# Official Title of Study:

# Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Investigate the Efficacy and Safety of Asapiprant in Hospitalized Adults With COVID-19

**Protocol Number:** BGE-175-201

**ClinicalTrials.gov Identifier:** NCT04705597

**Document Version [Date]:** Protocol Version 5.0, Amendment 04 [07 Sep 2021]

BIOAGE

**CONFIDENTIAL**

# PROTOCOL BGE-175-201

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|---|---|
| TITLE: | A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Investigate the Efficacy and Safety of Asapiprant in Hospitalized Adults With COVID-19 |
| DRUG: | Asapiprant (BGE-175) |
| IND: | 153475 |
| EUDRACT NO.: | Not applicable |
| SPONSOR: | BioAge Labs<br>1445A South 50th Street<br>Richmond, CA 94804 |
| COORDINATING PRINCIPAL INVESTIGATOR: | [redacted] |

| **Version Number:** | **Date** |
|---|---|
| Protocol Version 5.0, Amendment 04 | 07 Sep 2021 |
| Protocol Version 4.0, Amendment 03 | 19 May 2021 |
| Protocol Version 3.0, Amendment 02 | 26 April 2021 |
| Protocol Version 2.0, Amendment 01 | 19 March 2021 |
| Original Protocol 1.0 | 04 December 2020 |

# PROTOCOL SIGNATURE PAGE

**BioAge Labs, Inc. Approval**

| **Signature:** | **Date:** |
|---|---|
| [redacted] | |

**Investigator's Acknowledgement**
I have read this protocol for Study BGE-175-201.

**Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Investigate the Efficacy and Safety of Asapiprant in Hospitalized Adults With COVID-19**

I have thoroughly reviewed the objective(s) of this study and discussed the contents of this protocol with the clinical contract research organization (CRO) or BioAge Labs, as applicable.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the BioAge Labs. It is, however, permissible to provide the information contained herein to a subject to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an Investigator for this study.

I understand that the BioAge Labs may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the BioAge Labs.

| Investigator Name and Address:<br>(please print by hand or type) | |
|---|---|

**Signature:** _____ **Date:** _____

# EMERGENCY CONTACT INFORMATION

**Serious adverse events (SAEs) that occur from the time of signing the ICF through 30 days after last dose of study drug require that an SAE report form be completed in the electronic data capture (EDC) system and submitted to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug. In the event that EDC is unavailable, the SAE paper report form must be filled out by the Investigator and sent via email within 24 hours of awareness of the event to the [redacted] Pharmacovigilance Department [redacted], and then the information entered into the EDC once available.**

**The occurrence of an SAE should also be sent to BioAge Labs at the following e-mail addresses:**

- **BioAge Contact Information (send a copy to):**
  [redacted]

**For protocol- or safety-related questions or concerns, the Investigator must contact the CRO. If the CRO Medical Monitor is not available, the Sponsor may be contacted:**

[redacted]

# SUMMARY OF MAJOR PROTOCOL CHANGES

| Protocol Version | Summary of change | Rationale for change |
|---|---|---|
| 5.0, A0.4 | Updated estimated number of sites from 20 to 35 | Update to reflect better estimate of actual site number |
| 5.0, A0.4 | Increased sample size from 132 to 312 subjects, and updated statistical rationale for the sample size calculation | Recently published data indicate that progression in the control arm to meet the primary endpoint in similar studies occurs at a lower rate than the original estimate used for this study's sample size calculation. The sample size adjustment reflects these external data. An interim analysis will use conditional power calculations by the independent DMC for the final sample size determination. |
| 5.0, A0.4 | The timing of the interim analysis was changed from 66 subjects to 208 subjects | A larger sample size at interim analysis will provide a more accurate assessment of a potential treatment effect |
| 5.0, A0.4 | Added new secondary endpoint to assess the proportion of subjects who survive without progression to RF at Day 14, Day 28, and Day 57 | Provides an assessment of whether study drug not only improves survival but reduces the severity of disease |
| 5.0, A0.4 | Added time windows for laboratory sample collections at home visits, including not requiring the repeat of study procedures at Day 5 if they were completed at Day 4 prior to discharge | Reduces the burden on study patients and provides time for managing logistics of sample collection and shipping for outpatients, especially on weekends |
| 5.0, A0.4 | Updated Exclusion #4 to reflect requirement of positive test for influenza A or influenza B within 1 week prior to screening | Clarification |
| 4.0, A0.3 | Updated interim analysis to collect data from subjects through Day 28 | Matches interim analysis timing and primary endpoint timing per FDA request |
| 4.0, A0.3 | Randomization stratification factors added to the model as covariates in the primary analyses | Protocol now lists all covariates that are described in the statistical analysis plan per FDA request |

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| 4.0, A0.3 | Updated wording in IP Discontinuation or Study Withdrawal section to clarify that the only reason for withdrawal from study assessments is withdrawal of patient consent | Reinforces instructions that all patients should be followed even if IP is discontinued per FDA request |
| 4.0, A0.3 | Updated footer (h) on Table 1 by removing reference to viral titers being measured on the Day after treatment ends | The footer now agrees with the body of the table |
| 4.0, A0.3 | Updated Statistical Analysis Process section to specify that the primary analysis including covariates will use the log-odds model for superiority described in Ge et al., 2011. All covariates are now listed. Also clarifies how insufficient data will be handled. | FDA request |
| 4.0, A0.3 | Updated Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee section. Specifies how randomized patients will be assessed who reach Day 28 (or would have reached Day 28 had they not died, withdrawn, or been lost to follow-up) | FDA request |
| 3.0, A02 | Lowered patient eligibility age from 60 years to 50 years | Responds to changing COVID-19 patient demographics and Increases number of eligible patients without increasing safety risks or affecting anticipated efficacy |
| 2.0, A01 | Clarified that optional nasal swabs collected for local qualitative testing; quantitative testing nasopharyngeal swabs can be stopped with negative local qualitative results | Reduces patient burden, risk of staff exposure |
| 2.0, A01 | Updated inclusion criterion #7 to specify not allowing “critical COVID illness” rather than “respiratory failure” | Internal consistency with endpoint and FDA guidance for patient population |
| 2.0, A01 | Updated inclusion criterion #8 to define female subjects of childbearing potential | Clarification |
| 2.0, A01 | Deleted Exclusion #4 | Repeated from inclusion criterion #7 |
| 2.0, A01 | Updated Exclusion #5 and #6 to indicate “history” of HIV, Hepatitis B and hepatitis C to clarify that test results are not required at screening | Clarification |
| 2.0, A01 | Added new exclusion #8 for Hepatic function impairment defined as a Child-Pugh score of 7 or greater | FDA request |

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| 2.0, A01 | Updated exclusion #9 to reflect that stage 4 or worse renal failure is excluded | FDA request and clarification |
| 2.0, A01 | Clarified analysis populations and statistical methodology | FDA request |
| 2.0, A01 | Primary endpoint updated to be consistent with entry criterion definition of respiratory failure | FDA request and clarification |
| 2.0, A01 | New secondary endpoint to assess incidence of critical COVID disease | Internal consistency |
| 2.0, A01 | Updated secondary endpoint of time to extubation to "incidence and duration of intubation" | FDA Request |
| 2.0, A01 | Updated interim analysis to be performed by the independent data monitoring committee | FDA request |
| 2.0, A01 | Clarified that subjects are only discontinued from the study if they withdraw consent and will complete all visit assessments if treatment is stopped early | FDA Request |
| 2.0, A01 | Changed dosing regimen to 100 mg daily for all subjects | FDA Request, reduce risk for dosing errors |
| 2.0, A01 | Administrative changes/corrections throughout | Clarifications/corrections |

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# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| ARDS | Acute respiratory distress syndrome |
| AST | Aspartate aminotransferase |
| $AUC_{last}$ | Area under the curve from the time of dosing to the last measurable concentration |
| β-HCG | Beta-human chorionic gonadotropin |
| °C | Degree(s) Celsius |
| CCR7 | C-C motif chemokine receptor 7 |
| CD | Cluster of differentiation |
| CL/F | Total body clearance for extravascular administration divided by the fraction of dose absorbed |
| $C_{max}$ | Maximum concentration occurring at $t_{max}$ |
| COVID-19 | Coronavirus disease of 2019 |
| CP | Conditional power |
| CRA | Clinical research associate |
| CRF | Case report form |
| CRO | Contract research organization |
| CRP | C-reactive protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV% | Coefficient of variation |
| DC | Dendritic cell |
| DP | D prostanoid |
| DP1 | Prostaglandin D2 receptor 1 |
| DMC | Data Monitoring Committee |
| DVT | Deep vein thrombosis |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| ECMO | Extracorporeal membrane oxygenation |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |

| | |
|---|---|
| EOT | End of treatment |
| EU | European Union |
| FDA | Food and Drug Administration |
| $FiO_2$ | Fractional inspired oxygen |
| $\lambda_z$ | First-order rate constant associated with the terminal (log-linear) portion of the curve |
| GCP | Good Clinical Practice |
| GGT | Gamma glutamyl transferase |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| IA | Interim Analysis |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| IFN-α | Interferon alpha |
| IFN-γ | Interferon gamma |
| IL | Interleukin |
| INR | International normalized ratio |
| IP | Investigational product |
| IP-10 | Interferon gamma-induced protein 10 |
| IRB | Institutional review board |
| IRB/EC | Institutional Review Board / Independent Ethics Committee |
| IRT | Interactive response technology |
| ITT/FAS | Intention to Treat / Full Analysis Set |
| $K_2EDTA$ | Dipotassium ethylenediaminetetraacetic acid |
| LDH | Lactate dehydrogenase |
| MAP | Mean arterial pressure |
| MCP-1 | Monocyte chemoattractant protein-1 |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| mITT | Modified Intent-to-Treat population |
| NA | Not applicable |
| NG | Nasogastric tube |
| NIPPV | Noninvasive positive pressure ventilation |
| NK cell | Natural killer cell |
| NPO | Nothing by mouth (withhold food and fluids) |
| NYHA | New York Heart Association |
| $O_2$ | Oxygen |
| PCR | Polymerase chain reaction |
| PD | Pharmacodynamic(s) |
| PGD2 | Prostaglandin D2 synthase |
| PGD2-DP1 | the therapeutic target of the investigational drug BGE-175 to treat COVID-19 |
| PK | Pharmacokinetic(s) |
| PO | Oral administration |
| PT | Prothrombin time |
| QTcF | QT interval corrected for heart rate by Fridericia's formula |
| RDW | Red blood cell distribution width |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RF | Respiratory failure |
| RTI | Respiratory tract infection |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SD | Standard deviation |
| SOC | Standard of care |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{1/2}$ | Terminal half-life |
| TEAE | Treatment-emergent adverse event |
| TNF-α | Tumor necrosis factor alfa |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| US CFR | United States Code of Federal Regulations |

| | |
|---|---|
| $V_z$ /F | Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed |
| WHO | World Health Organization |
| WHO-UMC | World Health Organization-Uppsala Monitoring Center (system for standardized case causality assessment) |

# STUDY SYNOPSIS

**Title of Study:** A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Investigate the Efficacy and Safety of Asapiprant in Hospitalized Adults With COVID-19

**Name of Sponsor/Company:** BioAge Labs

**Name of Finished Product:** Not applicable (NA)

**Name of Active Ingredient:** Asapiprant

**Objectives:**

**Primary**

To evaluate the efficacy of asapiprant given by oral (PO) or nasogastric tube (NG) administration versus placebo on the clinical signs and symptoms of COVID-19 infection in hospitalized subjects ≥ 50 years of age

**Secondary**

- To evaluate the ability of asapiprant given by PO or NG administration to accelerate the clearance of the COVID-19 virus in subjects with symptomatic disease requiring hospitalization
- To determine the efficacy of asapiprant by demonstrating improvement in COVID-19 illness and prevention of progression to respiratory failure (RF) using various endpoints
- To evaluate the safety profile of asapiprant given by PO or NG administration in subjects ≥ 50 years of age hospitalized with COVID-19 infection

**Other Objectives**

- To investigate the effect of asapiprant on inflammation markers of COVID-19 infection, including but not limited to interleukin (IL)-6, C-reactive protein (CRP), IL-10, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interferon alpha (IFN-α), IFN-γ-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), cluster of differentiation (CD)4+ and CD8+ T cells, and absolute lymphocyte count
- Determine peak and trough concentrations of study drug after first dose and at steady state and, if possible, develop a population pharmacokinetic (PK) model

**Study Design:** This is a randomized, placebo-controlled, parallel-group, multicenter, double-blind study of asapiprant administered PO or NG in subjects ≥ 50 years of age and hospitalized with documented COVID-19 infection who are not yet in RF.

After signing informed consent, subjects will be screened upon presentation at the hospital. Screening will include full physical examination, vital signs, safety laboratory evaluation, oxygen ($O_2$) saturation, pre-diagnostics to measure prostaglandin D2 (PGD2) status, and baseline assessment of World Health Organization (WHO) Ordinal Scale for COVID-19 that is derived from the subject oxygen supplementation requirements. If confirmed that they qualify for this protocol according to listed inclusion and exclusion criteria, subjects will receive their first dose of study medication, PO. They will then receive study medication PO once daily, at approximately the same time each day for up to 13 additional days. Subjects

who progress to RF and require intubation or subjects who are unable to swallow will receive study medication by NG tube administration. Study medication will be administered in addition to standard of care deemed appropriate by the treating physician(s). Subjects will be randomized to receive asapiprant or placebo. Subjects will be monitored daily for all relevant efficacy outcomes, $O_2$ saturation and adverse events (AEs). Treatment will be discontinued in subjects who develop hepatic function impairment defined as a Child-Pugh score of 7 or greater. Blood will be drawn periodically for safety laboratory measurements, plasma kinetics, lymphocyte subsets, CRP, and cytokines (see Table 1). Nasopharyngeal swabs will be collected to measure viral load and separate nasal swabs may be collected for optional local qualitative testing. Subjects will be monitored at follow-up visits on Day 28 (approximately 14 days after last dose) and Day 57 (approximately 43 days after last dose).

