are confirmed by the site, the participant will enter the CLI Period and have an initial CLI visit within 48 hours. Participants who enter the CLI Period will be assessed as described in the CLI SoA (Table 3.4 and Section 3.5.3). Study visits described in the main SoA should not be conducted while a participant is following the CLI SoA.*
>
> *During the initial CLI Visit (CLI Day 1), an NP swab for RT-qPCR testing for SARS-CoV-2 and a saliva sample for assessing viral load will be collected for processing by a central laboratory. For the remainder of the CLI Period, vital signs and severity, duration, and outcome of CLI will be collected via daily telemedicine visits (on CLI Days 2 to 21) and at the final visit on CLI Day 28. Saliva samples will be collected by participants at home on CLI Day 3, 5, 8, 11, 14, and 21 to measure viral shedding over time. Participants will continue in the CLI Period unless a negative result on the CLI Day 1 central NP RT-PCR test is received. These participants will stop CLI assessments and will continue with the main SoA (Table 3.3). Participants with positive or pending central NP SARS-CoV-2 results*

will continue in the CLI Period, regardless of symptoms. Continuation in the CLI Period will not be guided by local RT-PCR testing.

As of protocol version 6.0, all participants in Cohort A have completed surveillance for asymptomatic SARS-CoV-2 infection and monitoring for CLI symptoms and CLI visits are discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

In Cohort A (PEP) only, surveillance for asymptomatic SARS-CoV-2 infection will be performed via SARS-CoV-2 RT-qPCR testing of nasal swabs collected by the Clinical Site on Day 1 (predose) and Day 8 and collected by the participant on Day 15.

Any participant who has a positive result on a nasal swab RT-PCR (Cohort A) or local RT-PCR test (either cohort) up to the Month 12 study visit will be instructed to monitor for onset of symptoms and to report any symptoms to the clinical site; if the participant reports qualifying symptoms within 14 days of collection of the positive RT-PCR, they will enter the CLI Period.

As of protocol version 6.0, collection of health care resource utilization data is discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

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

Sparse blood samples will be collected for PK and immunogenicity throughout the study, as indicated in the main SoA (Table 3.3) and CLI SoA (Table 3.4).

At the time of study entry, each participant will be asked to indicate to the Clinical Site the identity and location of their routine medical care physician and/or facility and the identity and location of where they would obtain emergency care and hospitalization, if necessary, should they get infected with SARS-CoV-2. If this information is not available, a plan for where such care could be obtained should be developed.

All necessary precautions (as per local regulations) should be taken to protect medical staff and other contacts of participants who are suspected of having COVID-19. In the event of a confirmed SARS-CoV-2 infection, the participant will be notified, and the participant will be asked to adhere to the appropriate measures and restrictions as defined by local regulations.

3.2. Study Duration

For Cohort A (PEP), the study will consist of a Screening Period of up to 5 days, a 1-month Study Period (including dosing on Day 1), a 5-month follow-up Period, and an 8-month LTFU Period.

For Cohort B (PrEP), the study will consist of a Screening Period of up to 21 days, a 6-month Study Period (including dosing on Day 1), and an 8-month LTFU Period.

3.3. Selection of Study Population

The study population will comprise adults (aged ≥18 years) and adolescents (aged 12 to <18 years); enrollment of adolescents will begin during the Phase 3 expansion in regions permitted by health authorities and local ethics committees. Participants whose circumstances place them at increased risk of acquiring SARS-CoV-2 infection and/or developing symptomatic COVID-19 will be included. This objective will be independently evaluated in participants with reported recent exposure to an individual diagnosed with a SARS-CoV-2 infection (Cohort A, PEP) and in participants with no reported recent exposure to SARS-CoV-2 (Cohort B, PrEP).

Approximately 20% of the study population is anticipated to be comprised of individuals at increased risk for severe COVID-19 or COVID-19 complications. Participants aged 12 to <55 years who are at an increased risk (as described in Appendix 4) will be included, and participants aged ≥55 years will be eligible for enrollment with or without underlying medical conditions that might place them at increased risk. These at-risk populations are likely to derive the greatest benefit from a preventive mAb therapy. Importantly, participants will be enrolled in the study only if they do not intend to receive a COVID-19 vaccine for 6 months after discussion of risks/benefits of study enrollment in the setting of current or potential future vaccine availability and their underlying risk for development of severe COVID-19.

Specific entry criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** the following criteria apply:

1. Adult aged ≥18 years or adolescent aged 12 to <18 years and weighs at least 40 kg at the time of Screening.

   Note: Adolescent enrollment will open only upon sponsor communication to sites after review of Phase 2 data, and only if permitted by the local health authority (see Appendix 7).

2. Tests negative for current or previous SARS-CoV-2 infection by RT-PCR and serology at the time of Screening.

   Note: Participants may be randomized in Cohort A without RT-PCR results, if these results are not available by Day 5 of Screening.

3. Is at high risk of SARS-CoV-2 infection as assessed by the Investigator, as follows:

   a. Cohort A (PEP): recent exposure to an individual with a diagnosis of SARS-CoV-2 infection (the index case).

      Note: Randomization must occur within 5 days (120 hours) from both exposure to and sample collection from the index case. Participants with recent exposure to a laboratory-confirmed index case must be asymptomatic at randomization. Exposure is generally defined as repeated contact lasting 15 minutes or more within a 24-hour period, where the individuals were within 2 meters (approximately 6.5 feet) of each other, and neither party was wearing a facemask of respirator.

b. Cohort B (PrEP): occupational, housing, recreational, and/or social conditions that are likely to increase risk of exposure to SARS-CoV-2 as assessed by the criteria in Appendix 3.

4. Agrees to defer receipt of COVID-19 vaccination for a minimum of 180 days (6 months) after dosing.
5. Provides written documentation of informed consent by signing a current IEC/IRB approved ICF at the time of screening. A legally authorized representative may be used in cases where inclusion criterion 9 is able to be fulfilled. In the case of adolescents, informed consent/assent must also be obtained as required by local guidelines.
6. Participants assigned female sex at birth who are not of reproductive potential are eligible without requiring the use of contraception and do not require a pregnancy test. This includes female participants who have not undergone menarche or who are documented to be surgically sterile (eg, hysterectomy, removal of both ovaries, or tubal ligation) or postmenopausal (ie, amenorrhea >1 year and follicle stimulating hormone >40 mIU/mL). Follicle stimulating hormone is not required in postmenopausal females with amenorrhea for >2 years.
7. Participants assigned female sex at birth and who are of childbearing potential may be enrolled in the study if the participant has practiced adequate contraception or has abstained from all sexual activities that could result in pregnancy for at least 28 days before the day of dosing (Day 1) and has agreed to continue adequate contraception for sexual activity that could lead to pregnancy through 6 months following dosing.

   Adequate contraception for participants assigned female sex at birth is defined as consistent and correct use of a contraceptive approved by the local Health Authority and used in accordance with the product label. For example:

   a. Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide.
   b. Intrauterine device.
   c. Hormonal contraceptive taken or administered via oral (pill), transdermal (patch), intravaginal, implantable, or injectable method.
   d. Sterilization of a female participant's male partner before entry into the study.
   e. 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 from providing consent 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. Participants assigned male sex at birth with partner(s) of childbearing potential who agree to use adequate contraception through 6 months after dosing. If their partner is pregnant, males

must agree to use a condom. Male participants must also refrain from sperm donation through 6 months after dosing.

9. Able to understand and comply with study requirements/procedures (if applicable, with assistance by a caregiver, surrogate, or legally authorized representative) based on the assessment of the Investigator.

3.3.2. Exclusion Criteria

A potential participant who meets **any** of the following exclusion criteria must be excluded from the study.

1. Prior receipt of a COVID-19 vaccine, convalescent plasma, or mAb, including in the setting of a clinical trial.

   Note: immune compromised participants (eg, due to hematological malignancy, anti-CD20 medication use, etc.) who have completed a COVID-19 vaccine series and who have a documented negative SARS-CoV-2 Spike ("S") protein serum antibody test drawn a minimum of four weeks after completion of the recommended dosing series may be screened and subsequently enrolled if other criteria are met, including a confirmatory negative "S" protein antibody test at the time of screening. This test must be confirmed negative prior to enrollment in either Cohort A or Cohort B.

2. Receipt of any investigational product within 30 days or 5 half-lives (whichever is longer) before the day of enrollment.

3. Is acutely ill or has any of the following symptoms:

Fever ≥38 °C (≥100.4 °F)	Loss of taste
Shortness of breath/difficulty breathing	Loss of smell
Chills (shivering)	Sore throat
Cough	Congestion (stuffy or runny nose)
Fatigue (low energy or tiredness)	Nausea
Muscle or body aches	Vomiting
Headache	Diarrhea

   Note: Participants meeting this criterion may be scheduled for rescreening within the relevant window periods.

4. Has received or plans to receive a non-COVID-19 vaccine within 28 days before or after dosing (except for seasonal influenza vaccine, which is not permitted within 14 days before or after dosing).

5. Known allergy/sensitivity or hypersensitivity to the study drug, including excipients.

6. Is pregnant, as confirmed with a positive pregnancy test at Screening or on the day of dosing (Day 1), or breastfeeding.

7. Known 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.

8. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, autoimmune disease or immune compromise, or neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed; see Appendix 4).
9. Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the Investigator, might confound the results of the study or confer an additional risk to the participant by their participation in the study.

3.3.3. Withdrawal from Study

A participant will be considered to have completed the study when they complete the Month 14 telephone visit or an ET visit. If a participant withdraws at any time after randomization into the study, the Investigator will make every effort to complete the ET assessments as indicated in Table 3.3.

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time and for any reason. If he/she chooses to withdraw, the Investigator must be informed immediately.

A termination eCRF page should be completed for every participant who receives the study drug, whether or not the participant completes the study. The reason for any ET should be indicated on this form.

3.3.4. Replacement of Participants

Participants prematurely withdrawn from the study for any reason will not be replaced.

3.4. Treatments

3.4.1. Details of Study Treatments

ADG20 is a fully human monoclonal immunoglobulin G1 antibody targeted to an epitope in the RBD of the spike glycoprotein of SARS-CoV-2. Information about the study drug is provided in Table 3.2.

Table 3.2 Details of 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 based on local requirements
Dose Form	Solution for injection 100 mg/mL OR Solution for injection 150 mg/mL	Solution for injection, 0.9% (weight/volume)
Route of Administration	Intramuscular	Intramuscular
Formulation	100 mg/mL: ADG20, 20 mM L-histidine, 150 mM sodium chloride, 0.01% polysorbate 80, pH 6.5 (all sites, including those in the US) 150 mg/mL: ADG20, 10 mM L-histidine, 100 mM sucrose, 75 mM L-arginine hydrochloride, 0.03% polysorbate 80, pH 5.5 (US sites only)	0.9% (weight/volume) sodium chloride
Dose	300 mg, administered as a single 2 mL or 3 mL injection	Matched volume of normal saline
Packaging and Labeling	Will be provided in a vial within an individual carton. Each carton and vial will be labeled as required per country requirement.	As required per local regulations

3.4.2. Treatment Assignment and Randomization

Participants will be randomly assigned in a 1:1 ratio in each cohort to receive either IM ADG20 or IM placebo. The randomization will be assigned in a blinded manner using a centralized Interactive Response Technology (IRT) system, in accordance with a pre-generated randomization schedule. A participant is considered randomly assigned when a randomization transaction is recorded in the IRT. A separate randomization list will be created for each cohort.

Randomization will be stratified by:

- Geography
  - United States/Western Europe (US/WEU)
  - Central/Eastern Europe (CEU/EEU)
  - Rest of the World (RoW)
- Age/risk for severe/critical COVID-19
  - Aged 12 to <55 years and low risk for severe/critical COVID-19
  - Aged 12 to <55 years and high risk for severe/critical COVID-19 (see Appendix 4)
  - Aged ≥55 years

3.4.3. Study Drug Packaging and Labeling

ADG20 drug product will be supplied in glass vials as a sterile solution. Each ADG20 drug product vial is supplied to the study site in a tamper-evident sealed and labeled carton. ADG20 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 labelled by study site staff according to the Pharmacy Manual.

3.4.4. Study Drug Storage and Handling

ADG20 will be shipped to the study site with temperature monitored throughout the transit period, and with temperature tracings available for review upon receipt. The investigator or designee must confirm appropriate temperature conditions per the Pharmacy Manual have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug. ADG20 drug product must be stored according to the Pharmacy Manual.

Placebo (normal saline) will be stored in the Clinical Site's pharmacy or designated area under conditions specified by the manufacturer.

All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the Pharmacy Manual and with access limited to the Investigator and authorized Clinical Site staff.

Please refer to the Pharmacy Manual for details on preparing and administering ADG20 and placebo dosing solutions and special handling instructions.

3.4.5. Breaking the Blind

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 intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or medical monitor before unblinding a participant's treatment assignment unless this could delay further management of the participant.

If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind without revealing the study treatment. The date and reason that the blind was broken must be documented.

The study-specific IRT reference manual will provide further details on the use of the IRT system.