**Number of Study Centers:** Approximately 35 sites will be selected based on likelihood of adequate patient population at the time of study implementation. Site selection will include an assessment of sites' prior research and COVID-19 study experience, current and projected rates of infection, concurrent clinical trials that may limit patient population availability, and current standard of patient care.

**Duration of Participation:** Each subject will participate in the study for approximately 8 weeks from the time the subject signs the informed consent form (ICF) through the final contact.

After screening, each subject will receive one daily dose of assigned treatment, Days 1 through 14.

WHO Ordinal Scale for COVID-19 will be derived daily while hospitalized, at Day 14, and at follow-up visits until the subject has completed the study.

**Duration of Study:** The study will require approximately 4 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject).

**Key Inclusion/Exclusion Criteria:** Subjects with a diagnosis of COVID-19 requiring hospitalization will be selected to participate in the study.

**Inclusion:**

1. Ability to voluntarily provide informed consent that is documented per local requirements
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions
3. Hospitalized subjects with a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
4. Laboratory (polymerase chain reaction [PCR]) confirmed infection with SARS-CoV-2
5. Age $\geq$ 50 years
6. COVID-19 illness of any duration, and $O_2$ saturation measurements $\leq$ 94% over 5 minutes on room air (Note: low flow $O_2$ is permitted, but room air $O_2$ saturation must be $\leq$ 94%)
7. Not with evidence of critical COVID-19 illness as defined by at least one of the following:
   a. RF defined by requiring at least one of the following:
      - Endotracheal intubation and mechanical ventilation

- $O_2$ delivered by high-flow nasal cannula at flow rates > 20 L/min with fraction of delivered $O_2 \geq 0.5$
- Noninvasive positive pressure ventilation (NIPPV)
- Extracorporeal membrane oxygenation (ECMO)
- Clinical diagnosis of RF (i.e., clinical need for one of the preceding therapies, but preceding therapies are not able to be administered in setting of resource limitation)

b. Hemodynamic compromise (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg) or requiring vasopressors
c. Multi-organ dysfunction/failure

8. Female subjects of childbearing potential must have a negative pregnancy test at screening or pre-treatment on Day 1

   **Note**: Female subjects of childbearing potential are defined as pre-menopausal, < 12 months of amenorrhea post-menopause, or no history of surgical sterilization (hysterectomy or oophorectomy) or tubal ligation.

9. Male and female subjects of childbearing potential must agree to use methods of contraception that are consistent with local regulations for those participating in clinical studies

**Exclusion:**

1. Participation in any other randomized, controlled clinical trial of an experimental treatment for COVID-19 (uncontrolled, compassionate use trials are allowed)
2. In the opinion of the Investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
3. Currently participating in a vaccination trial for SARS-CoV-2
4. Known positive test for influenza A or influenza B at the time of screening
5. History of human immunodeficiency virus (HIV) infection that is not controlled with current treatment
6. History of Hepatitis B surface antigen, or Hepatitis C positive prior to screening. Subjects who are positive for Hepatitis C but have Hepatitis C virus (HCV) RNA below the limit of quantitation may be enrolled. Subjects with Hepatitis B, but with undetectable viral load, may be enrolled.
7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × the upper limit of normal (ULN)
8. Hepatic function impairment defined as a Child-Pugh score of 7 or greater.
9. Stage 4 or higher severe chronic kidney disease (i.e., estimated glomerular filtration rate [eGFR] < 30 mL/min) or acute renal failure resulting in eGFR < 30 mL/min
10. Serious co-morbidity, including:
    a. Myocardial infarction (within the last month)
    b. Moderate or severe heart failure (New York Heart Association [NYHA] class III or IV)
    c. Acute stroke (within the last month)
    d. Uncontrolled malignancy. Uncontrolled malignancy would include cancers that are not considered in remission, or solid tumor or haematological malignancies with evidence of disease progression in the past 3 months (i.e., there is evidence of

disease progression by Response Evaluation Criteria in Solid Tumours [RECIST] or equivalent relevant criterion for the type of malignancy), and are not considered effectively managed with ongoing treatment as determined by the Investigator

e. Recent severe thromboembolic disease or evidence of severe thromboembolic disease defined as a current large vessel thromboembolic event or a thromboembolic event within the past 3 months (e.g., deep vein thrombosis [DVT], pulmonary embolism, ischemic stroke, transient ischemic attack) requiring interventional treatment. This exclusion does not prohibit prophylaxis for thromboembolic events, including those considered possible with concurrent SARS-CoV-2 infection.

11. History of severe allergic or anaphylactic reactions or hypersensitivity to the study drug
12. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive study treatment

**Investigational Product, Dose, Route of Administration, and Regimen:**

**Test product:** Asapiprant, a DP1 antagonist, will be provided as a 50 mg tablet for oral use

**Placebo:** Matching tablet without active drug

Two 50 mg tablets of asapiprant (100 mg) or matching placebo will be taken immediately after screening evaluation, confirmation of eligibility, and randomization on Day 1, and within 30 minutes of eating. Time of dosing in relation to meal will be documented. Subjects will continue dosing for 14 days, including if they are discharged or if the subject progresses to RF. Subjects taking nothing by mouth (NPO) or not being fed through an NG tube will take study medication at approximately the same time they received prior daily doses.

**Statistical Methods:**

**Analysis Populations:**

**Enrolled Analysis Set**: all patients who provided informed consent.

**Intent-to-Treat (ITT)**: all patients who have been randomized. The ITT will be used for efficacy endpoints. Patients will be analyzed according to the treatment group to which they were randomized. The ITT will be used for the primary efficacy analysis.

**Modified Intent-to-Treat population (mITT)**: all ITT patients with exclusion of randomized untreated patients and randomized ineligible patients.

**Per-protocol Set**: all mITT patients with further exclusion of patients with major protocol deviations related to data integrity or eligibility as judged by clinical/biostatistical study personnel prior to database lock. This population will be formed only if > 5% of patients would be excluded.

**Safety Analysis Set**: all patients who have received at least 1 dose of either asapiprant or placebo. The Safety Analysis Set will be used for safety analysis. Patients will be analyzed under actual treatment being received.

**Pharmacokinetic (PK) Set**: all patients who have received at least 1 dose of asapiprant and have at least 1 evaluable post-dose PK concentration value.

**Pharmacodynamic (PD) Set**: all patients who have received at least 1 dose of asapiprant and have at least 1 evaluable post-dose PD value.

**Sample Size:** The sample size estimate of 312 total subjects is based on 31% progressing to respiratory failure by Day 28 in the placebo group and 15% progressing to RF in the asapiprant group using data from recently published COVID-19 studies (Guimaraes et al 2021, Temesgen et al, 2021). Using a Fishers Exact test with two-sided 5% Type 1 error and 90% power, the sample size to detect a 16% absolute improvement in the primary endpoint is 312 subjects (1:1 randomization). Randomization will be stratified based on the subject's enrollment region (North America vs. South America) and age (50 to < 75 vs. ≥ 75 years of age).

Interim Analysis (IA): An IA for safety and efficacy will be conducted when 208 subjects complete assessments through the 28-day follow up (Day 28) approximately 14 days after the final dose of study drug. No α spend is incorporated into the sample size to account for this look, as there is no potential for early stopping for superiority. If the conditional power (CP) at IA is less than 34%, then by the IA rules, the study will continue to completion. If the CP is at least 90% the study can continue as planned. If the CP is between 34% and 90%, the study will be considered in the promising zone and the study sample size may be adjusted up to a maximum of 624 total subjects.

**Efficacy Analysis:**

**Primary endpoint** – proportion of subjects who have died or progressed to RF as defined by progressing to the need for high-flow nasal cannula $O_2$ delivery, noninvasive positive pressure ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) therapy at Day 28.

**Secondary Endpoints**

1. Safety as assessed by AEs as measured by the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0
2. Proportion of subjects surviving [Time Frame: at Day 14, at Day 28, at Day 57]
3. Proportion of subjects who survive without progression to RF [Time Frame: at Day 14, at Day 28, at Day 57]
4. Time to two successive negative viral titers in nasopharyngeal swab
5. Time to clinical worsening from baseline value (defined by time to ≥ 1-point worsening on WHO Ordinal Scale for COVID-19):

**World Health Organization Ordinal Scale for COVID-19**

| Subject State | Description | Score |
|---|---|---|
| Uninfected | No clinical or virological evidence of infection | 0 |
| Ambulatory | No limitation of activities | 1 |
| | Limitation of activities | 2 |
| Hospitalized, Mild Disease | Hospitalized, no oxygen therapy | 3 |
| | Oxygen by mask or nasal prongs | 4 |
| Hospitalized, Severe Disease | Noninvasive ventilation or high-flow oxygen | 5 |
| | Intubation and mechanical ventilation | 6 |
| | Ventilation + additional organ support – pressors, RRT, ECMO | 7 |
| Dead | Death | 8 |

Abbreviations: ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy

6. Proportion of patients who develop critical COVID-19 illness as defined by at least one of the following:
    A. RF defined by 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), NIPPV, ECMO, clinical diagnosis RF (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
    B. Hemodynamic compromise (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
    C. Multi-organ dysfunction/failure
7. Time to clinical improvement from baseline value (defined by time to ≥ 1-point

improvement on WHO Ordinal Scale for COVID-19 score – must be maintained through Day 28)
8. Mean change from baseline in WHO Ordinal Scale for COVID-19 score at Day 14/End of Treatment, Day 28, Day 57
9. Incidence and duration of intubation
10. Length of intensive care unit stay
11. Incidence and duration of supplemental $O_2$ administration
12. Incidence and duration of noninvasive ventilation or high-flow nasal cannula $O_2$ administration
13. Incidence and duration of mechanical ventilation
14. Incidence and duration of mechanical ventilation plus additional organ support using vasopressors, and/or renal replacement therapy and/or ECMO
15. Daily ratio of oxygen saturation ($SpO_2$) to fractional inspired $O_2$ ($SpO_2/FiO_2$)
16. Length of hospital stay
17. Incidence of re-hospitalization through Day 57
18. Proportion of subjects requiring intensive care unit admission post randomization

**Exploratory Endpoints**

1. Inflammation markers including: IL-6, CRP, IL-10, TNF-α, IFN-γ, IFN-α, IP-10, MCP-1, CD4+ and CD8+ T cells, and absolute lymphocyte count
2. Assess peak and trough concentrations of asapiprant at steady state
3. Assess PGD2 pre-diagnostic to assess correlation with response to treatment for COVID-19 based on change in the WHO Ordinal Scale for COVID-19 score

**Safety Analysis:**

Safety endpoints:

1. Incidence and severity of treatment-emergent AEs
2. Safety outcome measure:
   a. Occurrence of AEs
   b. Laboratory safety parameters such as complete blood count, blood glucose, electrolyte, hepatic and renal functions taken before the first dose and on Days 2, 5, 14, 28 and the time of discharge to find any changes or any systemic effect after treatment

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. The incidence of all AEs reported during the study will be summarized by treatment group and system organ class and preferred term. Safety will be evaluated by comparing the nature, severity, and frequency of AEs between/among the treatment groups.

**Safety Monitoring:** Study Investigators will monitor subject safety on an ongoing basis while hospitalized, including a review of vital signs, local safety laboratory measurements, and observations of subject status. If discharged prior to the end of treatment, subjects will be discharged to home, and home health resources will be utilized to manage daily subject dosing and status, including the collection of protocol-specified laboratory tests and assessments. The home assessments will be monitored by the study Investigator.

BioAge Labs will have a blinded Medical Lead assigned for safety oversight and will work closely with a contract research organization (CRO) partner to provide ongoing reviews of

subject safety data, including findings associated with laboratory tests, electrocardiograms (ECGs), vital signs, physical examinations, and AE. Routine Medical Monitor review will be conducted on an ongoing basis during study conduct. The CRO will provide a drug safety team to manage serious adverse event reporting.

An IA for efficacy will be planned when 208 subjects complete study assessments through the 28-day follow up (Day 28) approximately 14 days after the final dose of study drug.

An independent Data Monitoring Committee (DMC) will be utilized during the study to monitor subject safety throughout study conduct. A DMC charter will be developed before study initiation and will define DMC processes and meetings. The DMC will meet at regular planned intervals during study conduct and also meet ad hoc as required for any identified urgent safety findings. Independent of the Sponsor, the DMC will be responsible for performing the IA and evaluating the interim results.

To aid the DMC in their recommendation to BioAge regarding conduct of the trial beyond the IA, a table of multiple possible true effects and potential stopping rules will be developed by BioAge and presented in the DMC charter. The operating characteristics of potential decision rules will be shared and understood by the DMC.

**Interim Analysis:** An IA is planned when approximately 208 subjects complete study assessments through the 28-day follow up (Day 28) approximately 14 days after the final dose of study drug.