3.4.6. Counseling and Unblinding for Participants Wishing to Receive a COVID-19 Vaccination During the Study

Participants were counseled prior to enrollment regarding the risk of ADG20 receipt potentially interfering with COVID-19 vaccine induced immunogenicity and/or efficacy. Participants were only enrolled in the study if they did not intend to receive COVID-19 vaccination for at least 180 days (~6 months) following randomization. The ACIP originally recommended delaying COVID-19 vaccination after receipt of a SARS-CoV-2 mAb due to the potential for interference with vaccine-induced immunity (CDC 2022c) and enrolled participants were advised of this potential risk. Participants were also made aware of the risk involved in delaying vaccination during an active pandemic as part of the informed consent process. 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 2022c). The Sponsor instructed sites to communicate this updated guidance to study participants that received study drug (ADG20 or placebo). Vaccination(s) received during the study should be recorded as concomitant medications.

As of protocol version 6.0, additional counseling and assessments for participants who decide to proceed with vaccination are discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

> *If a participant becomes eligible for and wishes to receive a COVID-19 vaccine, the participant should inform the Investigator. Upon notification of the participant's wish to be vaccinated, the Investigator should counsel the participant on the potential risk of ADG20 interfering with vaccine immunogenicity and/or efficacy, particularly within the first 6 months after dosing. The Investigator should also communicate updated ACIP recommendations that any delay in vaccination after receipt of a SARS-CoV-2 mAb is no longer recommended. The Investigator should offer to unblind any participant who wishes to be vaccinated to better inform decision-making. If the participant chooses to be unblinded, the Sponsor must be notified within 24 hours after breaking the blind without revealing the study treatment. If after counseling the participant chooses to proceed with vaccination, the Investigator should encourage the participant to remain in the study for ongoing assessments.*
>
> *Participants who inform the Investigator of their decision to proceed with vaccination may undergo additional assessments pre- and post-vaccination, as described in Section 3.5.2.7. For these participants, treatment status must be unblinded to allow clinical site personnel to perform these assessments. The Sponsor should be notified within 24 hours after breaking the blind.*
>
> *For all instances of unblinding, the date the blind was broken must be recorded.*

3.4.7. Drug Inventory and Accountability

It is the responsibility of the unblinded Pharmacist or unblinded designee to ensure that current written records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor's unblinded representative and applicable regulatory authorities at any time.

Upon receipt of study drugs, the Pharmacist, or designee will acknowledge receipt, visually inspect the shipment, verify that the number shipped were received, document the condition of the study drugs received, and store the study drugs at the appropriate temperature. Refer to the Pharmacy Manual for additional information.

3.4.8. Study Drug Handling and Disposal

Participants are dosed at the site or during an at-home visit and will receive the study drug directly from the investigator or qualified designee. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

The investigator will maintain accurate records of receipt of ADG20, including dates of receipt. In addition, accurate records will be kept by unblinded site personnel regarding when and how much study drug is dispensed for use by 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 dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, ADG20 will be reconciled and returned or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

3.4.9. Prior and Concomitant Treatments

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products), taken by the participant within the 30 days before dosing (Day 1) must be recorded at Screening and before dosing on Day 1. Concomitant therapies, defined as treatments taken after dosing, associated with AEs (including COVID-19 illness), will be collected and recorded in the eCRF from the moment of dosing (Day 1) until the end of study.

3.4.9.1. Permitted Prior/Concomitant Medications

Participants may take concomitant medications prescribed by their primary care 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. Local standard-of-care treatment, including investigational agents, agents available under emergency use authorization, or other SARS-CoV-2 mAbs, is permitted in participants who develop COVID-19 after dosing.

Non-COVID-19 vaccinations (other than influenza) are permitted if administered ≥28 days before or after dosing. Licensed influenza vaccines are permitted if administered ≥14 days before or after dosing. Though participants were enrolled only if they intended to defer vaccination for at least 6 months, COVID-19 vaccination is permitted after dosing (see Section 3.4.6). Vaccines indicated in a postexposure setting (eg, rabies or tetanus), are permitted at any time during study.

3.4.9.2. Prohibited Prior/Concomitant Medications

The use of the following medications and/or vaccines are prohibited. Use of these concomitant medications by any participant should be recorded in the eCRF, but will not require withdrawal of the participant from the study:

- Any investigational or licensed non-vaccine products indicated or being studied for the prevention of SARS-CoV-2 or COVID-19 (eg, other SARS-CoV-2 mAbs, ivermectin).

  Note: Participants who develop confirmed COVID-19 at any time after study drug administration should be treated per local standard of care, which can include the use of these medications.

- Any vaccine (licensed or investigational), other than licensed influenza vaccines or vaccines indicated in a post-exposure setting, if received within 28 days before or after dosing.
- Any COVID-19 vaccine received prior to enrollment. This does not apply to immune compromised individuals who may have received a COVID-19 vaccine prior to enrollment but have no detectable antibody response (see Exclusion Criterion 1).
- Any seasonal influenza vaccine if received within 14 days before or after dosing.
- Receipt of any investigational product within 30 days or 5 half-lives (whichever is longer) before the day of enrollment.
- Any investigational agent or device is prohibited through 90 days after study drug administration (excluding products listed in Section 3.4.9.1 for the treatment of participants who develop COVID-19).

3.5. Assessments

Unless otherwise indicated, all assessments will be performed by the Investigator or designated study personnel.

3.5.1. Schedule of Assessments

The procedures to be performed throughout the study are outlined in the main SoA (Table 3.3) and a detailed description is provided in Section 3.5.2.

As of protocol version 6.0, CLI visits are discontinued, and the CLI SoA (Table 3.4) is no longer applicable. Prior to protocol version 6.0, participants following the CLI SoA did not concurrently perform assessments in the main SoA; once the CLI SoA procedures were completed, participants returned to following the main SoA.

Table 3.3 Schedule of Assessments

Study Period	Screening	Treatment		Follow-up							
Visit Timepoint	Cohort A: Day -5 to -1[a] Cohort B: Day -21 to -1	Day 1		D 8	D 15 Cohort A	D 28	6 Mo	9 Mo	12 Mo	14 Mo	
Visit Window		Predose[a]	Postdose	±2 d	±3 d	+5 d	±2 wk	±1 wk	±2 wk	±1 wk	ET
Visit Type[b]	Site	Site		In-person	NA[b]	In-person	In-person	Virtual	In-person	Virtual	In-person
Assessment/Procedure											
Clinical											
Informed consent	X										
Review of study inclusion/ exclusion criteria	X	X									
Demographic data	X										
Medical history	X	X									
Randomization		X									
Vital signs[c]	X	X	X	X		X	X		X		X
Weight	X										
Height	X										
Complete physical exam	X										
Targeted physical exam				X		X	X		X		X
Prior/concomitant meds[d]	X	X		X		X	X	X	X	X	X
Study drug administration[e]		X									
Telephone contact for safety monitoring[f]				Weekly				X		X	
e-Diary assessment of injection site reactions[g]			Daily on Days 1-4								
AEs[h]	X	X		X		X	X	X	X	X	X
Central Laboratory											
CBC w/differential	X			X		X	X		X		X
Serum chemistry	X			X		X	X		X		X
Coagulation	X			X		X	X		X		
SARS-CoV-2 RT-PCR		X									
SARS-CoV-2 serology	X					X	X				
Blood sample for PK		X		X		X	X		X[i]		X

Study Period	Screening	Treatment		Follow-up							
Visit Timepoint	Cohort A: Day -5 to -1[a] Cohort B: Day -21 to -1	Day 1		D 8	D 15 Cohort A	D 28	6 Mo	9 Mo	12 Mo	14 Mo	
Visit Window		Predose[a]	Postdose	±2 d	±3 d	+5 d	±2 wk	±1 wk	±2 wk	±1 wk	ET
Visit Type[b]	Site	Site		In-person	NA[b]	In-person	In-person	Virtual	In-person	Virtual	In-person
Assessment/Procedure											
Blood sample for ADA		X				X	X		X[j]		X
Nasal swab for SARS-CoV-2 RT-qPCR (Cohort A only)		X		X	X						
Local Laboratory											
Pregnancy test[k]	X	X					X				
SARS-CoV-2 RT-PCR	X										
SARS-CoV-2 serology POC rapid test (Cohort A only)[l]	X										

ADA=anti-drug antibodies; AE=adverse event; CBC=complete blood count; D=day; ET=early termination; ISR=injection site reaction; mo=month; NA=not applicable; PK=pharmacokinetic; POC=point-of-care; RT-PCR=reverse transcription-polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SAE=serious adverse event; wk=week.

[a] Participants in Cohort A may complete screening and randomization on the same day but must have a negative test from a local or POC serology test prior to randomization. If this occurs, Day 1 predose procedures only need to be performed if they were not completed as part of Screening on the same day.

[b] Visits will be performed at the clinical site, in-person (at the clinical site or at home), or virtually (via telephone, telehealth, videoconference, etc) as indicated. On Day 15, participants in Cohort A will collect a nasal swab at home; no visit with site personnel is expected.

[c] Vital signs include seated blood pressure, heart rate, respiratory rate, temperature, and pulse oximetry. For post-injection monitoring, vital signs will be recorded upon completion of the injection, ~15 minutes and ~30 minutes post injection, and then every ~30 minutes during the remainder of the observation period.

[d] After the Month 6 Visit, review of concomitant medications should focus on those taken to treat SAEs or during medically attended AEs, if any.

[e] Dosing is expected to occur on the same day as randomization into the study. If a participant is planned to receive their dose at home under a decentralized site model, dosing will occur later than the randomization date to allow sufficient time for IMP shipment to the participant's home but must still occur within the specified screening window.

[f] Collect information on AEs, SAEs, medically attended AEs (including new onset chronic disease), and concomitant medications.

[g] Participant reported ISRs to be collected daily on Day 1 through Day 4 via e-Diary (or a paper back-up copy provided to the participant). Study staff will assist the participant in reporting any Day 1 ISR findings in the e-Diary, provide a ruler, and instruct the participant on use of the diary and ruler prior to departing the clinical site on Day 1

[h] Record all AEs through Month 14. Hypersensitivity reactions occurring through Day 4 will be collected as AEs of special interest.

[i] Approximately 200 participants will have a blood sample for PK collected at Month 12. The Sponsor will communicate to sites when these samples are no longer required.

[j] Approximately 1500 participants will have a blood sample for ADA collected at Month 12. The Sponsor will communicate to sites when these samples are no longer required.

[k] For participants of childbearing potential only.

[l] Rapid serology tests may be conducted on-site or at a local lab, with results available prior to participant randomization.

Table 3.4 Schedule of Assessments for COVID-19-Like Illness Visits

As of protocol version 6.0, CLI Visits are discontinued, and the Schedule of Assessments for CLI Visits is no longer applicable. The information below is retained for reference only.

	Initial Visit[a]	*Home Collection Period*[b]	*Final Visit*	*CLI Recurrence Visit*[c]
Visit Timepoint (CLI Day)	*1*	*2 to 21 (Daily)*	*28*	
Visit Window (days)	*+2*		*±2*	
Visit Type[d]	*In person*	*Telemedicine*[e]	*In-person*	*In person*
Assessment/Procedure				
Clinical				
Physical examination	*X*		*X*	*X*
Concomitant medication[f]	*X*	*X*	*X*	*X*
Vital signs[g]	*X*	*X*	*X*	*X*
CLI symptom and severity recording	*X*	*X*	*X*	
AEs[h]	*X*	*X*	*X*	*X*
Health care resource utilization[i]	*X*	*X*	*X*	*X*
Local Laboratory				
Sample for SARS-CoV-2 testing (optional) [j]	*X*			*X*
Central Laboratory				
CBC w/differential	*X*		*X*	
Serum chemistry	*X*		*X*	
Coagulation	*X*		*X*	
Nasopharyngeal swab for SARS-CoV-2 RT-qPCR and sequencing	*X*			
Saliva sample for viral load	*X*	*self-collected on Days 3, 5, 8, 11, 14, and 21*[k]		*X*
SARS-CoV-2 serology	*X*			*X*
Serum PK sample	*X*			*X*
Blood sample for ADA	*X*			*X*

ADA=anti-drug antibodies; AE=adverse event; CBC=complete blood count; CLI=COVID-19-like illness; COVID-19=coronavirus disease 2019; PK=pharmacokinetic; RT-PCR=reverse transcription-polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=oxygen saturation.

[a] *CLI Day 1 Visit to occur within 2 days of CLI symptom confirmation. If an in-person visit is not possible, study assessments will be conducted remotely. The site will send a kit (via courier or other agreed mechanism) for the participant to collect a saliva sample for SARS-CoV-2 RT-PCR central testing. The sample will be returned to the site via courier or other agreed mechanism.*

[b] *All participants will enter the Home Collection Period and perform daily assessments until the result of the CLI Day 1 SARS-CoV-2 central laboratory test is known. Participants who test positive will continue in the CLI Period through Day 28. Participants who test negative will exit the CLI Period at the time the test result is received and return to the main schedule of study assessments.*

[c] *A CLI Recurrence Visit should be performed for participants who experience a recurrence of site-confirmed CLI qualifying symptoms after resolution of previously confirmed symptomatic COVID-19.*

[d] *Visits will be performed at the clinical site, in-person (at the clinical site or at home), or via telemedicine/virtually (telephone, telehealth, videoconference, etc) as indicated.*

[e] *Daily telemedicine visits (CLI Days 2 to 21) may be performed by medically qualified staff appropriately delegated by the Investigator. Telemedicine visits should be done in the evening if possible. The participant will be asked to verbally report all required information. If the participant assessed their vital signs more than once that day, only the highest temperature, lowest SpO_2, and highest heart rate should be recorded in the eCRF. The Investigator will determine if medical attention is required due to worsening of COVID-19 and will assign and record an overall COVID-19 severity grade for that day.*

[f] *Concomitant medications reporting should focus on medications taken to treat current illness/symptoms.*

[g] *At in person visits, heart rate, pulse oximetry, blood pressure, respiratory rate, and temperature will be assessed. During the Home Collection Period, participants will self-assess their temperature, SpO_2, and heart rate at approximately the same time daily and record the results on a memory aid provided by the site. Additional measurements may be taken at other times during the day if the participant feels feverish or short of breath at rest. Participants will be provided with the necessary equipment to perform these assessments.*

[h] *Record new onset AEs, including serious AEs, and medically attended AEs. The first instance of COVID-19 or SARS-CoV-2 infection and associated sequelae in a given participant will not be recorded as an AE; these data will be captured as efficacy assessment data. Recurrence of CLI symptoms in the same participant will be recorded as AEs.*

[i] *Record information regarding health care utilization including COVID-19-related emergency room visits, urgent care visits, visits to other outpatient medical facilities, hospital admissions, and ICU stays.*

[j] *Samples for testing at local laboratory for the purposes of case management may also be collected per local standard of care. Clinical care should be delivered per local standard of care and not wait for results of the central laboratory test. Any local positive RT-PCR test result should be recorded in source and eCRF.*

[k] *Collection of these samples was discontinued with protocol clarification letter 6.*

3.5.2. Study Visits

3.5.2.1. Screening/Baseline

Screening visit requirements are outlined in the main SoA (Table 3.3). The assessments during the Screening Period will determine a participant's eligibility for the study and a participant's ability to comply with protocol requirements by completing all Screening assessments. Screening procedures are to be completed within 5 days prior to study drug dosing in Cohort A or within 21 days prior to study drug dosing in Cohort B.

Written informed consent must be obtained before performing any protocol-specific procedure; this includes discussion of vaccine availability and the potential risks of vaccine deferral and/or administration within 180 days of receipt of study drug.

In addition to review of inclusion and exclusion criteria, for Cohort B, risk of exposure to SARS-CoV-2 will be reviewed with the participant using the risk worksheet in Appendix 3.

Participants may be rescreened once after initially failing to meet the inclusion/exclusion criteria.

3.5.2.2. Treatment Period

After the completion of the Screening assessments, eligible participants will be randomized to treatment on Day 1. Participants in Cohort A may be randomized on the same day as Screening. If this occurs, Day 1 predose procedures only need to be performed if they were not completed as part of Screening on the same day. Cohort A participants may be randomized before SARS-CoV-2 RT-PCR results are available but must have a negative serology result from a local or point of care test. Participants in Cohort B must have negative results from both RT-PCR and central serology prior to randomization.

Procedures to be performed predose and postdose on Day 1 are outlined in the SoA (Table 3.3). Before dosing on Day 1, the participant will be provided with access to the e-Diary for ISR assessments and instructed on its usage (see Section 3.5.5.4).

After study drug administration, the participant will be monitored for 1 to 2 hours, depending on the study phase. Participants in the sentinel group will be monitored for 4 hours and will be assessed daily by telephone for hypersensitivity reactions through Day 4 (see Section 3.5.5.5). Study staff will assist the participant in reporting any Day 1 ISR findings in the e-Diary. Participants may be provided with a paper back-up copy of the ISR diary if study staff assesses that this may be needed. In addition to the post-injection monitoring procedures outlined in the SoA, participants will be assessed during the same time points (or more frequently, as needed) for overall general health.

Note: as of protocol clarification letter 6, the use of an e-Diary for recording CLI qualifying symptoms was discontinued.

3.5.2.3. Follow-up Visits (Day 8 to Month 9)

The participant will return to the Clinical Site or will be visited at home for in-person follow-up visits on Days 8 and 28 and at Month 6. Procedures to be performed during these visits are outlined in the SoA (Table 3.3).

For Cohort A (PEP) only, a nasal swab for SARS-CoV-2 RT-qPCR central laboratory analysis will be collected by site staff on Day 8. The participant will be provided with a kit and instructions for self-collection of a nasal swab on Day 15 (see Section 3.5.4.4).

During the Follow-up Period, participants will be contacted for safety follow-up via phone once weekly through Month 6 and again at Month 9. During these phone calls, information on AEs, SAEs, MAAEs (including new onset chronic disease), and concomitant medications will be collected.

As of protocol clarification letter 6, the use of an e-Diary for recording CLI qualifying symptoms was discontinued. As of protocol version 6.0, monitoring for CLI symptoms (Table 3.1), including follow-up calls at Months 7, 8, 10, and 11, is discontinued. CLI symptoms reported spontaneously during the Follow-up Period will be captured as AEs as per Section 4.1.1 and Section 4.1.3 of the protocol.

3.5.2.4. Month 12 Visit

The participant will return to the Clinical Site or will be visited at home for the Month 12 Visit. Procedures to be performed during this visit are outlined in the SoA (Table 3.3). As indicated in the SoA, blood collection for PK analysis and ADA analysis is to be performed until Sponsor notification that these samples are no longer required.

3.5.2.5. Month 14

Participants will be contacted by telephone at Month 14 for safety monitoring (collection of AEs and concomitant medications), as indicated in the SoA (Table 3.3).

As of protocol version 6.0, the follow-up telephone contact at Month 13 for safety monitoring is discontinued.

3.5.2.6. Premature Termination Visit

If a participant withdraws or is withdrawn from the study for any reason, the participant will be encouraged to attend an ET Visit. Procedures to be performed during this visit are outlined in the SoA (Table 3.3).

3.5.2.7. Unscheduled Pre- and Post-COVID-19 Vaccination Visits

As of protocol version 6.0, unscheduled pre- and post-COVID-19 vaccination visits are discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

If at any time during the study a participant is eligible for and wishes to receive a COVID-19 vaccine, the participant should inform the Investigator and be counseled as described in Section 3.4.6.

After counseling, participants who choose to receive a COVID-19 vaccine may have their treatment status unblinded to undergo the pre- and post-vaccination procedures described in this section. Vaccine type and date(s) should be recorded as concomitant medications for all participants who receive COVID-19 vaccination.

An Unscheduled Visit should be conducted pre-vaccination for all participants intending to receive a vaccine until Sponsor notification that these visits are no longer required. Participants who go on to receive a vaccine will return for an Unscheduled Visit post-vaccination; this visit should take place approximately 2 weeks after receiving the final dose of the primary vaccine regimen.

The assessments to be performed at the pre-vaccination and post-vaccination Unscheduled Visits specific for placebo- and ADG20-treated participants are indicated in Table 3.5. *To assess immunogenicity of the vaccine, blood draws for sVNA titers may be performed in participants who are unblinded due to intent to receive a COVID-19 vaccine. Investigators will be notified by the Sponsor when these blood draws are no longer required.*

The Investigator should encourage these participants to remain in the study for ongoing safety and efficacy assessments. Participants will continue to follow the visit schedule and procedures as indicated on the main SoA (Table 3.3) and CLI SoA (Table 3.4) regardless of the Unscheduled Visits for the remainder of the study. All study procedures should be performed as indicated, except that ***placebo-treated participants*** *will NOT have blood draws for PK and ADA performed at any time after the pre-vaccination visit.*

Unblinded participants will continue to be monitored for CLI symptoms as detailed in Section 3.5.4.1.

Table 3.5 Assessments to be Performed at Unscheduled Visits for Participants Intending to Receive COVID-19 Vaccine

	COVID-19 Vaccination[a]			
	Initial (Pre-Vaccination) Visit		***Post-Vaccination Follow-up Visit***[b]	
Assessment	***Placebo***	***ADG20***	***Placebo***	***ADG20***
Health status including physical exam[c]	*X*	*X*	*X*	*X*
Blood sample for SARS-CoV-2 sVNA titers[d]	*X*	*X*	*X*	*X*[e]
Blood sample for ADA		*X*		*X*
Blood sample for PK		*X*		*X*

ADA=antidrug antibodies; PK=pharmacokinetics; sVNA=serum virus neutralizing antibody

[a] *Participants who request to be unblinded for COVID-19 vaccination will continue to be monitored for CLI symptoms (Table 3.4) and will undergo assessments according to the main SoA (Table 3.3), except that* ***placebo participants*** *will NOT have any blood draws for PK and ADA performed at any time after the pre-vaccination visit through the remainder of the study.*

[b] *The window for this visit is 2 to 6 weeks post-vaccination. This visit occurs after receipt of the final COVID-19 vaccination in the primary vaccination regimen. Record the type and date(s) of COVID-19 vaccination(s) received in the participant's eCRF.*

[c] *Collect only if not already done at the main study visit.*

[d] *Samples for sVNA titers may not be collected for all participants. The Sponsor will notify Investigators when these blood draws are no longer required.*

[e] *sVNA titer assessment will include both induced and ADG20 antibodies.*

3.5.2.8. Hypersensitivity Reaction Assessment Unscheduled Visit

Hypersensitivity reactions are described in Section 3.5.5.5. If a participant reports a hypersensitivity reaction outside of a regularly scheduled in-person visit, the Investigator may perform an unscheduled visit for further evaluation. The following assessments should be performed:

- If occurring **after** Day 4: blood samples for PK and ADA
- Local and/or central safety laboratory tests, at the discretion of the investigator (or qualified designee)
- Vital signs
- Targeted review of changes in health
- Review of concomitant medications
- Review of AEs
- Collection of medically attended visit information

3.5.2.9. 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.

3.5.3. CLI Period: Study Visits in the Event of COVID-19-Like Illness

As of protocol version 6.0, monitoring for CLI symptoms and CLI visits are discontinued. Sections 3.5.3, 3.5.3.1, 3.5.3.2, 3.5.3.3, and 3.5.3.4 are no longer applicable. The text is retained in these sections for reference only.

If at any time from Day 1 through the Month 12 Visit a participant experiences CLI qualifying symptoms (see Section 3.1.1.1) that are confirmed by the site, the participant will enter the CLI Period and follow the CLI SoA (Table 3.4). The participant should not complete study visits in the main SoA while in the CLI Period, and entry into the CLI Period does not affect the overall study duration for an individual study participant. A participant may have multiple CLI Periods throughout the course of the study if COVID-19 is not confirmed for a given CLI Period. Participants with recurrence of CLI symptoms after resolution of confirmed COVID-19 should be followed according to Section 3.5.3.4.

CLI visits will not be initiated for participants reporting a CLI after the Month 12 Visit.

3.5.3.1. CLI Initial Visit (CLI Day 1)

As of protocol version 6.0, this section is not applicable.

The CLI Day 1 Visit will be conducted in person, either at the Clinical Site or via a home visit. CLI Day 1 Visit requirements are outlined in the CLI SoA (Table 3.4). If a Clinical Site or home

visit is not possible, study assessments for the initial CLI Visit will be conducted remotely, and the participant will collect and submit a saliva sample for SARS-CoV-2 RT-PCR central testing. The site will send a saliva collection kit to the participant via courier (or other agreed mechanism) and the participant will return the saliva sample to the site via courier (or other agreed mechanism). If a sample for local SARS-CoV-2 RT-PCR testing is collected per local standard of care, the result should be recorded in the eCRF (see Section 3.5.4.3).

3.5.3.2. CLI Home Collection Period (CLI Day 2 to Day 21)

As of protocol version 6.0, this section is not applicable.

After the in-person CLI Day 1 Visit, all participants will enter the CLI Home Collection Period. The CLI Home Collection Period procedures should be performed as indicated in the CLI SoA (Table 3.4) for all participants until the result of the CLI Day 1 SARS-CoV-2 central NP RT-qPCR test is received. Participants will continue in the CLI Period according to the CLI SoA (Table 3.4) regardless of symptoms unless the Day 1 CLI central NP RT-PCR result is negative. Participants with missing or pending results will continue in the CLI Period. Participants with a negative central NP RT-PCR result will exit the CLI Period when the test result is received and return to following the main SoA, as described in Table 3.3 and Section 3.5.2.

Throughout the CLI Home Collection Period, daily telemedicine visits will be conducted via video or phone for clinical assessments as indicated in the CLI SoA (Table 3.4) and described in Section 3.5.4.2.3.

Throughout the CLI Home Collection Period, participants will report their vital signs daily as indicated in Section 3.5.4.2.2.

On Days 3, 5, 8, 11, 14, and 21, the participant will collect saliva samples for SARS-CoV-2 viral shedding test (see Section 3.5.4.3). Note: collection of these samples was discontinued with protocol clarification letter 6.

3.5.3.3. CLI Final Visit (CLI Day 28)

As of protocol version 6.0, this section is not applicable.

The final CLI Visit will be conducted in-person (either at the Clinical Site or via a home visit) on Day 28. Assessments will be performed as indicated in the CLI SoA (Table 3.4). Following the visit, the Investigator will also assign an overall COVID-19 severity grade for that day based on the participant's responses and according to Appendix 5 and record the severity on the eCRF.

3.5.3.4. Visit for CLI Recurrence After Resolution of COVID-19

As of protocol version 6.0, this section is not applicable.