## Table 1: Schedule of Assessments

| | Screening | Baseline | Treatment | | | | | | | | | | | | Time of Discharge[a] | 28-Day Follow-up | End of Study Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (Window)** | **Day -3 to -1** | **Day 1** | **2** | **3** | **4** | **5 + 2** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14/ EOT + 2** | | **Day 28 (±2 days)** | **Day 57 (±4 days)** |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria review | X | X | | | | | | | | | | | | | | | | |
| Medical history/ demographics | X | | | | | | | | | | | | | | | | | |
| Physical examination[b] | X | | | | | | | | | | | | | | | | | |
| Abbreviated physical examination[b] | | | | | | X | | | | | | | | | X | X | X | |
| Vital signs[b] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Prior medication review | X | | | | | | | | | | | | | | | | | |
| Safety laboratory tests | X[i] | | X | | | X | | | | | | | | | X | X | X | |
| $O_2$ Saturation/ $FiO_2$ | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| WHO Ordinal Scale for COVID-19[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG | | X | | X | | | | | | | | | | | X[e] | X[e] | | |
| Concomitant medication review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Assessment for AEs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Randomization | | X | | | | | | | | | | | | | | | | |
| Dosing | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| PK peak[g] | | X | | | | X | | | | | | | | | X[e] | X[f] | | |

| | Screening | Baseline | Treatment | | | | | | | | | | | | | Time of Discharge[a] | 28-Day Follow-up | End of Study Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day (Window)** | **Day -3 to -1** | **Day 1** | **2** | **3** | **4** | **5 + 2** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14/ EOT + 2** | | **Day 28 (±2 days)** | **Day 57 (±4 days)** |
| | | | X (Collect PK sample following first NG dosing, if applicable) | | | | | | | | | | | | | | | |
| PK trough[d, e, f] | | | | | | X | | | | | | | | | X[e] | X[f] | | |
| PGD2 pre-diagnostic sample collection | | X | | | | | | | | | | | | | | | | |
| Viral titers nasopharyngeal[h] | X | X | | X | | X | | X | | X | | X | | X | | | X | |
| Blood for inflammation markers | X | | X | | | X | | | | | | | | | X | X | | |
| Proteomic, metabolomics, and transcriptomic sample collection | | X | | | | | | | | | | | | | X | | | |

Abbreviations: AE = adverse event; $FiO_2$ = fractional inspired oxygen; ECG = electrocardiogram; EOT = end of treatment; NG = nasogastric tube; $O_2$ = oxygen; PGD2 = prostaglandin D2; PK = pharmacokinetic(s)

[a] Visit procedures at time of discharge will occur at the date of the dosing visit if visit occurs prior to Day 14, will occur at the Day 14 visit if occurs on Day 14, or will occur on the date of discharge after dosing if after Day 14. This visit is not required if discharge occurs within 2 days after Day 14. If discharge occurs on Day 4, the Day 5 assessments of abbreviated physical exam, safety labs, trough and peak PK, and blood for inflammation markers will not be collected if they were completed as part of the discharge procedures on Day 4.

[b] Same-day medical record examinations may be used for study purposes to reduce the possible exposure of site staff to COVID-19 risk. Physical examinations may be conducted as standard of care examinations. Abbreviated physical examinations may be conducted by qualified home health care providers or remote/telemedicine visits. Abbreviated physical examinations that cannot be performed at day 5 may be performed up to Day 7.

[c] WHO Ordinal Scale is derived from subject's oxygen supplementation requirements, hypotension or need for vasopressors, need for renal dialysis, and activity limitations for outpatients.

[d] Trough PK samples collected within 30 minutes prior to dose.

[e] ECG and PK sampling to be performed on last day of study treatment if subject remains hospitalized through Day 14. ECG and PK samples are not required on Day 14/EOT if subject is discharged to home before Day 14.

[f] ECG and PK sampling to be performed at the time of hospital discharge if subject is discharged prior to Day 14. ECG and PK sampling are not required at time of discharge if discharge occurs after the Day 14 visit.

[g] Peak PK samples collected 3-6 hours after dose.
[h] Done every other day until 2 qualitative test done at local laboratory is negative. After qualitative test is negative, do viral titer nasopharyngeal testing only on Day 28. For outpatients, scheduled viral titer tests may be skipped on Saturday or Sunday and/or may be skipped if dry ice shipments are not available. In the Saturday or Sunday situation Day 13 tests should be done on the following Monday.
[i] Safety labs collected within 48 hours prior to consent as part of standard of care can be used to confirm eligibility.

# 1 BACKGROUND INFORMATION

For clarification purposes, the investigational product (IP) "BGE-175", as identified in the Investigator's Brochure (IB), is referred to as asapiprant hereafter in this document, unless otherwise noted. BGE-175-201 refers specifically to the protocol number (identifier) for this study.

Always refer to the latest version of the asapiprant IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics (PK), efficacy, and safety of asapiprant.

## 1.1 Indication and Current Treatment Options

The effective treatment of COVID-19 remains an unmet medical need. Despite evolving treatments and intervention, mortality and morbidity associated with COVID-19 remains substantial, particularly in older patients, and there remains a clear need for novel treatments. To the best of our knowledge, there are no available treatments that address the clear deficits in the aging immune system that lead to accentuated morbidity and mortality.

Aging of the immune system increases COVID-19 severity, as seen in the exponential increase with age in hospitalizations and mortality in infected individuals. Compared to a 20-year-old with COVID-19, a 65-year-old is 5 times more likely to be hospitalized and 90 times more likely to die. An 85-year-old has even worse chances, with a 13 times higher risk of hospitalization and 630 times higher risk of death (Centers for Disease Control and Prevention, 2020). Age-related deficits in immune function that are already well understood in other infections like influenza, including reduced ability to mount an effective adaptive immune response, as well as an over-active innate immune response (macrophages and neutrophils), cause lung damage and lead to acute respiratory distress syndrome (ARDS) and mortality (Chen et al., 2020; Cunha et al., 2020; Wu et al., 2020). A therapy that specifically addresses the mechanisms underlying the age-dependence of COVID-19 severity is more likely to be effective in the most patients, and for those at highest risk of poor outcomes.

Building upon the existing safety database, this study will evaluate the efficacy of a novel oral small-molecule drug candidate in the highly vulnerable older patient population with COVID-19 infection that is inadequately served by the existing standard of care, resulting in high morbidity, disability, poor patient quality of life, and high costs to the healthcare system.

## 1.2 Investigational Product Asapiprant

### 1.2.1 Product Background

Asapiprant, a small molecule in the D prostanoid (DP) receptor antagonist drug class, is a novel inhibitor of the prostaglandin D2 (PGD2) DP1 signaling pathway. This mechanism of action is immune modulating with the potential to treat respiratory infections and reduce further complication of respiratory distress. Asapiprant is being developed to treat COVID-19 based on observations in animal models of severe acute respiratory syndrome coronavirus (SARS-CoV) infection, previous human experience (different indication), and established manufacturing processes (tablet formulation).

### 1.2.2 Immunomodulation in the Prostaglandin D2(PGD2)-D Prostanoid (DP)1 Signaling Pathway

PGD2-DP1 signaling inhibits an effective antiviral immune response via suppression of dendritic cell migration to draining lymph nodes as well as natural killer (NK) cell activation and interferon gamma (IFN-γ) production. The extent of this suppression strongly correlates with worse disease outcomes. This pathway is simultaneously dysregulated by immune aging and in COVID-19 patients. Older patients with COVID-19, as well as other patients at high risk for severe disease, have a less effective antiviral and adaptive immune response (via decreased dendritic cell and NK cell function), plus an exaggerated neutrophil response that results in increased tissue damage.

Furthermore, the mortality and morbidity of SARS-CoV-2 infection is largely mediated by damage to pulmonary tissue, which is infiltrated by excessive and ultimately damaging numbers of neutrophils. Although neutrophil activation is a normal component of the immune response to infection, COVID-19 patients exhibit neutrophil overactivation, exaggerated pulmonary inflammation, and cytokine storms leading to acute lung injury and death. Aging of the immune system is characterized by increased numbers of neutrophils and by nonspecific damage caused by overactive neutrophils that likely underlies much of the age-associated increase in mortality due to respiratory infections (Kulkarni et al., 2019; Li et al., 2014).

Modulation of PGD2-DP1 signaling has the potential to simultaneously boost the antiviral immune response against SARS-CoV-2 infection (mediated by dendritic cell and NK cells) while also reducing the nonspecific tissue damage caused by infiltration of neutrophils into the lungs of infected patients (Figure 2) (Jandl et al., 2016). Therefore, inhibition of PGD2-DP1 by asapiprant can potentially counteract age-related dysregulation of both the adaptive and innate immune systems and is expected to therapeutically benefit all COVID-19 patients, but most specifically older patients, who have the highest morbidity and mortality in this disease.

### 1.2.3 Preclinical Information

Refer to the asapiprant IB for a detailed preclinical (nonclinical) information and safety profile.

### 1.2.4 Clinical Information

Refer to the asapiprant IB for detailed Clinical Information.

## 1.3 Risk/Benefit and Ethical Assessment

Refer to the asapiprant IB for information on the Risk/Benefit and Ethical Assessment.

## 1.4 Compliance Statement

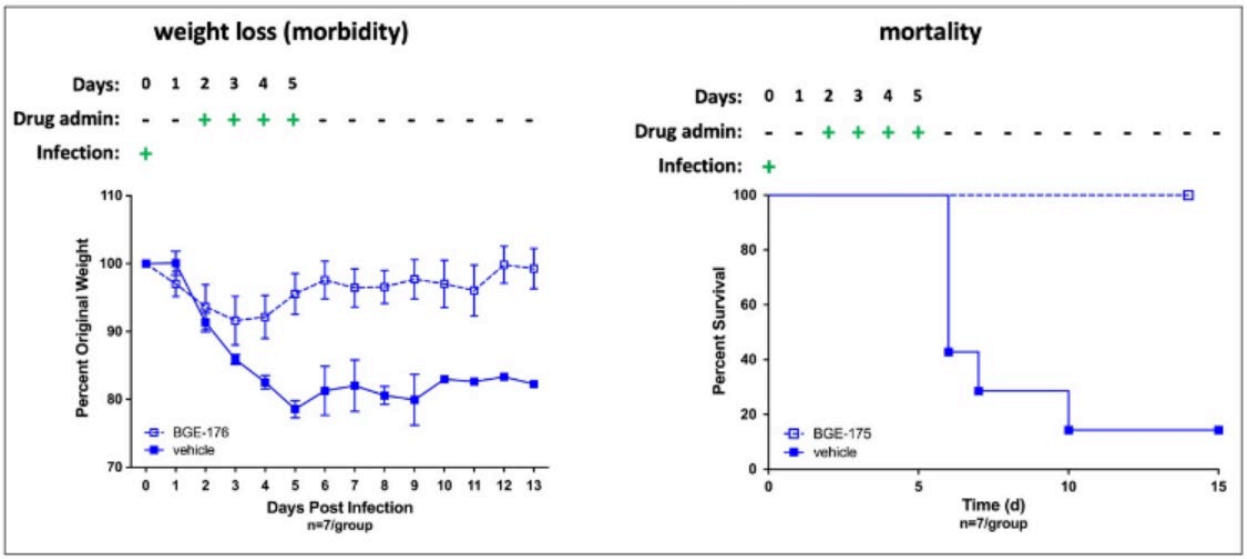
This study will be conducted in accordance with this protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the United States Code of Federal Regulations (US CFR), the European Union (EU) Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements. The responsibilities of BioAge Labs and Investigator(s) are described fully in Appendices 2.2 and 2.3, respectively.

# 2 STUDY RATIONALE, OBJECTIVES AND ENDPOINTS

## 2.1 Rationale for the Study

The effect of asapiprant treatment on SARS-CoV infection was evaluated in female 8-month old C57BL/6 mice that had been infected intranasally with mouse-adapted SARS-CoV. Mice were monitored daily for weight loss (morbidity) and mortality for up to 14 days. Asapiprant (30 mg/kg) was administered by oral gavage (PO) to fed mice once daily starting in the morning of Day 2 post infection and ending on the morning of Day 5 post infection (4 administrations). Two independent treatment studies were performed. Treatment with asapiprant was associated with a significantly reduced body weight loss as compared to control groups. As shown in Figure 1, untreated mice rapidly lost body weight after infection. Six of the 7 mice in the study shown were euthanized in the vehicle group for reaching the humane endpoint of ≥ 25% body weight loss. In contrast, when treatment with asapiprant started on Day 2, body weight loss stopped and reversed, and all 7 treated mice survived the infection. Therefore, once daily treatment with 30 mg/kg asapiprant for 4 days starting 2 days after infection effectively stopped weight loss (morbidity) and completely prevented mortality in a lethal mouse model of SARS-CoV. In a satellite group of 3 animals each, asapiprant-treatment was associated with an 84% reduction of lung virus titers at Day 5 after infection as compared to the vehicle control group.

**Figure 1: Mortality and Body Weight Change in SARS-CoV Infected Mice**

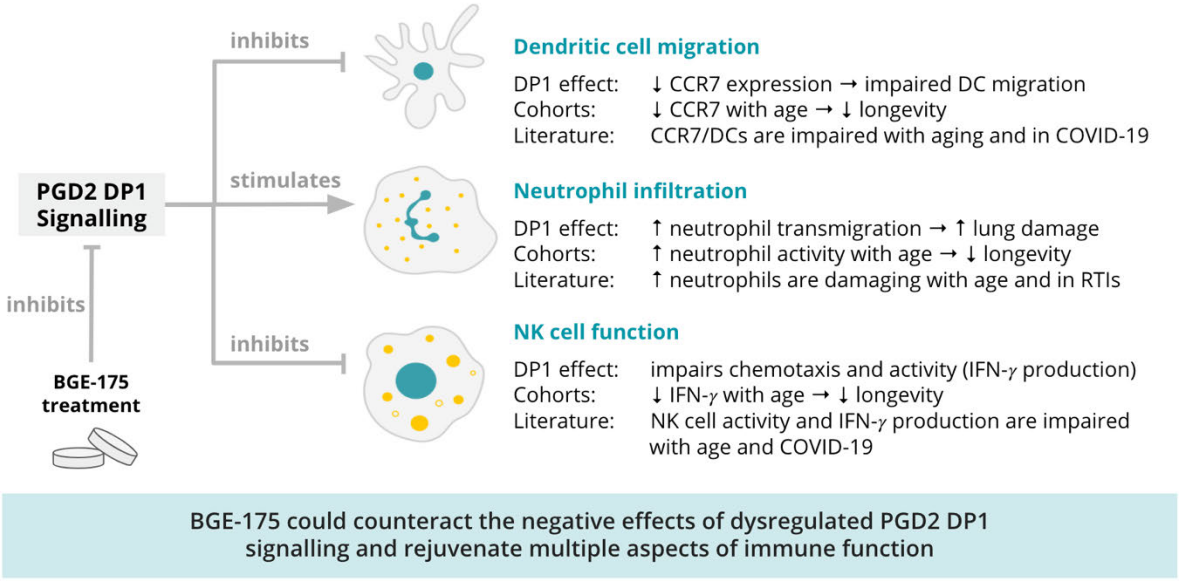



Once daily oral treatment with 30 mg/kg asapiprant for 4 days starting 2 days after infection. Mortality: log-rank (Mantel-Cox) Test; vehicle (n=7) vs asapiprant (n=7); p value = 0.0012. Source: Report BRR175001IVVP20

This clinical study will evaluate the PGD2-DP1 axis as a therapeutic target for severe COVID-19. This target is simultaneously dysregulated by immune aging and in COVID-19 patients. Therefore, inhibition of the PGD2-DP1 axis is expected to therapeutically benefit all COVID-19 patients, but most specifically older patients, who have the highest morbidity and mortality in this disease, and hence the highest unmet medical need. Modulation of this target can simultaneously boost the antiviral immune response against SARS--CoV-2 infection (mediated

by dendritic and NK cells) while also reducing the nonspecific tissue damage caused by infiltration of neutrophils into the lungs of infected patients (Figure 2) (Jandl et al., 2016).

**Figure 2: Investigational Product Asapiprant Inhibits PGD2 Signaling via the DP1 Receptor[1] to Potentially Treat COVID-19**




Abbreviations: CCR7 = C-C motif chemokine receptor 7; COVID-19 = coronavirus disease 2019; DC = dendritic cell; DP1 = prostaglandin D2 receptor 1; IFN-$\gamma$ = interferon gamma; NK cell = natural killer cell; PGD2-DP1 signaling = the therapeutic target of the investigational drug BGE-175 to treat COVID-19; RTIs = respiratory tract infections
[1] Consequences of DP1 inhibition include improved dendritic cell migration and NK-cell function (and thus a boost in the adaptive immune response), plus reduced neutrophil infiltration, thus reducing immune-mediated tissue damage. "Cohorts" refers to BioAge Labs longitudinal human cohort data where molecular profiling of blood samples have linked specific mechanisms to the aging process, future longevity, and healthspan in aging individuals.

## 2.2 Study Objectives

To evaluate the efficacy of asapiprant given by PO or nasogastric tube (NG) administration versus placebo on the clinical signs and symptoms of COVID-19 infection in hospitalized subjects ≥ 50 years of age.

### 2.2.1 Secondary Objectives

- To evaluate the ability of asapiprant given by PO or NG administration to accelerate the clearance of the COVID-19 virus in subjects with symptomatic disease requiring hospitalization
- To determine the efficacy of asapiprant by demonstrating improvement in COVID-19 illness and prevention of progression to respiratory failure (RF) using various endpoints
- To evaluate the safety profile of asapiprant given by PO or NG administration in subjects ≥ 50 years of age hospitalized with COVID-19 infection

### 2.2.2 Other Objectives

- To investigate the effect of asapiprant on inflammation markers of COVID-19 infection, including but not limited to interleukin (IL)-6, C-reactive protein (CRP), IL-10, tumor necrosis factor alpha (TNF-α), IFN-γ, interferon alpha (IFN-α), IFN-γ-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), cluster of differentiation (CD)4+ and CD8+ T cells, and absolute lymphocyte count
- Determine peak and trough concentrations of study drug after first dose and at steady state and, if possible, develop a population PK model

## 2.3 Endpoints

### 2.3.1 Primary Endpoint

Proportion of subjects who have died or progressed to RF as defined by progressing to the need for high-flow nasal cannula $O_2$ delivery, noninvasive positive pressure ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) therapy at Day 28.

### 2.3.2 Secondary Endpoints

1. Safety as assessed by adverse events (AEs) as measured by the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0
2. Proportion of subjects surviving [Time Frame: at Day 14, at Day 28, at Day 57]
3. Proportion of subjects who survive without progression to RF [Time Frame: at Day 14, at Day 28, at Day 57]
4. Time to two successive negative viral titers in nasopharyngeal swab
5. Time to clinical worsening from baseline value (defined by time to ≥ 1-point worsening on the World Health Organization (WHO) Ordinal Scale for COVID-19 [Table 2]):

**Table 2: World Health Organization Ordinal Scale for COVID-19**

| Patient State | Description | Score |
|---|---|---|
| Uninfected | No clinical or virological evidence of infection | 0 |
| Ambulatory | No limitation of activities | 1 |
| | Limitation of activities | 2 |
| Hospitalized, Mild Disease | Hospitalized, no oxygen therapy | 3 |
| | Oxygen by mask or nasal prongs | 4 |
| Hospitalized, Severe Disease | Noninvasive ventilation or high-flow oxygen | 5 |
| | Intubation and mechanical ventilation | 6 |
| | Ventilation + additional organ support – pressors, RRT, ECMO | 7 |
| Dead | Death | 8 |

Abbreviations: ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy

6. Proportion of patients who develop critical COVID-19 illness as defined by at least one of the following:

    A. RF defined 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, ECMO, clinical diagnosis respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
    B. Hemodynamic compromise (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
    C. Multi-organ dysfunction/failure
7. Time to clinical improvement from baseline value (defined by time to ≥ 1-point improvement on the WHO Ordinal Scale for COVID-19 score – must be maintained through Day 28)
8. Mean change from baseline in WHO Ordinal Scale for COVID-19 score at Day 14/EOT, Day 28, Day 57
9. Incidence and duration of intubation
10. Length of intensive care unit stay
11. Incidence and duration of supplemental $O_2$ administration
12. Incidence and duration of noninvasive ventilation or high-flow nasal cannula $O_2$ administration
13. Incidence and duration of mechanical ventilation
14. Incidence and duration of mechanical ventilation plus additional organ support using vasopressors, and/or renal replacement therapy and/or ECMO
15. Daily ratio of oxygen saturation ($SpO_2$) to fractional inspired $O_2$ ($SpO_2/FiO_2$)
16. Length of hospital stay
17. Incidence of re-hospitalization through Day 57
18. Proportion of subjects requiring intensive care unit admission post randomization

### 2.3.3 Exploratory Endpoints

1. Inflammation markers including: IL-6, CRP, IL-10, TNF-α, IFN-γ, IFN-α, IP-10, MCP-1, CD4+ and CD8+ T cells, and absolute lymphocyte count
2. Assess peak and trough concentrations of asapiprant at steady state
3. Assess PGD2 pre-diagnostic to assess correlation with response to treatment for COVID-19 based on change in WHO Ordinal Scale for COVID-19 score

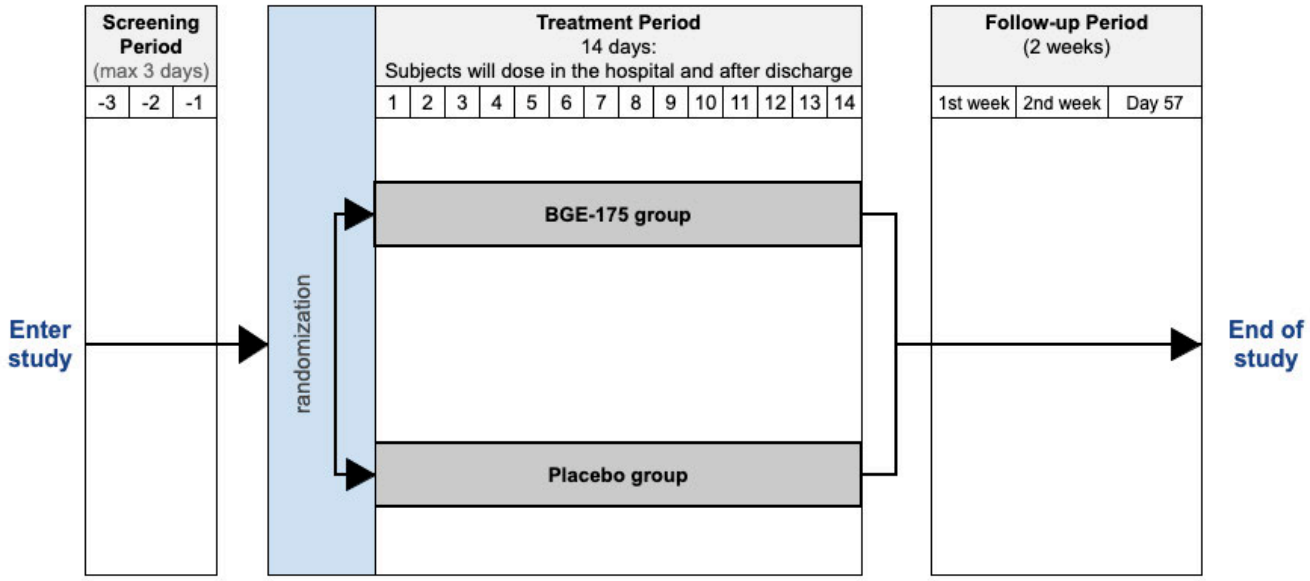
# 3 STUDY DESIGN

## 3.1 Study Design and Flow Chart

This is a randomized, placebo-controlled, parallel-group, multicenter, double-blind study of asapiprant administered PO or NG in subjects ≥ 50 years of age and hospitalized with documented COVID-19 infection who are not yet in RF.

After signing informed consent, subjects will be screened upon presentation at the hospital. Screening will include full physical examination, vital signs, safety laboratory evaluation, $O_2$ saturation, pre-diagnostics to measure PGD2 status, and baseline assessment of WHO Ordinal Scale for COVID-19 (Table 2) that is derived from oxygen supplementation requirements. Certain standard of care assessments completed within 1 day of consent (e.g. physical examination, safety laboratory evaluations) may be used for screening purposes. If confirmed that they qualify for this protocol according to listed inclusion and exclusion criteria, subjects will receive their first dose of study medication PO. They will then receive study medication PO once daily, at approximately the same time each day for 13 additional days. Subjects who progress to RF and require intubation or subjects who are unable to swallow will receive study medication by NG tube administration. Study medication will be administered and subjects will receive standard of care treatments deemed appropriate by the treating physician(s). Subjects will be randomized to receive asapiprant or placebo. Subjects will be monitored daily for all relevant efficacy outcomes, $O_2$ saturation and AEs. Treatment will be discontinued in subjects who develop hepatic function impairment defined as a Child-Pugh score (Appendix 4) of 7 or greater. Blood will be drawn periodically for safety laboratory measurements, plasma kinetics, lymphocyte subsets, CRP, and cytokines (see Table 1). Nasopharyngeal swabs will be collected to measure viral load and nasal swabs may be collected for optional local qualitative testing. Subjects will be monitored at follow-up visits on Day 28 (approximately 14 days after last dose) and Day 57 (approximately 43 days after last dose) to measure viral load. Subjects will be monitored for 14 days after administration of the last dose and followed through Day 57.

**Figure 3: Overall Study Design Flow Schematic**



## 3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 57 days.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). Please note that this includes the follow-up visit or contact, whichever is later (refer to Section **Error! Reference source not found.** for the defined follow-up period for this protocol).

## 3.3 Sites and Regions

This study will be performed at multiple study sites within the United States, Brazil and Argentina.

# 4 STUDY POPULATION

Each subject must and provide informed consent that is documented by a signed and dated consent form or documented by the local standard process before any procedures specified in the protocol are performed.

## 4.1 Sample Size

The planned size for this study is 312 subjects, randomized 1:1 Active + standard of care (SOC) vs. Placebo + SOC. Randomization will be stratified based on the subject's enrollment region (North America vs. South America) and age (50 to < 75 vs. ≥ 75 years of age). Subjects will receive IP per the randomization code. The blind for the treatment assignment must not be broken during the study except in emergencies where the identification of the IP is required for further treatment of the subject(s) or to assess any safety and tolerability questions.

## 4.2 Inclusion Criteria

The subject will be considered eligible for the study after meeting all of the criteria below.

1. Ability to voluntarily provide informed consent that is documented per local requirements
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions
3. Hospitalized subjects with a confirmed SARS-CoV-2 infection
4. Laboratory (polymerase chain reaction [PCR]) confirmed infection with SARS-CoV-2
5. Age ≥ 50 years
6. COVID-19 illness of any duration, and $O_2$ saturation measurements ≤ 94% over 5 minutes on room air (Note: low flow $O_2$ is permitted, but room air $O_2$ saturation must be ≤ 94%)
7. Not with evidence of critical COVID-19 illness as defined by at least one of the following:
   a. RF defined by requiring at least one of the following:
      - Endotracheal intubation and mechanical ventilation
      - $O_2$ delivered by high-flow nasal cannula at flow rates > 20 L/min with fraction of delivered $O_2$ ≥ 0.5)
      - Noninvasive positive pressure ventilation (NIPPV)
      - Extracorporeal membrane oxygenation (ECMO)
      - Clinical diagnosis of RF (i.e., clinical need for one of the preceding therapies, but preceding therapies are not able to be administered in setting of resource limitation)
   b. Hemodynamic compromise (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg) or requiring vasopressors
   c. Multi-organ dysfunction/failure
8. Female subjects of childbearing potential must have a negative pregnancy test at screening or pre-treatment on Day 1

**Note**: Female subjects of childbearing potential are defined as pre-menopausal, < 12 months of amenorrhea post-menopause, or no history of surgical sterilization (hysterectomy or oophorectomy) or tubal ligation.