If at any time after achieving sustained resolution of symptoms a participant with previously confirmed COVID-19 reports a recurrence of COVID-19-like symptoms, the site should perform a CLI Recurrence Visit as indicated in Table 3.4. Only the procedures indicated for the CLI Recurrence Visit should be followed; the participant will not re-enter or begin a new CLI period (ie, CLI Day 1). The recurrence of symptoms should be recorded as an AE (or SAE if meeting criteria) and followed accordingly.

3.5.4. Efficacy Assessments

Efficacy assessments will include SARS-CoV-2 testing, evaluation of signs and symptoms of COVID-19, and determination of health care resource utilization. Planned time points for all efficacy assessments are provided in the main SoA (Table 3.3) and CLI SoA (Table 3.4).

3.5.4.1. Monitoring for COVID-19 Symptoms

As of protocol clarification letter 6, the use of an e-Diary for monitoring for COVID-19 symptoms was discontinued. As of protocol version 6.0, monitoring for COVID-19 symptoms (Table 3.1) **and CLI visits are discontinued, and this section is no longer applicable. Spontaneously reported CLI symptoms will be captured as AEs as per Section 4.1.1 and Section 4.1.3 of the protocol.**

Prior to protocol clarification letter 6 and protocol version 6.0, the following procedures were in place and are described here for reference only:

Participants will be instructed to monitor throughout the study for COVID-19 symptoms and will also be monitored via e-Diary and regular phone calls from the site to monitor for COVID-19 symptoms, as described in Section 3.5.2.3. Participants who experience at least one COVID-19 qualifying symptom (see guidelines in Table 3.1) must contact the study team. Symptoms of fever, shortness of breath, or difficulty breathing should be reported to the study team as soon as possible.

Participants reporting symptoms of COVID-19 will be evaluated via phone call to confirm if symptoms qualify as CLI. CLI symptoms with a known alternative etiology (eg, seasonal allergies responsive to antihistamines) do not require a CLI visit. The results of the call should be recorded in the eCRF and appropriate source documentation. If CLI is confirmed by the site, CLI visits will be initiated as described in Section 3.5.3 and Section 3.5.4.2. Once CLI visits are complete, the participant will return to following the visits and assessments schedule in the main SoA, including continued monitoring for new or recurring CLI symptoms.

Use of Electronic Diaries

At the time of consent, participants must confirm they are willing to complete an e Diary in accordance with the main SoA (Table 3.3) and CLI SoA (Table 3.4) using an application downloaded to their mobile smart device (smartphone, tablet, etc.) at the time of enrollment. The e-Diary may also be accessed via a web browser on any device. Participants without a device capable of downloading the e-Diary application or accessing via a web browser will be provided with a device or paper back-up, as appropriate. Before dosing on Day 1, the participant will be instructed to download the e Diary application on their personal mobile smart device.

This study will utilize the e Diary application for the collection of solicited ISRs, surveillance of signs and symptoms of CLI, and to elicit a CLI Recurrence Visit if a participant with previously confirmed COVID 19 is experiencing a recurrence of CLI symptoms. Information on ISR monitoring via e-Diary is provided in Section 3.5.5.4.

Surveillance of CLI Signs and Symptoms

Participants will be instructed to record information regarding qualifying CLI symptoms (see Table 3.1) in the e-Diary twice weekly from Day 1 through the Month 6 Visit, then once weekly through the Month 12 Visit. The participant will be trained on how to complete the e-Diary at the Day 1 Visit and will be reminded to call the site immediately if they experience any qualifying CLI symptoms. If a participant does not complete the e-Diary within a 2-day window around the scheduled timepoint, study staff will follow-up directly with the participant via phone call or text message to confirm their health status and to remind the participant of the importance of maintaining contact via the e-Diary.

The e-Diary will inquire about the following:

- *Changes in health since the last time completing the e-Diary or the last contact with the study staff.*
- *Any known exposure to someone with a SARS-CoV-2 infection or COVID-19 since the last time completing the e-Diary or last contact with the study staff.*
- *Capture of any CLI symptoms (see Table 3.1) currently being experienced or experienced since the last time completing the e-Diary.*

A positive response by the participant will result in a notification to both the participant and study staff to arrange a call for further assessment, as described above.

3.5.4.2. COVID-19-Like Illness

3.5.4.2.1. CLI Assessment

As of protocol version 6.0, CLI assessment and CLI visits are discontinued, and this section is no longer applicable. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

Participants who experience site-confirmed qualifying CLI symptoms (see Table 3.1) up to the Month 12 Visit will visit the Clinical Site or will be visited at home by medically qualified staff within 48 hours of symptom confirmation for initiation of CLI assessments (CLI Day 1 Visit) as described in the CLI SoA (Table 3.4 and Section 3.5.3). CLI symptoms and participant/PI assessments of CLI severity will be recorded, and an NP swab and saliva sample will be collected on CLI Day 1 for detection of SARS-CoV-2 via central lab. The CLI Day 1 symptom severity assessment should take into account all CLI symptoms from the time they began through CLI Day 1, not only those present on CLI Day 1. If a Clinical Site or home visit is not possible, study assessments for CLI Day 1 Visit will be conducted remotely.

Results of any local SARS-CoV-2 RT-PCR testing conducted by the site or reported by the participant should also be recorded.

Following the CLI Day 1 Visit, participants will enter the CLI Home Collection Period and complete daily telemedicine visits until the results of the central lab SARS-CoV-2 RT-PCR NP swab are known. The CLI Home Collection Period begins on CLI Day 2 and continues through CLI Day 21. During the CLI Home Collection Period, participants will monitor their vital signs

(oral temperature, SpO_2, and heart rate) daily (see Section 3.5.4.2.2) and attend daily telemedicine visits (see Section 3.5.4.2.3) as indicated in the CLI SoA (Table 3.4). Saliva samples will be collected by participants at home on CLI Day 3, 5, 8, 11, 14, and 21 to measure viral shedding over time. (Note: collection of these saliva samples was discontinued via protocol clarification letter 6).

A final CLI Visit will be conducted in-person (either at the Clinical Site or via a home health visit) on Day 28.

CLI visits will not be initiated for participants reporting a CLI after the Month 12 Visit. Participants will report any CLI at the telephone contacts conducted at Month 13 and Month 14 as described in Section 3.5.2.5; any symptoms should be collected as AEs as described in Section 4.1.3 and Section 4.2.

3.5.4.2.2. Self-Assessed Vital Signs

As of protocol version 6.0, CLI assessments are discontinued, and this section is no longer applicable. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

Participants will assess and record their vital signs (oral body temperature, SpO_2, and heart rate) daily during the CLI Home Collection Period. Participants will be provided with a memory aid and the necessary equipment to assess and record vital signs. Vital signs should be assessed 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. The participant may also take and report their vitals during the telemedicine visit as appropriate. Participants will report the highest oral body temperature and heart rate, and lowest SpO_2 values during daily telemedicine visits.

3.5.4.2.3. Daily Telemedicine Assessments

As of protocol version 6.0, CLI assessments are discontinued, and this section is no longer applicable. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

Telemedicine visits will be conducted daily beginning on CLI Day 2 through CLI Day 21. 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. Telemedicine visits may be performed by medically qualified staff appropriately delegated by the Investigator.

During the telemedicine visit (preferably done in the evening) the participant will be asked to verbally report any CLI symptom and the severity of each symptom (according to Appendix 2). The participant will also report their highest body temperature, lowest SpO_2, and highest heart rate for that day; any medications taken to treat current illness/symptoms; and any new onset AEs. The Investigator will determine if medical attention is required due to worsening of COVID-19. Following the visit, the Investigator will also assign an overall COVID-19 severity grade for that day based on the participant's responses and according to Appendix 5 and record the severity on the eCRF.

The participant will be reminded to collect a saliva sample and will be provided with instruction on where and when to return the sample.

3.5.4.2.4. Health Care Resource Utilization

As of protocol version 6.0, this section is no longer applicable. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

Participants will be asked to report information in relation to their health care resource utilization throughout the CLI Period as indicated on the CLI SoA (Table 3.4).

The study site should make every effort to capture the dates and types of any COVID-19 related health-care visit, including primary care provider visits, emergency room visits, urgent care clinic visits, visits to other outpatient medical facilities, hospital admissions, and ICU stays. Information obtained will be captured in source documents and entered into the eCRF.

In the event a participant does not enter the CLI period but is known to be hospitalized with COVID-19, appropriate Health Care Resource Utilization data associated with the event should be captured on the eCRF.

3.5.4.2.5. Recurrence of CLI Symptoms

As of protocol version 6.0, CLI assessment and CLI visits are discontinued, and this section is no longer applicable. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

If a participant with confirmed symptomatic COVID-19 achieves sustained resolution of symptoms and later reports a recurrence of CLI symptoms (see Table 3.3), the investigator (or designee) will contact the participant to confirm CLI symptoms. If a CLI is confirmed, the site will perform a CLI Recurrence Visit as detailed in Section 3.5.3.4.

3.5.4.2.6. COVID-19 Confirmed Outside of a CLI Visit

As of protocol version 6.0, this section is no longer applicable. Confirmed COVID-19 cases will be captured as AEs as per Section 4 of the protocol. Prior to protocol version 6.0, the following procedures were in and are described here for reference only:

If a participant is diagnosed with COVID-19 outside of the study setting (eg, is hospitalized before a CLI visit can be performed), every effort should be made to collect and record the date and result of any local RT-PCR performed at the time of diagnosis. If the participant was hospitalized, the clinical site will complete the appropriate SAE documentation and the Healthcare Resource Utilization form (see Section 4.2.2 and Section 3.5.4.2.4).

3.5.4.3. SARS-CoV-2 Testing and Other Virology and Serology Assessments

As of protocol version 6.0, CLI visits are discontinued. **The samples indicated by italics below will no longer be collected** and are described for reference only.

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

- A nasopharyngeal swab for central testing will be collected by the site on Day 1 *and CLI Day 1* and tested for SARS-CoV-2 by authorized RT-PCR assays (qualitative on Day 1, *quantitative on CLI Day 1*). *A saliva sample for central RT-PCR testing may be self-collected on CLI Day 1 if an in-person visit with site personnel cannot be conducted.*
- *A nasopharyngeal swab will also be collected and tested for respiratory pathogens other than SARS-CoV-2 on CLI Day 1.*
- *Saliva will be collected by site personnel or by participant self-collection at home (using a kit provided by the site) to quantify duration and magnitude of viral shedding during the CLI Period as indicated in the CLI SoA (Table 3.4).*
- Nasal swabs for SARS-CoV-2 RT-qPCR will be collected from participants in Cohort A (PEP) on Days 1 (predose), 8, and 15 (self-collected) to detect any asymptomatic infections as detailed in Section 3.5.4.4.
- Blood samples will be collected and tested for SARS-CoV-2 serology as indicated in the main SoA (Table 3.3) *and CLI SoA (Table 3.4)*. A blood sample for point of care (POC) rapid serology testing will also be collected from participants in Cohort A (PEP) at Screening.
- *Any known positive local RT-PCR test result obtained during the study period, whether within or outside of the study, should also be recorded on the local SARS-CoV-2 eCRF.*

Evaluation of viral resistance will be conducted using genotypic characterization of viral isolates for reduced susceptibility to ADG20, with phenotypic evaluation as appropriate. Samples collected during the study will be used for these analyses. Details on viral resistance testing will be described in a separate bioanalytical analysis plan.

3.5.4.4. Monitoring for Asymptomatic Infection

Post-baseline blood samples will be collected according to the main SoA (see Table 3.3) for SARS-CoV-2 serology testing to detect antibodies to the nucleocapsid (N) protein to monitor participants for asymptomatic infection.

Nasal swabs for SARS-CoV-2 -RT-qPCR will be collected from participants in Cohort A (PEP) on Day 1 (predose), Day 8, and Day 15 (self-collected) to detect and quantify asymptomatic SARS-CoV-2 infection as indicated in the main SoA (Table 3.3).

As of protocol version 6.0, CLI assessment and CLI visits are discontinued. Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

> *Asymptomatic participants who are found to test positive, or any participant with a positive local RT-PCR test up to the Month 12 study visit, will be instructed to monitor for onset of qualifying symptoms (per Table 3.3) and to report symptoms to the clinical site. Any participant reporting qualifying symptoms within 14 days of collection of any positive RT-PCR test will begin a CLI period, as described in Section 3.5.3 and Section 3.5.4.2.*

3.5.5. Safety Assessments

Planned time points for all safety assessments are provided in the main SoA (Table 3.3).

As of protocol version 6.0, CLI visits are discontinued, and safety assessments indicated in the CLI SoA (Table 3.4) will not be performed. References to assessments performed at CLI visits (indicated in italics) are retained in the sections below for information only.

3.5.5.1. Physical Examinations

A complete physical examination will be performed at Screening followed by targeted physical examinations as specified in the main SoA (Table 3.3) *and CLI SoA (Table 3.4).*

- Complete physical examination will include, but not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at Screening will be recorded in the medical history.
- A targeted physical examination will be based on reported AEs *or ongoing sign/symptoms of COVID-19 (if any).*
- All physical examinations will be performed by a licensed health care provider (eg, physician, physician assistant, licensed nurse practitioner, or a licensed nurse being directed by a physician via live telemedicine).

3.5.5.2. Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, respiratory rate, and body temperature, will be performed as specified in the main SoA (Table 3.3) and CLI SoA (Table 3.4). The participant should be resting before the collection of vital signs.

Data collected through CLI telemedicine visits on heart rate, temperature, and SpO_2 level will be recorded but should not be reported as AEs unless meeting criteria for an SAE.

3.5.5.3. Clinical Laboratory Assessments

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical study. The clinical laboratory tests that will be performed on blood samples are listed in Appendix 6.

For participants of childbearing potential, a urine (or serum if required by local health regulations) sample for pregnancy testing will be collected at Screening and other timepoints according to the main SoA (Table 3.3). Urine pregnancy tests for beta human chorionic gonadotropin (β-hCG) may be performed at the Clinical Site using a licensed test (dipstick). If urine pregnancy result is indeterminate at Screening, the urine test will be repeated or a quantitative serum β-hCG can be performed for confirmation.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

3.5.5.4. Injection Site Reactions

This study will utilize an e-Diary application for the collection of solicited ISRs. At the time of consent, participants must confirm they are willing to complete the e-Diary in accordance with the main SoA (Table 3.3). The e-Diary may be accessed via an application downloaded to their mobile smart device (smartphone, tablet, etc.) or a web browser on any device. Participants without a device capable of downloading the e-Diary application or accessing via a web browser will be provided with a device or paper back-up, as appropriate. Before dosing on Day 1, the participant will be instructed to download the e-Diary application on their personal mobile smart device.

Solicited ISRs will be collected in the e-Diary daily on Days 1 through 4.

Participants will complete the e-Diary on site for evaluating any Day 1 ISRs. Study staff will instruct the participant on usage of the e-Diary and assist in reporting any findings on Day 1. Thereafter the participants will be required to self-monitor the injection site and record the results in the ISR e-Diary daily through Day 4.

Participants will be provided with a ruler and instructed on the use of the ruler. Participants will be instructed to record the presence and severity of the following local solicited AEs at the injection site: pain or tenderness, erythema/redness, and induration/swelling. Severity will be assessed for solicited AEs (ISRs) by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative). Reaction severity will be graded according to FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007), as described in Appendix 1.

Any reported ISR that is graded >2 by a participant in the e-Diary will alert the site. The site will then contact the participant by telephone or telemedicine to determine if further evaluation or care is needed. Participants will be provided an emergency 24-hour telephone number and may contact the clinical site directly to report an ISR of concern, including those graded ≤2.

Investigators or medically qualified designees will follow all ISRs that are ongoing beyond Day 4 to resolution and record the resolution date.

3.5.5.5. Hypersensitivity Reactions

All participants will be monitored closely for signs/symptoms of local or systemic hypersensitivity reactions for 1 to 4 hours after study drug administration (see Section 3.1.2). Participants in the sentinel groups will additionally be monitored for hypersensitivity reactions daily by telephone for 4 days after dosing.

Study drug administration will occur in a setting where health care providers have immediate access to medications to treat a severe hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

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

If such a reaction occurs, additional details describing each symptom should be provided to the sponsor in the appropriate CRF page.

Possible hypersensitivity reactions occurring within 4 days of study drug injection and after 4 days (possible delayed hypersensitivity reactions) will be adjudicated by the Sponsor.

3.5.5.6. Adverse Events

All AEs occurring after the participant signs the ICF and up to the last study visit will be recorded.

As of protocol version 6.0, any COVID-19-related event will be recorded as an AE.

Prior to protocol version 6.0, the following procedures were in place and are described here for reference only:

> *For the purposes of this study, the first case of COVID-19 or SARS-CoV-2 infection, including worsening or sequelae, will not be recorded as an AE, unless it meets 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. A participant-reported first case of COVID-19 occurring after Month 12 will be captured in the eCRF detailing date of onset of symptoms, date of positive RT-PCR, any treatment or medical care received, and date of resolution (or ongoing).*

See Section 4 for additional information.

3.5.5.7. 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 participant. There is no specific antidote for overdose of ADG20.

The occurrence of an overdose with no associated abnormal laboratory assessments or clinical symptoms should be reported to the Sponsor 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.

3.5.6. Pharmacokinetic and Immunogenicity Assessments

Blood samples for analyses of PK and ADA will be collected as described in the SoA (Table 3.3).

Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of ADG20 at a laboratory approved by the Sponsor. Antibodies may be further characterized for their ability to neutralize the activity of ADG20.

As of protocol version 6.0, CLI visits are discontinued, and PK and ADA assessments indicated in the CLI SoA (Table 3.4) will not be performed.

3.5.7. Appropriateness of Measurements

All assessments to be used in this study are commonly used, standard measurements frequently seen in mAb studies.

4. ADVERSE EVENT REPORTING

AEs will be monitored and recorded in an AE page of the eCRF, including the AE's description, start, and end date, seriousness, severity, action taken, and relationship to the study drug. If AEs occur, the first concern will be the safety of the study participants. All AEs will be followed until resolved or stable and the outcome documented in the eCRF.

4.1. Definitions and Criteria

4.1.1. Adverse Events

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are defined in Section 5.10.1.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

4.1.2. Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

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

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

"Immediately life-threatening": report if suspected that the patient was at substantial risk of dying at the time of the AE 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 AE.

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.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe (eg, an overnight hospitalization for a diagnostic procedure must be reported as an SAE because it is considered serious even though the occurrence is not considered medically severe). Furthermore, a severe AE is not necessarily serious (eg, nausea of several hours' duration may be rated as severe but may not be considered serious).

4.1.3. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the Clinical Site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

4.1.4. Adverse Events Based on Examinations and Tests

Any abnormal safety assessment (eg, vital sign measurement, physical examination) that in the medical and scientific judgment of the investigator is considered to be clinically significant, including worsening from baseline, is to be recorded as an AE or SAE. The medical diagnosis related to the abnormal finding (eg, hypotension) should be recorded, not the examination/test result or parameter/measurement. For AEs associated with vital sign abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions.

However, any clinically significant safety assessments that are associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

4.1.5. Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or that has worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded in the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests.
- Has accompanying or inducing symptoms or signs.
- Is judged by the Investigator as clinically significant.

If the AE qualifies as serious, this would be reported as an SAE.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges).

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor or designee notified.

4.1.6. Solicited Adverse Events

4.1.6.1. Injection Site Reactions

Predefined solicited AEs for ISR assessments are defined in Appendix 1. Solicited AEs for ISR will be captured and assessed for severity as described in Section 3.5.5.4 and Appendix 1.

Because solicited ISR AEs are expected to occur after injections, they will not be assessed for relationship to study drug.

Solicited ISR AEs should be reported as SAEs or MAAEs if they fulfill the criteria (see Section 4.1.2 and Section 4.1.8, respectively) for seriousness.

Solicited ISR AEs will be considered resolved on the day the participant reports "none" for a given symptom. If any symptom is scored higher than "none" on Day 4, the site will be notified and will follow the symptom until resolution.

4.1.6.2. Solicited CLI Symptoms

As of protocol version 6.0, CLI assessment and CLI visits are discontinued and CLI symptoms (Table 3.1) **will not be solicited.** Spontaneously reported CLI symptoms should be recorded as AEs only if these symptoms meet the AE criteria outlined in Section 4.1.1. In this

case, symptoms should be combined using a diagnostic term whenever possible, as described in Section 4.2.1.

Prior to protocol version 6.0, the following procedures were in place for recording of solicited CLI symptoms and are described here for reference only:

CLI symptoms are collected via site contact with participants throughout the study.

- *Outside of a CLI Period, solicited CLI symptoms are not captured as AEs when collected via telephone contacts for monitoring for CLI, including symptoms spontaneously reported by the participant according to self-monitoring guidelines or collected by the site during pre-specified telephone contacts, as described in Section 3.5.4.1.*
- *During the CLI Period, solicited CLI symptoms and severity, as predefined in Appendix 2 and collected during telemedicine/in-person visits, will be captured and assessed as described in Section 3.5.4.2.3.*
  - *Solicited CLI symptoms should not be reported as AEs for participants who test positive for SARS-CoV-2 within 14 days of the onset of these symptoms (ie, has confirmed COVID-19); these symptoms will be reported as efficacy endpoints.*
  - *For participants who enter a CLI Period and ultimately test negative for SARS-CoV-2, CLI symptoms reported during CLI visits should be recorded as AEs only if these symptoms meet the AE criteria outlined in Section 4.1.1. In this case, symptoms should be combined using a diagnostic term whenever possible and as described in Section 4.2.1.*

4.1.7. Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of study intervention safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF.

AESIs for ADG20 are hypersensitivity reactions, as defined in Section 3.5.5.5, which occur within 4 days of study drug administration.

Solicited AEs related to hypersensitivity reactions will be collected via telephone through 4 days in sentinel group participants.

4.1.8. 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 ER 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.

4.1.9. Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the study drug:

- Intensity refers to the severity of an event and references impact on a participant's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study drug.

4.1.9.1. Adverse Event Intensity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The intensity of all AEs (with the exception of injection site reactions) 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)

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

4.1.9.2. Adverse Event Relationship to Study Drug

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

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.

4.2. Reporting Procedures and Requirements

4.2.1. Adverse Events

Adverse events occurring from when the participant signs the ICF until the last study event will be recorded. Prior to randomization, only SAEs related to a study procedure are required to be reported. Complaints or diagnostic findings that occur from the time the ICF is signed until randomization that are not study procedure-related are to be recorded as medical history. Once randomized/assigned to study treatment, all AEs are reported. Also, any sign, symptom, or disease present before starting the treatment period is only considered an AEs/SAEs if it worsens after administration of study drug.

If the Investigator detects an SAE in a study participant within 3 months after the last scheduled follow-up visit and considers the event possibly related or related to study treatment, the Investigator should report it to Synteract.

The Investigator should report all AEs in the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg, “common cold” or “upper respiratory infection” rather than “runny nose, cough, mild fever”) and should be assessed for intensity and causality as described in Section 4.1.9.

4.2.2. Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria according to the definition in Section 4.1.2. If the AE is considered serious, the Investigator should report this event to Synteract as outlined below and to the IRB/IEC according to its SOPs.

Recording of SAEs is required on the AE eCRF and the paper SAE form within 24 hours of awareness. Upon collecting new information (follow up), the eCRF and the paper SAE form must be updated and continue to match, including, but not limited to, event term, start/stop date, relationship to investigational product and outcome.

Relevant, appropriately redacted hospital records should be sent to the CRO as soon as possible, including but not limited to: discharge summary, COVID-19 test results, diagnostic test results supporting the specific SAE event, evidence of number of days in ICU, requirement for intubation/mechanical ventilation, medications or procedures administered for treatment or management of the SAE, etc.

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 Synteract. If this occurs after the EDC closure, this will only be captured in the Safety Database.

All information about SAEs will be collected and reported via the SAE form and sent by email message (contact information will be contained in the Investigator site file). The Investigator

should send the initial report within 24 hours of becoming aware of the SAE. At a minimum, the initial report should include the following information:

- Event
- Study code
- Participant number, initials, and date of birth
- Study drug
- 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 up until resolution or stabilization and for reported deaths, the Investigator should supply Synteract and the IRB/IEC with any additional requested information (eg, hospital discharge summary, autopsy reports and terminal medical reports).

The original SAE form should be kept at the Clinical Site. The Investigator (or qualified designee) will be responsible for reviewing and signing each SAE form that is submitted. With each SAE form submission, the SAE from will be updated with the new SAE information. The Sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

Serious AEs that are ongoing at the Month 14 Visit should be followed until resolved.

4.2.3. Procedures for Documenting Pregnancy During Study

All pregnancies of female participants in the study will be collected and reported on the Pregnancy Form. Information regarding pregnancies occurring in female partners of male study participants will not be solicited.

Pregnancy in female participants 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.

If a 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. 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 or ET Visit. 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.

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.

4.2.4. Unanticipated Problems Involving Risks and Adverse Events

In the United States, Investigators are required to report all unanticipated problems involving risks to human participants promptly to the IRB and Sponsor. 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).

4.2.4.1. Definition of Unanticipated Problems

An AE observed during the conduct of a study should be considered an Unanticipated Problem (UP) involving risk to human participants, 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 participants.

4.2.4.2. Reporting of Unanticipated Problem

The Investigator will report UPs to their IRB and to the sponsor if required by local 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).

5. STATISTICAL ANALYSIS

5.1. Overall Analysis Plan

The statistical analysis will be undertaken by the Sponsor and representative.

Each cohort will be treated independently under this master protocol. Cohorts A and B will each have a separate randomization list. Efficacy and safety analyses will be performed separately for each cohort, with each cohort allocated a 2-sided alpha of .05.

A change to the data analysis methods described in this master protocol will require a protocol amendment only if it alters a principal feature of the protocol. Otherwise, any changes to the SAP before unblinding for the primary efficacy analyses of each cohort will be documented in an amendment to the SAP. Changes made to analyses in the SAP after unblinding and ad hoc analyses will be described in the Clinical Study Report. In addition, any deviations from the analyses described below will be included in the SAP and documented in the Clinical Study Report as appropriate.

Enrollment in Cohort A (PEP) and in Cohort B (PrEP) was suspended on 11-Jan-2022 after emergence and global spread of the Omicron variant in regions enrolling the trial, beginning in December 2021, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. Therefore, the primary analysis is focused on evaluating ADG20 300 mg IM treatment in the population randomized prior to the emergence of the Omicron variant.