9. Male and female subjects of childbearing potential must agree to use methods of contraception that are consistent with local regulations for those participating in clinical studies

### 4.3 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met.

1. Participation in any other randomized, controlled clinical trial of an experimental treatment for COVID-19 (uncontrolled, compassionate use trials are allowed)
2. In the opinion of the Investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
3. Currently participating in a vaccination trial for SARS-CoV-2
4. Known positive test for influenza A or influenza B within 1 week prior to screening.
5. History of human immunodeficiency virus (HIV) infection that is not controlled with current treatment
6. History of Hepatitis B surface antigen, or Hepatitis C positive prior to screening. Subjects who are positive for Hepatitis C but have Hepatitis C virus (HCV) RNA below the limit of quantitation may be enrolled. Subjects with Hepatitis B, but with undetectable viral load, may be enrolled.
7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × the upper limit of normal (ULN)
8. Hepatic function impairment defined as a Child-Pugh score of 7 or greater. See Appendix 4 for description of the Child-Pugh system.
9. Stage 4 or higher severe chronic kidney disease (i.e., estimated glomerular filtration rate [eGFR] < 30 mL/min) or acute renal failure resulting in eGFR < 30 mL/min
10. Serious co-morbidity, including:
    a. Myocardial infarction (within the last month)
    b. Moderate or severe heart failure (New York Heart Association [NYHA] class III or IV)
    c. Acute stroke (within the last month)
    d. Uncontrolled malignancy. Uncontrolled malignancy would include cancers that are not considered in remission, or solid tumor or hematological malignancies with evidence of disease progression in the past 3 months (i.e., there is evidence of disease progression by Response Evaluation Criteria in Solid Tumours [RECIST] or equivalent relevant criterion for the type of malignancy), and are not considered effectively managed with ongoing treatment as determined by the Investigator
    e. Recent severe thromboembolic disease or evidence of severe thromboembolic disease defined as a current large vessel thromboembolic event or a thromboembolic event within

the past 3 months (e.g., deep vein thrombosis [DVT], pulmonary embolism, ischemic stroke, transient ischemic attack) requiring interventional treatment. This exclusion does not prohibit prophylaxis for thromboembolic events, including those considered possible with concurrent SARS-CoV-2 infection.

11. History of severe allergic or anaphylactic reactions or hypersensitivity to the study drug
12. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive study treatment

## 4.4 Restrictions

Concurrent use of other investigational therapies are generally prohibited in this study; however, therapies being used under Emergency Use Authorization will be permitted.

## 4.5 Stopping Criteria

Given the lack of toxicity observed to date, this study has no specific stopping criteria associated with asapiprant use. Nonetheless, asapiprant is an investigational drug and is being evaluated for a new indication in this study. Investigators should monitor for any new serious, unexpected AEs and assess for possible causality. Any serious adverse event (SAE) thought to be related to study drug will be reviewed by the Data Monitoring Committee (DMC), and the DMC will provide guidance for ongoing study conduct. Treatment will be discontinued in subjects who develop hepatic function impairment defined as a Child-Pugh score (Appendix 4) of 7 or greater.

## 4.6 Discontinuation of Subjects

A subject may withdraw consent to participate in the study at any time for any reason without prejudice to his/her future medical care.

If IP is discontinued, regardless of the reason, the end of treatment evaluations listed in Table 1 are to be performed as completely as possible. Whenever possible, all subjects with IP administration discontinued should undergo follow-up evaluations. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for IP discontinuation, date of IP discontinuation, and the total amount of IP administered must be recorded in the source documents. If a subject has been discharged, then the dosing diary and IP supplies must be collected.

### 4.6.1 Reasons for IP Discontinuation

The reason for IP discontinuation must be determined by the Investigator and recorded in the subject's source document. If a subject's IP administration is discontinued for more than one reason, each reason should be documented in the source document, and the most clinically relevant reason should be indicated. Subjects should continue to be followed with study assessments after discontinuing IP administration unless they withdraw consent.

### 4.6.2 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused IP.

# 5 PRIOR AND CONCOMITANT TREATMENT

## 5.1 Prior and Concomitant Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of first dose of IP. Concomitant treatment refers to all treatment taken between the dates of the first dose of IP and the end of the follow-up period, inclusive. Prior and concomitant treatment information must be recorded on the appropriate CRF page.

### 5.1.1 Permitted Treatment

Any medication which is considered necessary for the subject's safety and wellbeing may be given at the discretion of the Investigator. The administration of all medications (including IP) must be listed on the appropriate CRF page. As noted previously in Section 4.4 concurrent use of other investigational therapies are generally prohibited in this study; however, therapies being used under Emergency Use Authorization will be permitted.

# 6 INVESTIGATIONAL PRODUCT

## 6.1 Identity of Investigational Product

The test product, asapiprant will be provided as 50 mg tablets for oral use. Additional information is provided in the current asapiprant IB. The reference/comparator product is placebo, which will be provided as a tablet to match the active IP asapiprant. The placebo tablet will be identical to the active tablet except for the active ingredient.

All IP will be provided in 30-count bottles. All IP will be shipped to the site as blinded supply.

### 6.1.1 Blinding the Treatment Assignment

This is a double-blind, placebo-controlled study. The blind will be maintained for the entirety of the 57-day study conduct for every subject, until unblinding for the final Day 28 topline results for all subjects or unless unblinding is required for subject safety reasons. The actual treatment given to individual subjects is determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment are available from the interactive response technology (IRT). The IRT will assign bottle numbers in a blinded manner and will be dispensed by appropriately delegated study staff.

Each bottle of IP will be assigned a unique 5-character alphanumeric packaging identification number. When a bottle of IP is assigned to a subject, the packaging identification number will be recorded in the drug accountability records.

## 6.2 Administration of Investigational Product(s)

### 6.2.1 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study.

Subject (screening) numbers are assigned to all subjects by the EDC as they consent to take part in the study. Within the site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The actual treatment given to individual subjects is determined by a randomization schedule.

The randomization number represents a unique number corresponding to IP allocated to the subject and will be allocated prior to dosing after eligibility has been determined.

A 5-digit *alpha and/or numeric -Identifier,* will be allocated immediately prior to dosing after eligibility has been determined. If a randomization number is allocated incorrectly, the study monitor must be notified as soon as the error is discovered. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. For randomized subjects, the randomization number will be the identifying number used throughout CRF.

### 6.2.2 Dosing

Subjects will be dosed concurrently with their meal (± 30 minutes) at 100 mg. Subjects will take two 50 mg tablets of asapiprant or matching placebo immediately after the screening evaluation,

confirmation of eligibility, and randomization on Day 1. Dosing will continue daily at approximately the same time of day for the next 13 days. Subjects who are not eating will take the same 100 mg (two 50 mg tablets) total daily dose. The fed status and prescribed 100 mg dose will be entered into the electronic data capture (EDC)/IRT [redacted] daily. Subjects will continue dosing for 14 days, including if they are discharged or if they progress to RF. Subjects taking nothing by mouth (NPO) or not being fed through an NG tube will take study medication at approximately the same time they received prior daily doses.

#### 6.2.2.1 Treatment Period

Each subject will participate in the study for approximately 8 weeks from the time the subject signs the informed consent form (ICF) through the final contact. After screening, each subject will receive, daily, 1 dose of assigned treatment between Day 1 and Day 14. The WHO Ordinal Scale for COVID-19 (Table 2) will be derived daily while hospitalized, at Day 14, and at follow-up visits until the subject has completed the study (Day 57 or at time of early withdrawal).

### 6.2.3 Unblinding the Treatment Assignment

The treatment assignment must not be unblinded during the study except in emergency situations where the identification of the IP is required for further treatment of the subject.

In the event that the treatment assignment is unblinded, the date, the person who unblinded the code, and the reason for unblinding the code will be recorded. Upon unblinding, IP administration will be discontinued, and the subject should be followed with study assessments. Any unblinding that occurs must be reported to the contract research organization (CRO) or Sponsor, as appropriate. Unblinding information will be available using the study IRT.

## 6.3 Labeling, Packaging, Storage, and Handling

### 6.3.1 Labeling

Labels containing study information and pack identification are applied to the IP container.

All IP containers are labeled with a minimum of the protocol number, medication identification number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), lot number and/or packaging reference, the statements ‘For clinical trial use only’, and/or ‘CAUTION: New Drug - Limited by Federal (or United States) Law to investigational use’, ‘Keep Out of Sight and Reach of Children’, and the Sponsor name, address and phone number. Additional labelling will be completed to comply with local regulations.

Additional labels (e.g., those used when dispensing product) may, on a case-by-case basis, be applied to the IP in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the Sponsor’s prior full agreement.

### 6.3.2 Packaging

Investigational product will be packaged in labeled containers as 30-count, white, round bottles with an induction seal.

Changes to BioAge Labs-supplied packaging prior to dosing may not occur without BioAge Labs' prior full agreement.

### 6.3.3 Storage

The Investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the IP bottle/carton labels as they are dispensed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the IP is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The Sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor or its representative(s) will determine the ultimate impact of excursions on the IP and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the Sponsor (or a nominated designee).

The Sponsor (or a nominated designee) should be notified immediately if there are any changes to the storage area of the IP that could affect the integrity of the product(s), e.g., fumigation of a storage room.

## 6.4 Drug Accountability

The Investigator will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of subjects. The Investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator has overall responsibility for administering/dispensing IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will administer the IP only to subjects included in this study following the procedures set out in the study protocol.

Each subject will be given only the IP carrying his/her treatment assignment. All administered/dispensed medication will be documented in the subject's source and/or other IP record.

No IP stock or returned inventory from a BioAge Labs-Sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor (or a nominated designee), all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor (or a nominated designee) must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

With the written agreement of the Sponsor (or a nominated designee) at the end of the study, all unused stock and empty/used IP packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the Sponsor (or a nominated designee). Destruction of IP must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile IPs delivered with those used and returned. All IPs must be accounted for and all discrepancies investigated and documented to the Sponsor (or designee) satisfaction.

## 6.5 Subject Compliance

Subject compliance will be ensured with a combination of the following methods:

- Inpatient: Compliance must be assessed by observation of dosing by the Investigator or designee. The Investigator/designated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured in the appropriate CRF.
- Outpatient: subjects will be instructed how to dose daily, and home health visits or other subjects contact (e.g., virtual teleconferences with the subject and Investigator or a designee may be held) to verify subject compliance and comprehension of dose assignment. Subjects will be instructed to return all used and unused study medication and bottles to complete drug accountability.

## 6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not Applicable.

# 7 STUDY PROCEDURES

## 7.1 Study Schedule

The following "priority order" will be in effect when more than 1 procedure or assessment is required at a particular time point.

- Spontaneous or solicited AE reporting
- Electrocardiogram (ECG)
- Vital signs
- PK blood sampling
- Pharmacodynamic (PD) blood sampling
- $O_2$ saturation
- Clinical laboratory tests
- Physical examination
- Viral titers nasopharyngeal
- WHO Ordinal Scale for COVID-19 (Table 2) derived from oxygen supplementation requirement, hypotension or need for vasopressors, need for renal dialysis, and activity level in outpatients
- Documentation of administered supplemental oxygen (e.g. flow rates, equipment)

NOTE: Blood sampling for PK and PD evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate CRF. Pharmacokinetic samples should always be collected prior to PD samples, when scheduled at the same timepoint.

### 7.1.1 Screening Period

The screening procedures must be completed within 3 days prior to the administration of the dose or first dose of IP. All screening assessments and procedures are to be performed by the Principal Investigator or a qualified designee.

Signed and dated informed consent from the subject prior to the performance of any study related procedures must be obtained by the Investigator or designee. A copy of the signed informed consent form must be given to the subject for their records.

See Table 1 for a complete list of screening procedures to be performed.

#### 7.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been enrolled/randomized or administered IP.

For purposes of data collection, all subjects who give consent to the study, but are not enrolled and/or randomized, will be considered as screen failures even if they were otherwise fully eligible for the study, for example alternates/reserve subjects.

#### 7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point. However, subjects may be re-screened if screen failure occurred due to administrative reasons.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on Investigator discretion and Sponsor (or a nominated designee) approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is re-screened, and new informed consent must be documented. The sponsor will provide guidance regarding screening procedures that must be repeated if a subject is rescreened so that unnecessary site staff exposure is minimized.

### 7.1.2 Treatment Period

#### 7.1.2.1 Visits Summary

Subjects who meet all the eligibility criteria before will be allowed to enter the Treatment period (Day 1). They will then be randomized to an IP (asapiprant or placebo). Subjects will take study drug for 14 days according to the randomization schedule.

If screening and Day 1 occur on the same day, screening procedures do not need to be repeated if also required on Day 1. Standard of care labs can be used to confirm eligibility and baseline safety assessments if completed within 48 hours prior to screening.

This is a double-blind, placebo-controlled study. The Investigator, study site staff, and the subject are blinded to study treatment, but not to the dose (number of tablets) or dosing frequency. The Sponsor and designees, except the personnel analyzing the PK samples, are blinded to study treatment, dose, and dosing frequency. Sponsor study team members responsible for IRT system are blinded to study treatment and can, in exceptional cases, be unblinded to dose and dosing frequency.

Asapiprant and matching placebo tablets will be identical in appearance, packaging, and labeling to maintain the blind. Treatment assignments will be unblinded after database lock.

Any intentional or unintentional unblinding should be reported and documented. Unblinding (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator for the subject's care. Unplanned unblinding will result in the discontinuation of subject participation from the study treatment but the subject should participate in protocol-defined follow-up procedures.

#### 7.1.2.2 End of Treatment, Follow-up and End of Study Period

The end of treatment visit is the date when the subject has completed the final study treatment as outlined in the schedule of assessments.

There is a follow-up visit to occur at Day 28 (approximately 14 days after the final dose of study drug).

The end of study visit is to occur on Day 57 (approximately 43 days after the final dose of study drug). This visit will be a telephone call initiated by the site staff to query for SAEs, AEs, and concomitant treatments. All AEs and SAEs that are not resolved through 30 days after the last dose of study drug will be followed to closure (see Appendix 3.2).

### 7.1.3 Additional Care of Subjects After the Study

No after care is planned for this study.

## 7.2 Study Evaluations and Procedures

The name and address of each third-party vendor (e.g., clinical laboratory) used in this study will be maintained in the Investigator's and Sponsor (or designee) files. The Sponsor expects that the Investigator will ensure that every reasonable effort is made to perform all assessments at the protocol-scheduled time.