A preliminary efficacy and safety analysis was conducted with a data cutoff of 02-Mar-2022. The primary efficacy objective was to assess efficacy of ADG20 in the setting of susceptible variants (pre-emergence of Omicron); thus, the primary efficacy population included participants randomized on or prior to 30-Nov-2021 and followed for at least 2 weeks (up to 15-Dec-2021) when Omicron became the predominant variant in the US. The efficacy of ADG20 after the emergence of the Omicron variant was evaluated independently as an exploratory analysis in participants randomized after 30-Nov-2021. A full analysis of efficacy following a database soft lock (data cutoff: 11-Apr-2022) was carried out when all enrolled participants had a minimum of 3 months follow-up or had discontinued. A 6-month safety analysis will be carried out following a database soft lock when all enrolled participants have a minimum of 6 months follow-up or have discontinued. A final safety analysis is planned after all enrolled participants have been followed through 14 months or have discontinued.

5.2. Blinding

This study will be double-blinded. The investigator, participant, all clinical site staff, and Sponsor personnel (or designees) involved in study intervention and evaluation will be blinded to

study drug assignment on the participant level. Investigators and participants will remain blinded to each participant's assigned study treatment throughout the course of the study, except as described in Section 3.4.5 and Section 3.4.6. Sponsor personnel (or designees) will become unblinded as described below. An iDMC will review data in an unblinded manner as described in Section 5.12 and in the iDMC Charter.

Efficacy and short-term safety analyses will be performed at the time of the database soft locks. Participants will continue to be followed through the Month 14 visit/EOS or discontinuation from study for the long-term safety. After the soft locks, all participants and site staff will continue to stay blinded to the individual study drug assignment until the final database lock; any unblinding of sponsor personnel (or designees) will be documented as described in the study unblinding plan.

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.

Further details will be included in the study unblinding plan.

5.3. Analysis Sets

The analysis sets that will be used for statistical analyses of Cohorts A and B are defined in Table 5.1.

Table 5.1 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.
Pre-Emergence of Omicron Analysis Set	Includes all participants randomized on or prior to 30-Nov-2021, allowing participants to be followed a minimum of 2 weeks through 15-Dec-2021 when Omicron became the predominant variant.
Modified Full Analysis Set – RT-PCR-negative and seronegative (mFAS)	Includes all randomized participants without prior or current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative and seronegative). If either central RT-PCR or central serology is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.
Modified Full Analysis Set – RT-PCR-negative (mFAS-1)	Includes all randomized participants without current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative regardless of serology status). If central RT-PCR is missing at baseline, a negative baseline status can be imputed for a participant if there is a post-baseline negative central serology sample collected at least 14 days from Day 1 and prior to any positive local/central RT-PCR.
Modified Full Analysis Set – RT-PCR-negative and seropositive (mFAS-2)	Includes all randomized participants with prior infection but without current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative and seropositive). No imputation is performed if any baseline test is missing.

Defined Analysis Data Sets	Description
Modified Full Analysis Set – RT-PCR-negative and seronegative (mFAS-3)	Includes all randomized participants without prior or current SARS-CoV-2 infection at baseline based on central tests (RT-PCR-negative and seronegative). No imputation is performed if any baseline test is missing.
Per-Protocol (PP)	All randomized participants who receive the full dose of study drug, do not have missing data for the primary efficacy endpoint, and have no other important protocol deviation, as determined and documented by the Sponsor before database lock and unblinding, that could impact the assessment of efficacy.
Safety	All participants who receive study drug.
Immunogenicity	All participants who received study drug and had a valid immunogenicity test result before the dose of study drug and at least 1 valid result after the dose of study drug.
Pharmacokinetic	All participants in the Safety Analysis Set who have ADG20 concentration data for at least 2 post-injection time points.

The primary efficacy population is defined as follows for each cohort:

- Cohort A: baseline RT-PCR-negative participants pre-emergence of Omicron (mFAS-1 pre-Omicron).
- Cohort B: baseline RT-PCR-negative and seronegative participants pre-emergence of Omicron (mFAS pre-Omicron).

In the efficacy analysis, participants will be analyzed based on the treatment they are randomized to, irrespective of what they actually might have received. In the safety analysis, participants will be analyzed based on the study drug received.

5.4. Sample Size Determination

Cohort A (PEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 28 days after randomization. The original sample size of 1078 participants was planned with 90% power, 2-sided alpha .05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 5% per 28 days in the placebo group and 1.5% in the ADG20 group. A sample size of 1270 participants was planned to account for 15% of participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort A on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort A only included events through 28 days after randomization or the emergence of Omicron, whichever was earlier. Prior to suspension of enrollment, 487 participants were randomized in Cohort A, of which approximately 377 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 351 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative pre-Omicron). The primary efficacy population yielded approximately 14 events through 28 days or

emergence of Omicron, whichever was earlier, for the analysis. With 14 events, any observed efficacy >68% would be statistically significant at 2-sided α=.05.

Cohort B (PrEP): The primary endpoint is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 3 months. The original sample size of 4628 participants was planned with 84% power, 2-sided alpha .05, and a 1:1 randomization ratio to detect a statistically significant RR when the true RR is 0.30 (70% efficacy) with an attack rate of 1% per 3 months in the placebo group and 0.3% in the ADG20 group. A sample size of 5142 participants was planned to account for 10% of participants enrolled with a prior or current SARS-CoV-2 infection at baseline.

Enrollment was suspended in Cohort B on 11-Jan-2022 following the emergence of Omicron variant, against which 300 mg ADG20 was not expected to have adequate efficacy due to decreased neutralization activity. As such, the analysis of the primary efficacy endpoint for Cohort B only included events through 3 months after randomization or the emergence of Omicron, whichever was earlier. Prior to suspension of enrollment, 2094 participants were randomized in Cohort B, of which approximately 1639 were enrolled prior to the emergence of Omicron with a minimum of 2 weeks follow-up through 15-Dec-2021, and 1477 were estimated to be eligible for inclusion in the primary efficacy analysis population (RT-PCR-negative and seronegative pre-Omicron). A higher than expected aggregate attack rate resulted in a sufficient number of cases to enable this cohort to be a fully powered study to detect clinically meaningful and statistically significant treatment differences. Based on a 3.6% aggregate attack rate, 974 participants in a 1:1 randomization ratio provides 90% power to detect a statistically significant treatment effect when the true RR is 0.3 with 2-sided α =.05. Therefore, the current sample size of 1477 provided sufficient statistical power to carry out the primary efficacy analysis, as well as preliminary evaluation of safety.

The sample size calculations were performed using SAS software version 9.4 (SAS Institute).

5.5. Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis in a blinded fashion; major deviations that are considered to have an impact on the efficacy assessment will lead to the relevant participant being excluded from the PP Analysis Set before any unblinded analysis is performed. For the interim analysis, all deviations identified before the formal data cut will be assessed at that time. All other deviations will be assessed before unblinding of the data. The numbers and percentages of participants with at least one important protocol deviation will be presented by study drug group and overall. Important protocol deviations will also be summarized by deviation type.

Examples of protocol deviation types are:

- Randomized without meeting inclusion criteria or with meeting an exclusion criterion.
- Received the wrong study drug or incorrect dose; and
- Missed study visits or missed assessments.

5.6. Participant Disposition

The number of participants screened, the number of screen failures, and the reasons for screen failure will be tabulated. The numbers and percentages of participants in each analysis set will be summarized by and across study drug groups. The numbers and percentages of participants who completed the study will be presented as will the numbers and percentages of participants who withdrew from the study and the reason for withdrawal. If the proportion of participants discontinuing from the Follow-up Period is high or imbalanced across study drug groups, the timing of withdrawal may be explored further.

5.7. Demographic and Baseline Characteristics

Demographic and baseline data will be summarized using the FAS and the primary efficacy population. Demographic variables include age, age group (12 to <18, 18 to <55, 55 to <75, and ≥75 years), sex at birth, race, ethnicity, and geographic category. Baseline variables include weight, height, BMI, presence of comorbidities (including those that increase the risk of severe COVID-19 as indicated in Appendix 4), age/risk of severe COVID-19 (12 to ≤54 years and low risk, 12 to ≤54 years and high risk, and ≥55 years), and baseline SARS-CoV-2 status by RT-PCR and by serology.

Study drug groups will be compared with respect to participant demographics and baseline characteristics using descriptive statistics, but no formal statistical analysis tests will be performed.

5.8. Concomitant Medication and Medical History

The numbers and percentages of participants receiving prior and concomitant medications will be summarized by World Health Organization Drug Anatomic Therapeutic Chemical Classification level 2 and preferred drug name.

Medical history incidence will be summarized by MedDRA SOC and PT.

5.9. Efficacy Analyses

The analysis approach for the primary and secondary efficacy endpoints in Cohorts A and B are summarized in Table 5.2 and Table 5.3, respectively. Subgroup and sensitivity analysis methods are described as applicable.

Table 5.2 Efficacy Endpoints and Statistical Analyses Methods: Cohort A (PEP)

Endpoint (Analysis Population) – Cohort A (PEP)	Statistical Analysis Method and Analysis Timing
Primary Endpoint	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron, whichever is earlier (mFAS-1 pre-Omicron)	Primary analysis: Logistic regression model using the method that computes a population-level estimates adjusted for covariates including treatment, baseline serostatus, and stratification factors (Ge 2011). • Sensitivity analyses based on multiple imputations will be performed on the primary estimand. • Sensitivity analysis will be performed using Per-Protocol Analysis Set. • A supportive analysis based on the Cochran-Mantel-Haenszel test will be performed adjusting for the same factors that are used in the primary analysis model. • Subgroup analyses by baseline serostatus or stratification factors will be performed. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Key Secondary Endpoints	
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier (mFAS-1 pre-Omicron)	Key Secondary Endpoints: Same method as primary • Performed sequentially if the preceding analysis is statistically significant at 2-sided, .05 level. • Baseline serostatus or RT-PCR status will be included as covariate when applicable. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron, whichever is earlier (mFAS pre-Omicron)	
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier (mFAS pre-Omicron)	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron, whichever is earlier (FAS pre-Omicron)	
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through Day 28 or emergence of Omicron, whichever is earlier (FAS pre-Omicron)	

Endpoint (Analysis Population) – Cohort A (PEP)	Statistical Analysis Method and Analysis Timing
Other Secondary Endpoints	
• Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 • Probability of RT-PCR-confirmed symptomatic COVID-19 (mFAS-1/mFAS/FAS pre-Omicron)	Methodology: Time-to-symptomatic COVID-19 plot and probability of cumulative incidence at 28 days and 3 months will be summarized using Kaplan-Meier methodology. The stratified log-rank test will be used to test the treatment effect. Stratified Cox proportional hazard model to estimate the HR and its 95% CI. The model will include treatment and stratification factors as strata. Baseline serostatus or RT-PCR status will be included as covariate when applicable.
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier (mFAS-1/mFAS/FAS pre-Omicron)	Methodology: Same method as primary. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier (mFAS-1/mFAS/FAS pre-Omicron)	Methodology: Same method as primary. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through Day 28 and 3 months after randomization or emergence of Omicron, whichever is earlier (mFAS-2 pre-Omicron)	Methodology: Same analysis as primary. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) on Days 8 and 15 after randomization (mFAS-1 pre-Omicron)	Descriptive statistics: number and frequency on Day 8 and on Day 15
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology through Day 28 (mFAS-1 pre-Omicron)	Descriptive statistics: number and frequency through Day 28
Peak post-baseline SARS-CoV-2 viral load as measured by RT-qPCR (nasal sample)	Descriptive statistics in participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) on Days 8 and 15
SARS-CoV-2 viral load assessed by RT-qPCR (nasal sample) change from baseline to Day 8 and Day 15	Descriptive statistics in participants with asymptomatic SARS-CoV-2 infection as determined by positive RT-qPCR (nasal sample) at baseline, Day 8, and Day 15.
Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
All-cause mortality through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19

Endpoint (Analysis Population) – Cohort A (PEP)	Statistical Analysis Method and Analysis Timing
COVID-19-related mortality through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
Time from reported symptom onset to sustained resolution of symptomatic COVID-19 through CLI Day 28	Descriptive statistics and Kaplan-Meier methodology in participants with laboratory-confirmed symptomatic COVID-19
Viral load from CLI Day 1 sample assessed by RT-qPCR.	Descriptive statistics in participants with laboratory-confirmed symptomatic COVID-19.
Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
Proportion of participants with COVID-19-related hospitalizations through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19

Table 5.3 Efficacy Endpoints and Statistical Analyses Methods: Cohort B (PrEP)

Endpoint (Analysis Population) – Cohort B (PrEP)	Statistical Analysis Method and Analysis Timing
Primary Endpoint	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier (mFAS pre-Omicron)	Primary analysis: Logistic regression model using the method that computes a population-level estimates adjusted for covariates including treatment and randomization stratification factors (Ge 2011). • Sensitivity analyses based on multiple imputations will be performed on the primary estimand. • Sensitivity analysis will be performed using Per-Protocol Analysis Set. • A supportive analysis based on the Cochran-Mantel-Haenszel test will be performed adjusting for the same factors that are used in the primary analysis model. • Subgroup analyses by stratification factors will be performed. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Key Secondary Endpoints	
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier (mFAS-1 pre-Omicron)	Key Secondary Endpoints: Same method as primary • Performed sequentially if the preceding analysis is statistically significant at 2-sided, 0.05 level.