Study Investigators will monitor subject safety on an ongoing basis while hospitalized, including a review of vital signs, local safety laboratory measurements, and observations of subject status. If discharged prior to the end of treatment, subjects will be discharged to home, and home health resources will be utilized to manage subject daily dosing and status, including the collection of protocol-specified laboratory tests and assessments. The home assessments will be monitored by the study Investigator.

BioAge Labs will have a blinded Medical Lead assigned for safety oversight and will work closely with a CRO partner to provide ongoing reviews of subject safety data, including findings associated with laboratory tests, ECGs, vital signs, physical examinations, and AEs. Routine Medical Monitor review will be conducted on an ongoing basis during study conduct. The CRO will provide a drug safety team to manage SAE reporting.

An independent DMC will be utilized throughout the study to monitor subject safety. A DMC charter will be developed preceding study initiation, which will define DMC processes and meetings. The DMC will meet at regular planned intervals during study conduct and also meet ad hoc as required for any identified urgent safety findings.

An interim analysis (IA) will be planned when 208 subjects complete study assessments though the end of treatment and 14-day follow-up (Day 28). The IA will include an assessment of safety and efficacy and will include stopping rules. Independent of the Sponsor, the DMC will be responsible for performing the IA and evaluating the interim results.

#### 7.2.1.1 Adverse Event Collection

Adverse events will be assessed and monitored from when the subject signs the informed consent form to completion of the study (including screen failure or drop/out discontinuation, if applicable). During the study, subject safety will be closely monitored by vital sign measurements, ECG measurements, clinical safety laboratory measurements, and physician oversight.

All AEs spontaneously reported by the subject or reported in response to the open question at scheduled time points (i.e., "Have you had any health problems since you were last asked {or since the last visit})?" will be collected from the time informed consent is signed.

AEs include worsening of a preexisting medical condition as well as clinically significant changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (e.g., diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A preexisting condition that has not worsened during the study is not considered an AE.

#### 7.2.1.2 Independent Data Monitoring Committee

An independent DMC, whose members who are not affiliated with the Sponsor or CRO, will be utilized during the study to monitor subject safety throughout study conduct. The DMC will have access to unblinded data to perform comparative analyses during study conduct. A DMC charter will be developed preceding study initiation, which will define DMC processes and meetings. The DMC will meet at regular planned intervals during study conduct and also meet ad hoc for any identified urgent safety findings. Additionally, the DMC charter will define when a pause in enrollment is required pending a DMC safety review. The following criteria will trigger a pause in enrollment pending a DMC safety review:

- Death in any subject in which the cause of death is judged to be related to the study drug by the Investigator.
- One occurrence of an AE of special interest, which will be defined as an SAE considered related to the study drug and consistent with the toxicity profile defined in the IB. For asapiprant, there are no known AEs of special interest.

### 7.2.2 Medical History / Demographic Information

Concomitant medications, including over-the-counter medications and supplements used during the study, will be recorded in the CRF. Drug names and start/stop dates, including dose, route of administration, and dosing frequency, will be recorded for concomitant medications (e.g., iron, anti-hypertensive medications).

A complete medical and medication history, as well as demographic information, will be collected at the screening visit/time points as described in Table 1 by a qualified licensed physician, physician's assistant, or nurse practitioner. The medical history will be reviewed, and clinically relevant history (per the Investigator) is to be recorded in the source records and on the appropriate history CRF page(s), including:

- Date of birth
- Sex
- Race and ethnicity
- Use of medication within 30 days before entering the screening period
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- SARS-CoV-2 (COVID-19) history

### 7.2.3 Physical Examination (Including Height at Screening Visit Only and Weight)

A complete physical examination will be performed at the time points described in Table 1 by a qualified licensed physician, physician's assistant, or nurse practitioner.

The physical examination will include a review of the following body systems:

| | | |
|---|---|---|
| • General appearance | • Skin | • Head, eyes, ears, nose, and throat |
| • Spine/neck/thyroid | • Musculoskeletal | • Respiratory |
| • Cardiovascular | • Neurological | • Abdomen (including liver and kidneys) |

Clinically significant abnormalities identified at the screening visit will be documented in the subject's source documents and on the Medical History CRF. Clinically relevant changes after the initial screening period visit will be captured on the AE CRF page, as deemed by the Investigator.

Weight should be collected at screening but will not be required for any other visits throughout the study.

#### 7.2.3.1 Abbreviated Physical Examination

An abbreviated examination will be performed at the time points described in Table 1 by a qualified licensed physician, physician's assistant, nurse practitioner, or registered nurse. The abbreviated physical examination will consist of a review of the following body systems plus a targeted review for those areas where a subject may raise concern through AE questioning.

| | | |
|---|---|---|
| • Cardiovascular | • Respiratory | • Abdomen (including liver and kidneys) |
| • A targeted physical review for areas/systems of medical relevance | | |

Clinically relevant changes will be captured as AEs on the AE CRF page, as deemed by the Investigator.

### 7.2.4 Vital Signs

Vital signs consisting of blood pressure, temperature, respiratory rate, and pulse rate will be taken at the time points described in Table 1 by appropriately delegated personnel. One reading of blood pressure and pulse rate will be taken and recorded in the source document and the CRF.

**Blood pressure**

One reading of supine systolic blood pressure/diastolic blood is to be collected at the described time points.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be lying comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

The area in which the vital signs are measured should be controlled and as consistent as possible during the study to minimize the external variability of the readings. It should be collected at a comfortable room temperature with little to no background noise, using the appropriately sized cuff placed at the same location of the same arm during the study. The bladder should be deflated (calibrated for oscillometric method or manually by the auscultatory method) at a rate of 2-3 mmHg/second. The first and last audible sounds recorded are the systolic and diastolic pressure, respectively.

At the Screening Visit, blood pressure should be compared between both arms. When there is a consistent inter-arm difference confirmed over 3 consecutive measurements (> 10 mmHg), the arm with the higher blood pressure should be used for inclusion at screening and the last measurement recorded in the CRF. The same (right or left) arm with the higher blood pressure will be used throughout the study.

**Pulse rate**

One reading of the supine pulse rate should be collected at the described time points. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, the pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained before the nominal time of the blood collection. The same measurement technique for obtaining pulse should be used throughout the study for all subjects (and documented).

**Body Temperature**

Temperature should be taken as per hospital protocol.

### 7.2.5 Safety Laboratory Tests

Blood for safety laboratory tests will be taken at the time points described in Table 1 by an appropriately delegated employee.

All safety laboratory tests will be performed according to the laboratory's standard procedures. The laboratory will supply reference ranges. The Investigator should determine out-of-range safety laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Out-of-range values and changes within the "normal range" during the study may be associated with, or constitute, an AE. Abnormal safety laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the Investigator or BioAge Labs, be repeated as soon as possible until confirmed, explained, or resolved.

The safety laboratory assessments described in the following sections will be performed.

#### 7.2.5.1.1 Biochemistry

Blood samples (8.5 mL) for serum biochemistry will be collected into a red top gel separator tube at the time points described in Table 1. The following parameters will be assessed:

| | |
|---|---|
| Sodium | Phosphate |
| Potassium | Protein |
| Glucose | Carbon dioxide |
| Urea nitrogen | Albumin |
| Creatinine | Aspartate aminotransferase (AST) |
| Calcium | Alanine aminotransferase (ALT) |
| Chloride | Gamma glutamyl transferase (GGT) |
| Thyroid stimulating hormone (TSH)[a] | Alkaline phosphatase (ALP) |
| Lactate dehydrogenase (LDH) | Total bilirubin |
| | Indirect bilirubin |
| | Uric acid |

[a] See Table 1

#### 7.2.5.1.2 Hematology

Blood samples (3 mL) for hematology will be collected into a $K_2$EDTA tube at the time points described in Table 1. The following parameters will be assessed:

| | |
|---|---|
| Hemoglobin | Total neutrophils (absolute and percent)* |
| Hematocrit | Eosinophils (absolute and percent)* |
| Red blood cells | Monocytes (absolute and percent)* |
| Platelet count | Basophils (absolute and percent)* |
| White blood cell count; total and differential | Lymphocytes (absolute and percent)* |
| Mean corpuscular volume (MCV) | Reticulocyte count |
| Mean corpuscular hemoglobin (MCH) | |
| MCH concentration (MCHC) | *absolute and percent preferred, but it will be acceptable to only collect one based on local lab reporting |
| Red blood cell distribution width (RDW) | |

#### 7.2.5.1.3 Coagulation

Blood samples (2.7 mL) for coagulation will be collected into a sodium citrate tube at the time points outlined in Table 1. The following parameters will be assessed:

| | | |
|---|---|---|
| Prothrombin time (PT) | Activated partial thromboplastic time (aPTT) | International normalized ratio (INR) |

#### 7.2.5.1.4 Urinalysis

A urine sample for urinalysis will be collected at the time points described in Table 1. The following parameters will be assessed:

| | | |
|---|---|---|
| pH | Blood | Nitrites |
| Glucose | Ketones | Leukocyte esterase |
| Protein | Bilirubin | Specific gravity |

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

#### 7.2.5.1.5 Serology Screen

At the Screening Visit, a blood sample of approximately 8.5 mL will be drawn into a serum separator tube to test for the presence of HIV, Hepatitis B surface antigen (HBsAg), and HCV antibody among other parameters.

The test results from the Screening Visit need not be confirmed negative prior to enrollment in the study. Patients with a previous history of HIV that is not controlled with current therapy will be excluded. Patients with previous positive serology for Hepatitis B or Hepatitis C will be excluded unless viral RNA blood levels are below the level of detection (see exclusion criteria for details). Results of the serology screen will be reviewed and verified by the study monitor and will be collected in the CRF database.

### 7.2.6 $O_2$ Saturation/$FiO_2$

The $O_2$ saturation/$FiO_2$ ratio will be collected on the study days as specified in Table 1.

Oxygen saturation will be documented as a representative value at approximately the same time daily and will use a finger pulse oximeter to approximate $O_2$ saturation.

$FiO_2$ values will be obtained at the corresponding time to the $O_2$ saturation values daily. If a subject is receiving supplemental $O_2$ using a device that reports $FiO_2$ values, then the $FiO_2$ value will be reported from the device and recorded in the CRF. However, if there is no $FiO_2$ readout available (e.g., subject is receiving supplemental $O_2$ by nasal prongs), the site will record the method of $O_2$ delivery and the flow rate in liters of $O_2$ per minute (L/min) in the CRF. If the subject is breathing room air, this will be captured in the CRF rather than the $O_2$ delivery flow rate. Note: High Flow Oxygen will only be documented when using a high flow oxygen delivery device that warms and humidifies the oxygen.

The Sponsor will derive the $O_2$ saturation/$FiO_2$ ratio, using accepted standards for converting $O_2$ delivery rates to $FiO_2$ values.

### 7.2.7 Pre-dose Serological Markers - PGD2

A single predose blood sample for circulating PGD2/PGD2 metabolites will be obtained at the time specified in Table 1. Sample collection, handling, storage and shipment instructions will be provided in the study laboratory manual.

### 7.2.8 Nasopharyngeal Viral Titers

Nasopharyngeal swabs for quantitative viral titer assessments will be collected at the times specified in Table 1 by appropriately delegated study staff. These nasopharyngeal swabs will be completed every other day until two confirmed negative qualitative tests are obtained. Qualitative COVID-19 tests are not required and may be elected by the subject and Investigator. Qualitative tests are performed at the site's local laboratory. When a qualitative negative result is confirmed (two consecutive tests are negative), the site will verify that a final quantitative nasopharyngeal swab has been collected for at least one visit following the first qualitative negative result. The study laboratory manual will outline proper sample handling for quantitative viral titer assessments. Qualitative testing will be performed per the site's local laboratory standard testing procedures.

### 7.2.9 Blood for Inflammation Markers

Blood samples will be collected at the times specified in Table 1 for measurement of IL-6, CRP, IL-10, TNF-α, IFN-γ, IFN-α, IP-10, MCP-1, CD4+ and CD8+ T cells, and absolute lymphocyte count. Sample collection, handling, storage and shipment instructions will be provided in the study laboratory manual.

### 7.2.10 Proteomic, Metabolomic and Transcriptomic Sample Collection

Blood collection samples (4 mL) will be taken at the time points described in Table 1. The name and address of the laboratory(ies) performing these assessments for this study will be maintained in the Investigator's files at each site and in the Trial Master File at the Sponsor. A full description of the blood collection, handling, storage, and shipping can be found in the laboratory manual.

Following completion of the study, blood collection samples from one or more time points may undergo untargeted transcriptomic, metabolomic, or proteomic analysis. For untargeted transcriptomic analysis, the appropriate amount of collected blood will be sent to [redacted] for RNA-seq analysis. For untargeted proteomics, the appropriate amount of collected blood will be sent to [redacted] for analysis using the [redacted].

Actual blood sample collection times must be captured, and these data will be collected. The Sponsor expects the Investigator to ensure that a reasonable effort is made to collect all blood samples at time points in described in Table 1.

### 7.2.11 Twelve-lead Electrocardiogram (ECG)

Twelve-lead ECGs will be performed at the times specified in Table 1 by appropriately delegated study staff. The following parameters will be recorded on the appropriate CRF page: heart rate,

rhythm, PR, RR, QRS, and QT intervals, and any wave form abnormalities. The QT interval corrected for heart rate by Fridericia's formula (QTcF) will be from the Investigator's read. The Investigator's assessment of the ECG tracing as normal or abnormal must be documented. If the Investigator feels that the ECG is abnormal, he/she needs to determine if the abnormality is significant or not. Overall, ECG significance is to be documented on the tracing and recorded in the CRF.

The subject will be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject must be resting in the supine position for at least 5 minutes before collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time to achieve precise ECG recordings.

A single ECG recording, including a 10-second rhythm strip, will be obtained for all assessments. ECG results will be recorded in the CRF. The ECG recording should be immediately assessed to verify that it is a valid recording and if not valid, it should be repeated to obtain a valid recording. Invalid recordings will not be entered in the CRF.