Endpoint (Analysis Population) – Cohort B (PrEP)	Statistical Analysis Method and Analysis Timing
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier (mFAS pre-Omicron)	• Baseline serostatus or RT-PCR status will be included as covariate when applicable. Analysis Timing: After the last pre-omicron participant is randomized and followed for 2 weeks.
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier (mFAS-1 pre-Omicron)	
Other Secondary Endpoints	
• Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 • Probability of RT-PCR-confirmed symptomatic COVID-19 (mFAS/mFAS-1/FAS pre-Omicron)	Methodology: Time-to-symptomatic COVID-19 plot and probability of cumulative incidence at 3 months will be summarized using Kaplan-Meier methodology. The stratified log-rank test will be used to test the treatment effect. Stratified Cox proportional hazard model to estimate the HR and its 95% CI. The model will include treatment and stratification factors as strata. Baseline serostatus or RT-PCR status will be included as covariate when applicable.
Proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier (FAS pre-Omicron)	Methodology: Same method as primary. Baseline serostatus and RT-PCR status will be included as covariates.
Proportion of participants with SARS-CoV-2 infection (asymptomatic or symptomatic) as determined by positive RT-PCR or serology test through 3 months or emergence of Omicron, whichever is earlier (FAS pre-Omicron)	Methodology: Same method as primary. Baseline serostatus and RT-PCR status will be included as covariates.
Proportion of participants with asymptomatic SARS-CoV-2 infection as determined by serology at Month 6. (mFAS pre-Omicron)	Descriptive statistics: number and frequency of asymptomatic SARS-CoV-2 infection
Proportion of participants with RT-PCR-confirmed mild, moderate, or severe/critical COVID-19 through CLI Day 28 (mFAS/mFAS-1/FAS pre-Omicron)	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
All-cause mortality through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
COVID-19-related mortality through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19

Endpoint (Analysis Population) – Cohort B (PrEP)	Statistical Analysis Method and Analysis Timing
Time from reported symptom onset to sustained resolution of COVID-19 symptoms through CLI Day 28	Descriptive statistics and Kaplan-Meier methodology in participants with laboratory-confirmed symptomatic COVID-19
Viral load from CLI Day 1 sample assessed by RT-qPCR	Descriptive statistics in participants with laboratory-confirmed symptomatic COVID-19.
Proportion of participants with at least 1 COVID-19-related medically attended outpatient visit (physician's office, telemedicine, emergency rooms, or urgent care centers) through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19
Proportion of participants with COVID-19-related hospitalizations through CLI Day 28	Descriptive statistics: number and frequency in participants with laboratory-confirmed symptomatic COVID-19

5.9.1. Primary Efficacy Endpoint

The primary efficacy endpoint for Cohort A (PEP) is the proportion of RT-PCR-confirmed symptomatic COVID-19 through Day 28 or emergence of Omicron, whichever is earlier.

The primary efficacy endpoint for Cohort B (PrEP) is the proportion of RT-PCR-confirmed symptomatic COVID-19 through 3 months or emergence of Omicron, whichever is earlier.

RT-PCR-confirmed symptomatic COVID-19 is determined by the protocol defined COVID-19 symptoms (Section 3.1.1.2) occurring within 14 days from the sample collection date of a positive central or local (in the absence of central test) RT-PCR. Any COVID-19-related hospitalization with a positive local SARS-CoV-2 test (within 14 days) or all-cause death are counted toward the endpoint. The date of event is the earliest date of COVID-19 symptom onset, COVID-19-related hospitalization, or all-cause death.

The analysis of the primary estimand, incidence of RT-PCR-confirmed symptomatic COVID-19 for ADG20 versus placebo will be analyzed using the methodology for determining a standardized estimator for a binary outcome as detailed in (Ge 2011) with adjustment for the prognostic factors. The standardized risk difference, associated p-value and 95% CI, and the standardized relative risk reduction with 95% CI will be provided for efficacy assessment.

A treatment policy strategy will be used to handle the intercurrent events (ICEs) of interest in the primary analysis. The ICEs include the use of rescue medications (eg, COVID-19 vaccine, COVID-19 mAb for the purposes of prevention), subject unblinding by Investigator prior to the primary endpoint outcome, or others as specified in the SAP. Participants with missing primary endpoint outcome will be imputed as not having the primary endpoint outcome in the primary analysis. Sensitivity analyses using multiple imputation for missing outcome and hypothetical strategy of handling the ICEs will be fully described in the SAP.

5.9.2. Secondary Efficacy Endpoints and Analyses

The analyses of secondary efficacy endpoints are presented for Cohort A (PEP) in Table 5.2 and for Cohort B (PrEP) in Table 5.3.

In each cohort, a hierarchical testing approach will be used to test the key secondary hypotheses to preserve the type I error at 2-sided .05 level. The first key secondary hypotheses will be tested if the null hypothesis for the primary endpoint is rejected at 2-sided .05 level. The subsequent key secondary hypotheses will be tested if the null hypothesis for the preceding key secondary endpoint is rejected at 2-sided, .05 level.

5.9.3. Multiplicity

To control for the inflation of the overall type I error rate (alpha), a hierarchical testing procedure will be used within each cohort as described in Section 5.9.2.

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

5.9.4. Exploratory Endpoints

Exploratory endpoint analyses will be detailed in the SAP. For Cohorts A and B, these may include analyses of the primary efficacy and virological endpoints in randomized participants regardless of SARS-CoV-2 variant. Additional subgroup or covariate adjusted analyses may be performed.

5.10. Safety Analyses

All safety analyses will be performed using the Safety Analysis Set in each cohort.

Safety endpoints include:

- AEs (including SAEs and MAAEs)
- AESIs (hypersensitivity reactions)
- ISRs (solicited AEs)
- Clinical laboratory assessments
- Vital signs

5.10.1. Adverse Events

All AEs will be coded using the latest version of MedDRA.

A TEAE is defined as any AE that has an onset during or after the administration of study drug through the Month 14 Follow-up Visit, or any pre-existing condition that has worsened during or after the administration of study drug through the Month 14 Follow-up Visit. Because solicited AEs (ISRs) are expected to occur after the IM injection all solicited AEs (ISRs) will be considered a TEAE.

The incidence of TEAEs (including solicited ISRs), SAEs, TEAEs related to the study drug, SAEs related to the study drug, and AESIs will be summarized by MedDRA SOC, PT, and study drug group.

The incidence of TEAEs will also be summarized by DAIDS grading of severity for unsolicited AEs and FDA Toxicity scale for solicited ISRs by MedDRA SOC, PT, and study drug group.

The incidence by study drug group as well as by intensity and duration will be summarized for solicited ISRs.

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. Safety summaries through 14 months will be presented.

5.10.2. Laboratory Data

Descriptive statistics for clinical laboratory results (hematology and chemistry) will be presented for each study visit by study drug group. Descriptive statistics for the change from baseline at each post-baseline study visit for each laboratory parameter will also be presented by study drug group. In addition, laboratory parameters will be defined as potentially clinically significant in the SAP, and shift tables from baseline will be provided for each post-baseline visit.

5.10.3. Vital Signs

Descriptive statistics of vital sign parameters will be presented by study drug group and study visit, as well as the change from baseline at each study visit. Potentially clinically significant values will be defined in the SAP, and the numbers and percentages of participants with a potentially clinically significant value will be summarized by study drug group for the worst post-baseline value.

5.10.4. Immunogenicity

Immunogenicity data will be provided in listings 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.

5.11. Pharmacokinetics

Descriptive statistics of ADG20 serum concentration at each sampling time will be provided. PK parameters may include, but are not limited to: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, CL/F, $t_{1/2}$, T_{max}, and V_{ss}/F. The calculation method will be detailed in the SAP.

5.12. Independent Data Monitoring Committee Safety Monitoring

Table 5.4 presents the safety monitoring performed by iDMC.

Table 5.4 Independent Data Monitoring Committee Safety Monitoring

Parameter	Analysis Set	Statistical Method	Criterion	Monitoring Plan
Potential Harm Confirmed COVID-19 cases	FAS	RR significantly >1 (ADG20 relative to placebo) based on an exact 2-sided 90% CI	Constant CI monitoring controlling 1-sided α at 5%	After every event starting after 8 cases of confirmed symptomatic COVID-19 across Cohorts A and B until the finalization of protocol version 6.0.
Potential Harm Severe/Critical COVID-19 Cases	FAS	RR significantly >1 (ADG20 relative to placebo) based on an exact 2-sided 90% CI	Constant CI monitoring controlling 1-sided α at 5%	Routine reviews starting after 4 cases of severe/critical COVID-19 across Cohorts A and B.
Safety	Safety	Incidence of AESIs, unsolicited study drug-related AEs ≥Grade 3, and study drug-related SAEs COVID-19[a]	Safety guidelines provided in iDMC charter	Real-time monitoring Interim analysis after the Phase 2 population is followed for 4 weeks Routine reviews across all cohorts

[a] As of protocol version 6.0, surveillance for COVID-19 will no longer be performed. Thus, monitoring will be limited to severe/critical cases of COVID-19 as reported through routine safety follow-up.

Available unblinded safety data collected through 4 weeks postdosing, including relevant data for confirmed COVID-19 cases, for the first 200 participants (Phase 2) enrolled across both cohorts will be reviewed by the iDMC. Enrollment will continue during the iDMC review. If any single severe or >1 moderate acute hypersensitivity reaction, single study drug-related severe AE, or single study drug-related SAE occurs prior to the planned iDMC analysis, enrollment will be paused and an ad hoc iDMC meeting called.

After the scheduled analyses, the iDMC will review all cases of severe acute hypersensitivity reactions, drug-related severe AEs, or drug-related SAEs on an ongoing basis.

The iDMC will meet routinely to review safety data, including relevant data regarding symptomatic COVID-19 cases. Review of COVID-19 cases will include monitoring for potential ADE which may present as an increase in the incidence or severity of COVID-19 in ADG20-treated participants compared with placebo-treated participants. In participants with asymptomatic/pre-symptomatic SARS-CoV-2 infection at baseline detected by positive SARS-CoV-2 RT-PCR, ADE also has the potential to manifest as acute worsening of disease in association with ADG20 as a result of antigen-antibody complex formation leading to pro-inflammatory cytokine release and/or complement activation/deposition. For these reasons, iDMC will review the incidence and severity of symptomatic COVID-19 cases as part of their regular safety review.

To aid in the detection of potential ADE, continuous safety monitoring of the incidence of severe/critical COVID-19 in the FAS will also be conducted by an independent unblinded statistician as detailed in the iDMC charter.

6. STUDY MANAGEMENT

6.1. Ethics and Consent

6.1.1. Regulations and Guidelines

The study will be performed in accordance with this protocol, US investigational new drug regulations (21 CFR 312) or local national laws (as applicable), and ICH guidelines for GCP. These guidelines are on file at Synteract.

6.1.2. Institutional Review Board/Independent Ethics Committees and Competent Authorities

The clinical trial authorization granted by the competent authority and a favorable opinion from the relevant IEC(s)/IRB(s) will be obtained before the start of the study. The local authorities will be notified about the study as required by law.

The competent authority and the EC/IRB will be notified about the end of the trial and a report summarizing the study results will be sent to the competent authority and the EC within 1 year after the end of the trial. If the trial is terminated early, the competent authority, and the EC will be notified within 15 days. Favorable opinion is required for the study protocol, Investigator brochure, protocol amendments, ICFs, participant information sheets, and advertising materials. No study drug will be shipped to a Clinical Site until written IRB/IEC favorable opinion has been received by the Sponsor or its representative.

6.1.3. Informed Consent

For each trial participant, informed consent will be obtained before any protocol-related activities. As part of this procedure, the Investigator, or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the participant and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Participants should be informed that they may withdraw from the study at any time without any resulting disadvantage. They will receive all information that is required by local regulations and ICH guidelines.

All participants will be insured against injury caused by their participation in the study according to legal requirements. They will be informed about the insurance and the resulting obligations on their part.

6.2. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

6.3. Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this Clinical Site or at multiple sites, or to terminate the study at any time for safety, administrative, or other reasons. In particular, a Clinical Site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the Clinical Site closed for whatever reason, all documentation, and study drug pertaining to the study must be returned to the Sponsor or its representative.

6.4. Study Documentation

By signing a copy of Form FDA 1572 or other country-specific regulatory forms, the principal Investigator acknowledges that he/she has received a copy of the IB on ADG20 and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572 and other country-specific forms. No changes in this protocol can be made without the Sponsor's written approval.

6.5. Data Management and Quality Control

6.5.1. Electronic Case Report Forms

In this study, eCRF data and eSource records (if applicable) will be entered into the data collection platform.

The data collection platform is compliant with all legislation relevant to EDC (FDA 21 CFR Part 11, GCP).

The Investigator Clinical Site staff will enter and edit the data via a secure network, with secure access features (username and password). A complete electronic audit trail will be maintained. The Investigator will approve the data using an electronic signature (FDA 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded. Electronic case report forms will be used for all participants. The Investigator's data will be accessible from the Investigator's Clinical Site throughout the trial. The eCRF must be kept current to reflect participant status at each phase during the course of the trial. The eCRF will not capture personalized data. The Investigator must make a separate confidential record of personalized details (name and initials) on the participant identification and enrollment log. All changes to data are done through the EDC system and approved by the Investigator.

It is the responsibility of the Principal Investigator of the respective Clinical Site to ensure that all participant discontinuations or changes in study or other medications entered on the participant's eCRF are also made on the participant's medical records. The eCRFs for any

participant leaving the study should be completed at the time of the final visit or shortly thereafter.

6.5.2. Data Management Considerations

Queries will be issued for any inconsistencies, omissions, and discrepancies, and will be resolved by the appropriate parties.

6.5.3. Study Monitoring and Quality Assurance

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, SOPs, GCP guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site and/or remote review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each participant. Note that a variety of original documents, data, and records will be considered as source documents in this trial. Clinical sites may elect to utilize the direct data entry feature in the study data collection system, in which case select data that would normally be transcribed from source documents into the EDC system are integrated with the system, preventing the need for re-entry.

Medical advisors and clinical research associates or assistants may request to witness participant evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the Sponsor to assure acceptable protocol execution. The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required participant records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

6.6. Collection and Update of Contacts

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. These 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 SoA.

6.7. Retention of Records

The Investigator must arrange for retention of study records at the Clinical Site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The Investigator should take measures to prevent accidental or premature destruction of these documents.

6.8. Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

6.9. Publications

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 Clinical 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 written authorization from the sponsor, but data and publication thereof will not be duly withheld.

7. REFERENCES

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8. APPENDICES

Appendix 1. Injection Site Reaction e-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 (ISR) e-Diary (or paper back-up if deemed appropriate for the participant) 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 (ISRs) by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). 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	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening[a] (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/ swelling[b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

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

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

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

Appendix 2. Collection of Coronavirus Disease 2019 Symptoms

Please ask questions in a location where, and during a time when, the participant will not be distracted.

Assessment of Common COVID-19-Related Symptoms and Global Impression Items

*"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=0 Mild=1 Moderate=2 Severe=3
2) Chills (shivering)	
3) Cough	
4) Sore throat	
5) Congestion (stuffy or runny nose)	
6) Shortness of breath (difficulty breathing)	
7) Muscle or body aches	
8) Fatigue (low energy or tiredness)	
9) Headache	
10) Nausea (feeling like you want to throw up)	
11) Loss of smell or taste	
12) Vomiting (throwing up) or diarrhea (loose or watery stools)	
13) In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?	Yes or No
14) In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?	Yes or No
15) In the past 24 hours, what was the severity of your overall COVID-19-related symptoms at their worst?	None, Mild, Moderate, or Severe
Based on above response, in the Investigator's opinion, indicate overall COVID-19 severity per protocol definitions. Refer to the protocol Appendix 5: FDA Scale for COVID-19 Severity.	Asymptomatic, Mild, Moderate, or Severe

Appendix 3. Worksheet for Assessment of Risk Factors for Exposure to SARS-CoV-2

Note: This worksheet is to be used by the site at screening to determine if a potential participant is at high risk of exposure to SARS-CoV-2. Any affirmative answer qualifies a participant as being at increased risk.

Do you work in any of the following locations/industries?

☐ Hospital, clinic, or outpatient medical center
☐ Long-term care, assisted-living, nursing home, or elder care home
☐ Correctional facility
☐ Teacher/instructor or childcare provider in an indoor setting with more than 5 children
☐ Shelter or group home setting
☐ Other location or facility that does not allow for physical distancing and mask-wearing
☐ None of the above

Do you live in any of the following?

☐ Long-term care facility
☐ Assisted-living facility
☐ Dormitory, sorority/fraternity, or multi-student campus apartment
☐ Multi-family home (eg, more than one family/generation in the same home)
☐ Shelter
☐ Other adult group setting (eg, employee group housing)
☐ Home with children participating in indoor extra-curricular/social activities
☐ No stable residence
☐ None of the above

Do you frequently eat/drink in an indoor restaurant/bar/pub where you and/or others might not be wearing masks? ☐ **Yes** ☐ No

Do you frequently exercise or play sports indoors where you and/or others might not be wearing masks? ☐ **Yes** ☐ No

Are you frequently in an indoor setting with people not from your household, where you and/or others might not be wearing masks? Some examples are work, church, or social gatherings.
☐ **Yes** ☐ No

Do you frequently travel more than 100 miles (170 kilometer) from your home and interact with others indoors at your destination(s)? ☐ **Yes** ☐ No

Do you frequently use any form of group transportation where you and/or others might not be wearing masks? Some examples are taxis/rideshares, buses, trains, or airplanes. ☐ **Yes** ☐ No

Appendix 4. Risk Factors for Severe Coronavirus Disease 2019

The following are examples of chronic, stable conditions or illnesses that place an individual at increased risk for severe COVID-19. Individuals with these illnesses should be considered eligible for enrollment if medically stable and deemed appropriate by the Investigator.

Adults:

- Obesity (BMI >30 kg/m^2)
- Diabetes (Type 1 or Type 2)
- 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)
- Chronic lung disease (emphysema/chronic obstructive pulmonary disease, chronic bronchitis, interstitial lung disease [including idiopathic pulmonary fibrosis]), cystic fibrosis, or asthma requiring daily therapy)
- Cardiac disease (heart failure, coronary artery disease, cardiomyopathies, or hypertension [with at least one medication prescribed or recommended])
- Sickle cell disease or thalassemia
- Solid organ or blood stem cell transplant recipients
- Other immunodeficiency due to underlying illness or immunosuppressant medication (eg, corticosteroids ≥20 mg/day prednisone or equivalent)
- Down Syndrome
- Stroke or cerebrovascular disease, which affects blood flow to the brain
- Substance use disorder

Adolescents:

- BMI >85^{th} percentile for age and sex based on CDC growth charts
- Diabetes (Type 1 or Type 2)
- Chronic kidney disease
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (eg, cerebral palsy, Down syndrome)
- A medically-related technological dependence (eg, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19)
- Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control
- Solid organ or blood stem cell transplant recipients
- Other immunodeficiency due to underlying illness or immunosuppressant medication
- Substance use disorder

Appendix 5. Modified FDA Scale for COVID-19-Like Illness Severity

The following COVID-19-like illness severity categorizations are adapted from the FDA COVID-19 Developing Drugs and Biological Products for Prevention or Treatment Guidance for Industry (FDA 2021a).

Infection Without Symptoms

- No symptoms.

Mild COVID-19-Like Illness

- Symptoms of mild COVID-19-like illness that could include fever, cough, sore throat, malaise, headache, muscle pain, or gastrointestinal symptoms, without shortness of breath or dyspnea.
- No clinical signs indicative of moderate, severe, or critical illness severity.

Moderate COVID-19-Like Illness

- Symptoms of moderate COVID-19-like illness, which could include any symptom of mild illness or shortness of breath with exertion.
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥20 breaths per minute, with saturation of oxygen (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-Like Illness

- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress including the need for initiation of oxygen therapy.
- Clinical signs suggestive of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300.
- No criteria for critical severity.

Critical COVID-19-Like Illness

- 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).
- 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.

Appendix 6. Clinical Laboratory Tests

Hematology (Complete Blood Count with differential):	**Chemistry Panel Serum Concentrations of:**
Hemoglobin	Non-fasting glucose
Hematocrit	Calcium
Erythrocyte count	Albumin
Mean cell volume	Total protein
Mean cell hemoglobin	Sodium
Mean cell hemoglobin concentration	Potassium
Leukocyte (white blood cell) count	Bicarbonate
Neutrophils	Chloride
Lymphocytes	Urea nitrogen
Monocytes	Creatinine
Eosinophils	Alkaline phosphatase
Basophils	Alanine aminotransferase
Platelets	Aspartate aminotransferase
Coagulation tests	Total bilirubin
Prothrombin time/International Normalized Ratio	
Partial thromboplastin	
Other tests	
Follicle-stimulating hormone	
Urine (or serum, if required by local regulations) pregnancy test	

Appendix 7. Country-Specific Requirements

The country-specific requirements provided in the following subsections supersedes the content in the indicated section of the main protocol and MUST be followed for all sites enrolling participants in that country.

Appendix 7.1 Argentina-specific Requirements

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

Section 3.3.1 Inclusion Criterion

Inclusion Criterion 1:

Adult aged ≥18 years.

Section 3.5.5.3 Clinical Laboratory Assessments

In addition to the requirements described in this section, monthly urine pregnancy testing is required for all participants of childbearing potential from the time of randomization through the end of study.

Appendix 7.2 Czech Republic-specific Requirements

No adolescents will be enrolled in the Czech Republic. All content in the protocol specific to enrollment of adolescents is not applicable to sites in the Czech Republic. Specific changes related to the exclusion of adolescents from the study in the Czech Republic and other changes and clarifications to the protocol specific to clinical sites enrolling participants in the Czech Republic are outlined in the sections below.

Section 3.3.1 Inclusion Criterion

Inclusion Criterion 1:

Adult aged ≥18 years.

Inclusion Criterion 5:

Is able and willing to provide informed consent. A legally authorized representative may be used in cases where inclusion criterion 9 is able to be fulfilled.

Inclusion Criterion 7:

Participants assigned female sex at birth and who are of childbearing potential may be enrolled in the study if the participant has practiced highly effective contraception or has abstained from all sexual activities that could result in pregnancy for at least 28 days before the day of dosing (Day 1) and has agreed to continue highly effective contraception for sexual activity that could lead to pregnancy through 6 months following dosing.

Highly effective contraception for participants assigned female sex at birth is defined as consistent and correct use of a contraceptive as described by the Clinical Trial Facilitation Group (CTFG) and used in accordance with the product label. For example:

a. Bilateral tubal ligation
b. Intrauterine device.
c. Hormonal contraceptive taken or administered via oral (pill), transdermal (patch), intravaginal, implantable*, or injectable method.
d. Sterilization of a female participant's male partner before entry into the study.
e. Sexual abstinence.**

* If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation

**Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from providing consent 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. Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

Section 3.3.2 Exclusion Criterion

Exclusion Criterion 3:

Is acutely ill or febrile 72 hours before or at Screening or has other COVID-19 symptoms including cough, fatigue, muscle or body aches, headache, or loss of taste or smell (for guidance on COVID-like illness symptoms, refer to Table 3.1). Fever is defined as a body temperature ≥38.0 °C (≥100.4 °F).

Note: Participants meeting this criterion may be scheduled for rescreening within the relevant window periods.

Exclusion Criterion 4:

Has received or plans to receive a non-COVID-19 vaccine within 28 days before or after dosing (except for seasonal influenza vaccine, which is not permitted within 14 days before or after dosing) or a live vaccine 30 days before or 90 days after dosing.

Section 3.5.5.3 Clinical Laboratory Assessments

In addition to the requirements described in this section, a urine pregnancy test is required for all participants of childbearing potential on Day 28.

Section 4.2.4.2 Reporting of Unanticipated Problem

Clarification: The Investigator will report unanticipated problems to the IRB and to the Sponsor only if required by local country regulations. If reporting of unanticipated problems to the IRB and Sponsor is not required by local country regulations, this section is not applicable.

Appendix 7.3 Germany-specific Requirements

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

Section 3.3.1 Inclusion Criterion

Inclusion Criterion 1:

Adult aged ≥18 years.

Inclusion Criterion 5:

Provides written documentation of informed consent by signing a current IEC/IRB approved ICF at the time of screening.

Inclusion Criterion 7:

Participants assigned female sex at birth and who are of childbearing potential may be enrolled in the study if the participant has practiced highly effective contraception or has abstained from all sexual activities that could result in pregnancy for at least 28 days before the day of dosing (Day 1) and has agreed to continue highly effective contraception for sexual activity that could lead to pregnancy through 6 months following dosing.

Highly effective contraception for participants assigned female sex at birth is defined as consistent and correct use of a contraceptive as described by the Clinical Trial Facilitation Group (CTFG) and used in accordance with the product label. For example:

a. Bilateral tubal ligation
b. Intrauterine device.
c. Hormonal contraceptive taken or administered via oral (pill), transdermal (patch), intravaginal, implantable*, or injectable method.
d. Sterilization of a female participant's male partner before entry into the study.
e. Sexual abstinence.**

* If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation
**Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from providing consent 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. Note: periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

Inclusion Criterion 9:

Able to understand and comply with study requirements/procedures based on the assessment of the Investigator.

Section 3.3.2 Exclusion Criterion

Exclusion Criterion 10:

Subjects who are legally detained in an official institution.

Section 6.1.3 Informed Consent

For each trial participant, informed consent will be obtained before any protocol-related activities. As part of this procedure, the Investigator, or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the participant is aware of the potential risks, inconveniences, or adverse effects that may occur. Participants should be informed that they may withdraw from the study at any time without any resulting disadvantage. They will receive all information that is required by local regulations and ICH guidelines.

All participants will be insured against injury caused by their participation in the study according to legal requirements. They will be informed about the insurance and the resulting obligations on their part.

Section 6.3 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this Clinical Site or at multiple sites for safety or administrative reasons at any time. In particular, a Clinical Site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the Clinical Site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative.

From a participant safety point of view, the study must be discontinued due to unacceptable serious adverse events.

The study will be discontinued if the applicable evaluation or approval by the authorities is revoked or canceled.

The study will also be discontinued if the insurance coverage cannot be adjusted or maintained accordingly.

Appendix 7.4 Ukraine-specific Requirements

No adolescents will be enrolled in Ukraine. All content in the protocol specific to enrollment of adolescents is not applicable to sites in Ukraine. Specific changes related to the exclusion of adolescents from the study in Ukraine are outlined in the sections below.

Section 3.3.1 Inclusion Criterion

Inclusion Criterion 1:

Adult aged ≥18 years.