To ensure the safety of the subjects, a qualified individual at the Investigator site will make comparisons to baseline measurements.

If a machine-read QTcF value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

### 7.2.12 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory performing the PK assessment for this study will be maintained in the Investigator's files at the/each site and in the Trial Master File at BioAge Labs.

Actual PK blood sample collection times versus time of dosing will be monitored. The time of meal will also be captured, as dosing should occur within 30 minutes of eating. The BioAge Labs expectation is that the Investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. Pre-dose (trough) pharmacokinetic blood collection should be collected within 30 minutes prior to the dose. If subjects are being dosed at home, the subject should be instructed to not dose until the home health visit is conducted. Post-dose (peak) PK blood samples should be collected between 3 and 6 hours after the daily dose. Samples drawn outside these parameters will be considered a protocol deviation.

#### 7.2.12.1 Blood Sample Collection and Handling Procedures

Pharmacokinetic blood samples will be collected at the times specified in Table 1 to measure plasma concentrations of asapiprant and metabolites thereof. A full description of PK blood collection, handling, storage and shipping can be found in the provided laboratory manual.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CPU. The labels will contain the following information:

- Study number (BGE-175-201)
- Subject identifier (This number consists of a 5-digit number. The first digit will identify the Study Part the subject is assigned to; the second and third digit will identify the cohort number that the subject is assigned to within the study part; and the fourth and fifth digits will identify the subject number within a cohort).
- Nominal day (e.g., Day 1)
- Nominal time (e.g., predose)
- Matrix identifier (plasma)
- Split (primary or back-up).

#### 7.2.12.2 Shipment of Plasma Pharmacokinetic Samples

Instructions for shipment of PK samples (along with the corresponding documentation) can be found in the laboratory manual, provided separately.

Pharmacokinetic samples will be stored nominally at -70°C or below prior to and after analysis at the CRO until further directions are authorized by the Sponsor (or a nominated designee).

#### 7.2.12.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to relevant Sponsor (or a nominated designee) Standard Operating Procedures.

Plasma concentrations will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

### 7.2.13 Pharmacodynamic Assessments

The name and address of the bioanalytical laboratory performing the PD assessment for this study will be maintained in the Investigator's files at the/each site and in the Trial Master File at the Sponsor.

Actual PD blood sample collection times versus time of dosing will be monitored. The Sponsor's expectation is that the Investigator will ensure that every reasonable effort is made to collect all PD blood samples at time points in Table 1.

A blood sample to assess proteomics, metabolomics, and transcriptomics will be collected at Day 1 and at the End of Treatment visit as described in Table 1.

#### 7.2.13.1 Blood Sample Collection and Handling Procedures

Pharmacodynamic blood samples will be collected at the times specified in the laboratory manual to measure plasma concentrations. A full description of PD blood collection, handling, storage and shipping can be found in the provided laboratory manual.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the central lab. The labels will contain the following information:

- Study number (BGE-175-201)
- Subject identifier
- Nominal day (e.g., Day 1)
- Nominal time (e.g., predose)
- Matrix identifier (e.g., plasma)
- Split (primary or back-up).

#### 7.2.13.2 Shipment of Plasma Pharmacokinetic and Pharmacodynamic Samples

Instructions for shipment of PK and PD samples (along with the corresponding documentation) can be found in the laboratory manual, provided separately.

Pharmacodynamic samples will be stored nominally at -70°C or below prior to and after analysis at the CRO until further directions are authorized by the Sponsor (or a nominated designee).

### 7.2.14 Volume of Blood to be Drawn from Each Subject

During this study, it is expected the total volume of blood taken will not exceed 500 mL for any subject in any part of the study, regardless of sex.

The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the same time point/period, if they require the same type of tube, the assessments may be combined.

Table 3 provides the estimated volume of blood to be drawn for each subject.

**Table 3: Estimated Volume of Blood to be Drawn from Each Subject**

| Assessment | | Sample Volume (mL) | Number of Samples | Total Volume (mL) |
|---|---|---|---|---|
| Pharmacokinetic samples [a] | | 4 | 7 | 28 |
| Pre-dose Serological markers - PGD2 | | 4 | 1 | 4 |
| Blood for Inflammation markers [b] | | 4 | 10 | 40 |
| Proteomic, metabolomic, and transcriptomic samples | | 4 | 2 | 8 |
| Safety | Biochemistry [c] | 8.5 | 6 | 51 |
| | Coagulation (PT, aPTT, INR) | 3 | 6 | 18 |
| | Hematology | 3 | 6 | 18 |
| **Total** | | | | **167 mL** |

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; TSH = thyroid stimulating hormone

a If a catheter is used for any blood draw or series of blood draws, then the first 1 mL is to be discarded. The 1-mL discard has been taken into account in the table above and the total blood volume required for this study.

b Two 2.7-mL samples are to be drawn for each pharmacodynamics blood sampling time point.
c Serology panel (HBsAg, HIV, HCV), and thyroid panel (TSH) will be included in the biochemistry panel and collected at screening only.

# 8 DATA MANAGEMENT AND STATISTICAL METHODS

## 8.1 Data Collection

A validated EDC System will be used during study conduct. The Investigators' authorized site personnel must enter the information required by the study CRF Completion Guidelines or similar for all data requiring transcription of the source. This study will be monitored according to ICH GCP Guidelines.

A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel (in an auditable manner). Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the study visit date.

## 8.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the Data Management Plan and according to the study CRF Completion Guidelines. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

## 8.3 Data Handling

Data that may potentially unblind the treatment assignment (e.g., IP serum concentrations, treatment allocation, and IP preparation/accountability data) will be handled with special care during the data cleaning and review process. Unless otherwise specified, these data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

All analyses/summaries will be based on observed data, with no imputation for missing data, unless otherwise specified in the statistical analysis plan (SAP).

## 8.4 Statistical Analysis Process

The study will be analyzed by the Sponsor (or a nominated designee).

The primary endpoint (proportion who have died or progressed to RF at Day 28) will be analyzed using a logistic regression with treatment group and covariates, age group (50 to <75 years, and > 75 years), baseline WHO ordinal clinical scale (3 or 4), and region. Other covariates including previous COVID-19 therapy may be explored. Estimation of the covariate-

adjusted difference in proportion responding will be reported using Cochran-Mantel-Haenszel (CMH) weighting and estimates from the logistic regression (LR) as described by Ge and colleagues (Ge et al., 2011, Appendix C). This analysis will be repeated without the covariate. Deaths prior to Day 28 will be included in the endpoint (RF, death). WHO Ordinal Scale for COVID-19 scores (Table 2) will be analyzed by carrying forward any early deaths through Day 28; other categorical and continuous outcomes will be described. The primary analysis will be based on the Intent-to-Treat population (ITT), analyzed as randomized. The denominator for the proportions alive and RF-free at Day 28 will include all randomized subjects. Subjects lacking sufficient data to confirm RF-free and alive at Day 28 will be included in the primary analysis as treatment failures. If more than 5% of subjects have insufficient data to confirm RF-free and alive at Day 28, BioAge will employ a MI strategy (SAS MI, MIANALYZE) based on the patients last known status. For example, the last known WHO Score for a patient lost to follow-up can be used to impute missing primary outcome from patients with known primary outcome and similar WHO Scores. For the primary comparison, analysis by treatment group will be, "as randomized". Secondary analyses of the primary endpoint may be repeated for the mITT and the per protocol populations, analyzed as treated. Time-to-RF will be analyzed using methods of Kaplan-Meier (KM), with time zero at randomization. Hazard ratios (Cox PHREG) with 95% confidence intervals will describe the treatment effect.

A sensitivity analysis may be completed to assess concurrent treatments and prior SARS-CoV-2 vaccinations in relation to the primary endpoint.

Secondary endpoints that are proportions will be analyzed like the primary endpoint, using logistic regression with and without the designated covariates and by FET. 95% confidence intervals and p-values (without correction) will be presented for these descriptive analyses. Time-to-event analyses will use the methods of Kaplan-Meier with censoring rules for the different endpoints provided in the SAP. Descriptive statistics for TTE will be median times to event with 95 confidence intervals and log-rank statistics to test for treatment differences; Cox proportional hazards with 95% CI will be presented.

"Incidence and duration" secondary endpoints will be analyzed by counting days per subject and then forming 95% confidence intervals and Wilcoxon tests and t-tests to compare treatments. Incidence will also be compared using FET.

These analyses of secondary endpoints will be done using the ITT population and may be repeated for the mITT and PP populations.

No secondary endpoints are designated as, "key" for any labeling purposes.

Results of secondary endpoint analyses will not be corrected for multiplicity.

The Sponsor does not intend formal statistical analyses for safety data. However, odds ratios (95% CI) for common adverse events will be displayed.

The SAP will further describe the statistical methods and definitions for the analysis of the efficacy endpoints, PK, PD, and safety data, as well as describe the approaches to be taken for summarizing other study information, such as subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications. The SAP will also include further description of how missing and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to the IA. Analysis rules and methods for the IA are planned to be the same as the rules and methods for the final analysis.

Unless noted otherwise, all statistical analyses will be performed using SAS® Version 9.3 or later (SAS Institute, Cary, NC 27513).

## 8.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

An IA for safety and efficacy will be conducted after 208 subjects complete assessments through the end of treatment (Day 28). Unblinded IA results will be reviewed by the independent DMC for safety evaluation. The interim efficacy analysis will be performed by an unblinded independent statistician.

Analysis at the interim look will be a logistic regression as described for the final analysis. The IA will be restricted to patients who reach Day 28 (or would have reached Day 28 had they not died, withdrawn, or been lost to follow-up). Patients included in the IA will have been randomized at least 28 days prior to IA. It is BioAge's intent that the final and interim analysis do not differ in any important way.

An α spend is not incorporated into the sample size to account for this look.

Efficacy analyses at IA may yield Conditional Power (CP) results in the Mehta and Pocock promising zone (0.34, 0.90) (Mehta and Pocock, 2011). If so, to maintain the statistical power of the study and to avoid any type 1 error penalty, the Sponsor will consider the option of increasing the sample size (according to the rules provided by Mehta and Pocock), not to exceed N=624 (twice the planned sample size). For this planned IA, Z-score evidence at the IA of between Z=1.41 and 2.21 would define the promising zone and opportunity for BioAge to expand the study. For example, if at IA, Z=1.8 (CP=0.66), then to maintain the power at 0.90 the study could be expanded from 312 subjects to 431. For results in the Mehta and Pocock unfavorable zone, or in the favorable zone, the study will continue to conclusion at N=312 subjects.

The decision to stop the study at IA will be based on a full safety and an early review of efficacy by the Data Monitoring Committee (DMC). To aid the DMC in their recommendation to BioAge regarding conduct of the trial beyond the IA, a table of multiple possible true effects and potential stopping rules will be developed by BioAge and presented in the DMC charter. The operating characteristics of potential decision rules will be shared and understood by the DMC.

## 8.6 Sample Size Calculation and Power Considerations

Assuming a 31% RF rate in the placebo group and a 15% RF rate in the asapiprant group, for a Fishers Exact test with two-sided 5% Type 1 error and 90% power, the sample size to detect a 16% absolute improvement in the primary endpoint is 312 subjects (1:1 randomization). Randomization will be stratified based on the region within which a subject is enrolled (North America vs. South America) and age (50 to < 75 vs. ≥ 75 years of age).

## 8.7 Study Population

**Enrolled Analysis Set**: all patients who provided informed consent.

**Intent-to-Treat (ITT):** all patients who have been randomized. The ITT will be used for efficacy endpoints. Patients will be analyzed according to the treatment group to which they were randomized. The ITT will be used for the primary efficacy analysis.

**Modified Intent-to-Treat population (mITT):** all ITT patients with exclusion of randomized untreated patients and randomized ineligible patients.

**Per-protocol Set:** all mITT patients with further exclusion of patients with major protocol deviations related to data integrity or eligibility as judged by clinical/biostatistical study personnel prior to database lock. This population will be formed only if > 5% of patients would be excluded.

**Safety Analysis Set:** all patients who have received at least 1 dose of either asapiprant or placebo. The Safety Analysis Set will be used for safety analysis. Patients will be analyzed under actual treatment being received.

**Pharmacokinetic (PK) Set**: all patients who have received at least 1 dose of asapiprant and have at least 1 evaluable post-dose PK concentration value.

**Pharmacodynamic (PD) Set**: all patients who have received at least 1 dose of asapiprant and have at least 1 evaluable post-dose PD value.

### 8.7.1 Pharmacokinetic Analysis

PK parameters will be calculated from plasma asapiprant concentration-time data using noncompartmental methods, and all calculations will be based on actual sampling times. PK parameters will include, but not be limited to, the following:

**Table 4: Pharmacokinetic Endpoint Summary**

| Pharmacokinetic Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum concentration occurring at $t_{max}$ |
| $t_{max}$ | Time of maximum observed concentration sampled post-dose |
| $AUC_{last}$ | Area under the curve from the time of dosing to the last measurable concentration |
| $t_{1/2}$ | Terminal half-life |
| $\lambda_z$ | First-order rate constant associated with the terminal (log-linear) portion of the curve |
| CL/F | Total body clearance for extravascular administration divided by the fraction of dose absorbed |
| $V_z$ /F | Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed |

#### 8.7.1.1 Statistical Analysis of Pharmacokinetic Parameters

Single samples for PK analysis will be drawn at the time described in Table 1. The times of dosing and sample collection are to be captured. Attempts will be made to develop a PK Population model based on the data. The results of the Population PK analysis will be published in a separate report.

Listing of individual PK concentrations and individual PK parameters of asapiprant will be based on the PK Analysis Sets. Individual concentrations and PK parameters of asapiprant will be listed and summarized by treatment with descriptive statistics (number, arithmetic mean, standard deviation [SD], coefficient of variation [CV%], median, minimum, maximum, geometric mean, and CV% of geometric mean). Figures of individual and mean (± SD) concentration-time profiles of asapiprant by treatments and study parts will be generated based on nominal time points.

### 8.7.2 Pharmacodynamic Analysis

Exploratory inflammation markers are planned for this study. Pharmacodynamic samples may be maintained for up to 5 years after the clinical study report has been finalized.

Remaining aliquots of blood or tissue samples from any of the scheduled time points may also be analyzed for additional exploratory inflammation markers or PK-related activities (i.e., validation of a new bioanalytical method). This exploratory research is intended to aid the further understanding of asapiprant provided it does not add to the blood volume presented in Table 3.

Any results from this additional exploratory research will be reported separately from the main clinical study report. The results may be used internally to help support the design of further clinical studies, form part of scientific publication, or be made known to the regulatory authorities as part of a new drug application. The Sponsor has no obligation to perform this additional exploratory research.

#### 8.7.2.1 Statistical Analysis of Pharmacodynamic Parameters

## 8.8 Safety Analyses

Safety endpoint:

1. Incidence and severity of treatment-emergent AEs (TEAEs)
2. Safety outcome measure:
   a) Occurrence of AEs
   b) Laboratory safety parameters such as complete blood count, blood glucose, electrolyte, hepatic and renal functions taken before the first dose and on Days 2, 5, 14, 28 and at the time of discharge to find any changes or any systemic effect after treatment

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group for each cohort and treatment group. The number and percentage of subjects with TEAEs will be further summarized

by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit for the study. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data. Baseline for safety data will be defined as the last value prior to dose. Potentially clinically important findings will also be summarized or listed.

## 8.9 Other Analyses

No other analyses are planned in this study.

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# 10 APPENDICES

# APPENDIX 1

# PROTOCOL HISTORY

| Document | Date | Global/Country/Site Specific |
|---|---|---|
| Version 5.0, Amendment 04 | 07 September 2021 | Global |
| Version 4.0, Amendment 03 | 19 May 2021 | Global |
| Version 3.0, Amendment 02 | 26 April 2021 | Global |
| Version 2.0 (Amendment 01) | 19 March 2021 | Global |
| Original Protocol (V1.0) | 04 Dec 2020 | Global |

# APPENDIX 2

# 1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

## REGULATORY AND ETHICAL CONSIDERATIONS

This study is conducted in accordance with current applicable regulations including ICH E6(R2), EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the Investigator's and Sponsor's files, as appropriate.

# 2 SPONSOR'S RESPONSIBILITIES

## Good Clinical Practice Compliance

The study Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP guideline E6 (1996 [R2, 2016]), EU Directive 2001/20/EC Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor (or a nominated designee) ensures that local regulatory authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

## Indemnity/Liability and Insurance

The Sponsor (or a nominated designee) ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the Investigator as necessary.

## Public Posting of Study Information

The Sponsor (or a nominated designee) is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

The timing for study registration and results summary posting must be in accordance with applicable local and national requirements.

## Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The Sponsor (or a nominated designee) will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

## Study Suspension, Termination, and Completion

The Sponsor (or a nominated designee) may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the Sponsor (or a nominated designee) will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

# 3 INVESTIGATOR'S RESPONSIBILITIES

## Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and E6 R2 (2017), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks, and shall, upon request of the Sponsor (or a nominated designee), provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for Investigators and sub-Investigators are provided to the study Sponsor (or a nominated designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal Investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

## Protocol Adherence and Investigator Agreement

The Investigator and any sub-Investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an Investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor (or a nominated designee) and the IRB/EC and provide them with a detailed written explanation. The Investigator will also return all investigational product, containers, and other study materials to the Sponsor (or a nominated designee). Upon study completion, the Investigator will provide the Sponsor (or a nominated designee), IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor (or a nominated designee), applicable CRO, Investigator, or for multicenter studies, the coordinating principal Investigator according to national provisions and will be documented in the Investigator agreement.

# 4 DOCUMENTATION AND RETENTION OF RECORDS

## Case Report Forms

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the Investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the Sponsor (or a nominated designee) must be endorsed by the Investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

## Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, and original clinical laboratory reports. All key data must be recorded in the subject's source documents.

The Investigator must permit authorized representatives of the Sponsor (or a nominated designee), the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor (or a nominated designee), national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor (or a nominated designee).

# 5 AUDIT/INSPECTION

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the Sponsor (or a nominated designee) and the IRB/EC for each site.

# 6 FINANCIAL DISCLOSURE

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the Investigator received from the Sponsor (or a nominated designee). The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

# 7 ETHICAL CONSIDERATIONS

## Informed Consent

It is the responsibility of the Investigator to obtain documented informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. Because of biosafety concerns with COVID-19 infected patients' investigational sites may have developed alternatives to written signature documentation. These alternative documentation methods are acceptable for this study. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms or alternative consent documentation forms must remain in each subject's study file and must be available for verification at any time.

The principal Investigator provides the Sponsor (or a nominated designee) with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the Sponsor (or a nominated designee), prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (e.g., Sponsor [or a nominated designee]) or coordinating principal Investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the Sponsor (or a nominated designee), the documentation supporting this requirement must be provided to the Sponsor (or a nominated designee).

## Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor (or a nominated designee) or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the Sponsor (or a nominated designee) or the Investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal Investigator or Sponsor (or a nominated designee), according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement.

Investigational product supplied will not be released until the Sponsor (or a nominated designee) has received written IRB/EC approval.

Prior to implementing changes in the study, the Sponsor (or a nominated designee) and the IRB/EC must approve any revisions of all informed consent documents and amendments to the

protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the Investigator is responsible for keeping the IRB/EC appraised of the progress of the study and of any changes made to the protocol, at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the Sponsor (or a nominated designee) or Investigator for sites within the EU; or for multicenter studies, the coordinating principal Investigator, according to national provisions. The Investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

**Privacy and Confidentiality**

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the Sponsor (or a nominated designee).

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the Sponsor (or a nominated designee) reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market BGE-175; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

# 8 STUDY RESULTS / PUBLICATION POLICY

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other Investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the Sponsor (or a nominated designee) in conjunction with the Sponsor (or a nominated designee) presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the Sponsor (or a nominated designee) within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the Sponsor (or a nominated designee) confirms there shall be no multicenter study publication of the study results, an Investigator may individually publish the study results from the specific site in accordance with this section. The Investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the Sponsor (or a nominated designee) by the site for review. Upon the Sponsor (or a nominated designee)'s request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the Sponsor (or a nominated designee) time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

BioAge Labs is committed to transparent dissemination of all scientific, technical, and medical manuscripts generated from BioAge Labs-supported research. Therefore, after January 1, 2018, BioAge Labs will require the submission of all BioAge Labs-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an Investigator does not confer any rights to authorship of publications.

# APPENDIX 3

# ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

# 1 ADVERSE EVENT DEFINITIONS

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this investigational product or medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

## Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event emerging or manifesting at or after the initiation of treatment with an investigational product or medicinal product or any existing event that worsens in either intensity, frequency or relationship following exposure to the investigational product or medicinal product.

## Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening.
  Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, that are the result of elective or previously scheduled investigations procedures or surgery for pre-existing conditions and have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality/birth defect
- Is an important medical event.
  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include bronchospasm associated with anaphylaxis 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.

**Unexpected Adverse Event**

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). "Unexpected" also refers to the AEs that are mentioned in the IB and/or prescribing information as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the Sponsor (or a nominated designee) and Investigator using the IB and/or prescribing information as the RSI. This determination will include considerations such as the number of AEs previously observed, but not based on what might be anticipated form the pharmacological properties of a product.

**Suspected Unexpected Serious Adverse Reaction**

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any suspected adverse reaction to study treatment (e.g., including active comparators) that is both serious and unexpected.

The event(s) must meet all the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

**Clinical Laboratory and Other Safety Assessment**

A change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease or expected disease evolution) is found for the abnormal values.

The Investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

# 2 COLLECTION OF ADVERSE EVENTS

All AEs/SAEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section **Error! Reference source not found.**. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered.

All AEs/SAEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained.

Any subject who discontinues study treatment due to an AE will be followed through resolution and study completion and will be included in safety statistical analysis. Subjects who discontinue study drug early will be followed with follow-up visits per the protocol visit schedule and/or phone calls after the study visit schedule is completed.

# 3 ASSESSMENT OF ADVERSE EVENTS

## Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates. Events that increase in severity will have the severity updated and the highest severity will be assigned to the event. Worsening medical conditions, signs or symptoms present prior to initiation of investigational product, must be recorded as new AEs.

For example, if a subject reports mild intermittent dyspepsia prior to initiation of dosing with the investigational product, and the dyspepsia becomes severe and more frequent after first dose of a new AE of severe dyspepsia (with the appropriate date of onset) should be documented in the source.

The Investigator will assess the Grade of the AE per the NCI-CTCAE version 5.0 or higher.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

## Relationship Categorization

A physician/Investigator must make the assessment of relationship to investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the IP. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

| Term | Relationship Definition |
|---|---|
| Related | The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident. |

| | |
|---|---|
| Not Related | The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event. |

Another source of guidance is provided in the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality categories descriptions. When applying the WHO-UMC categories in this study any AE fitting the causality term of Possible or higher (Probable/Likely or Certain) should be consider related. Any AE fitting the causality term of Unlikely or lower (Conditional / Unclassified or Unassessable / Unclassifiable) should be considered not related.

WHO-UMC Causality Categories

| *Causality term* | *Assessment criteria** |
|---|---|
| **Certain** | • Event or laboratory test abnormality, with plausible time relationship to drug intake<br>• Cannot be explained by disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)<br>• Rechallenge satisfactory, if necessary |
| **Probable / Likely** | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not required |
| **Possible** | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Could also be explained by disease or other drugs<br>• Information on drug withdrawal may be lacking or unclear |
| **Unlikely** | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)<br>• Disease or other drugs provide plausible explanations |
| **Conditional / Unclassified** | • Event or laboratory test abnormality<br>• More data for proper assessment needed, or<br>• Additional data under examination |
| **Unassessable / Unclassifiable** | • Report suggesting an adverse reaction<br>• Cannot be judged because information is insufficient or contradictory<br>• Data cannot be supplemented or verified |

* All points should be reasonably complied with

**Outcome Categorization**

The outcome of AEs must be recorded in the Case Report Forms during the course of the study. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

# 4 SAFETY REPORTING

## Reference Safety Information

The reference for safety information for this study is the Investigator Brochure which the Sponsor has provided under separate cover to all Investigators.

## Reporting Procedures

**SAEs that occur from the time of signing the ICF through 30 days after last dose of study drug require that a** SAE report form be completed in the electronic data capture (EDC) system and submitted to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to study drug. In the event that EDC is unavailable, the SAE paper report form must be filled out by the Investigator and sent via email within 24 hours of awareness of the event to the [redacted], and then the information entered into the EDC once available.

## SERIOUS ADVERSE EVENT COLLECTION TIME FRAME

All SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Safety Follow-up visit or 30 days after the last dose of study drug.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the Investigator at any interval after the study has completed must be reported to the CRO using EDC data entry within 24 hours of the first becoming aware of the event.

## SERIOUS ADVERSE EVENT ONSET AND RESOLUTION DATES

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations occurring after discharge from the original hospitalization at the time of study qualification, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms reported by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

## FATAL OUTCOME

Any SAE that results in the subject's death (e.g., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

# 5 PREGNANCY

All pregnancies are to be reported from the time informed consent is signed until the last follow-up visit.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the CRO. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the EDC.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the EDC. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

# 6 ABUSE, MISUSE, OVERDOSE, AND MEDICATION ERROR

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor (or a nominated designee) according to the SAE reporting procedure whether or not they result in an AE/SAE.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication error s unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the Sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

# 7 URGENT SAFETY MEASURES

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect subjects participating in a clinical trial from immediate harm, these do not constitute de facto deviation from the protocol. Urgent safety measures may be taken by the Sponsor (or a nominated designee) or clinical Investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety

The Investigator may implement urgent safety measures to protect study subjects from immediate hazard to their health or safety. The measures should implement immediately and does not require prior authorization from the Sponsor (or a nominated designee). In the event(s) of an apparent direct hazard to the subject, the Investigator will notify the Sponsor (or a nominated designee) immediately by phone and confirm notification to the Sponsor (or a nominated designee) in writing as soon as possible, and within 1 calendar day after the change is implemented. The Sponsor (or a nominated designee) will also ensure the responsible EC(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

# 8 REGULATORY AGENCY, INSTITUTIONAL REVIEW BOARD, ETHICS COMMITTEE, AND SITE REPORTING

The Sponsor (or a nominated designee) and CRO are responsible for notifying the relevant regulatory authorities/US local IRB of related, unexpected SAEs.

In addition, the Sponsor (or a nominated designee) is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the asapiprant program.

The Investigator is responsible for notifying the local IRB/EC of SAEs or significant safety findings, or the relevant local regulatory authority of all SAEs that occur at his or her site as required by IRB/EC procedures.

# APPENDIX 4

## CHILD-PUGH SYSTEM[1]

| | Points Scored for Observed Findings | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| **Encephalopathy grade[2]** | **none** | **1 or 2** | **3 or 4** |
| **Ascites** | **absent** | **slight** | **moderate** |
| **Serum bilirubin, mg/dL** | **< 2** | **2 to 3** | **> 3** |
| **Serum albumin, g/dL** | **> 3.5** | **2.8 to 3.5** | **< 2.8** |
| **Prothrombin time, sec prolonged** | **< 4** | **4 to 6** | **> 6** |

**[1] Assessment as good operative risk (A or mild) if 5 or 6 points; moderate risk (B or moderate) if 7 to 9 points; and poor operative risk (C or severe) if 10 to 15 points. (Developed for surgical evaluation of alcoholic cirrhotic.)**

**[2] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram**
**Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves**
**Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves**
**Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves**
**Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity**

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