A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Immunogenicity of ADM03820 in Adults

Resilience Government Services Protocol Number: ADM03820-001

IND Sponsor: Resilience Government Services, Inc.

Version: 7.0

August 8, 2023

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, and 21 CFR Part 312);
- International Conference on Harmonization (ICH) E6; 62 Federal Register 25691 (1997);
- Department of Defense (DOD) Clinical Terms of Award, as applicable.
- Applicable Laws and Regulations

Compliance with these standards provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States of America (US) federal regulations and ICH guidelines.

Site Investigator: _____

Signature: _____

Date: _____

Sponsor: Wael El-Amin, MD / Medical Lead

Signature: Wael El-Amin, M.D.

Date: 8/21/2023

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LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADE	Antibody-dependent enhancement
AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per Minute
BUN	Blood Urea Nitrogen
CAR	Clinical Agents Repository
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	Maximum Plasma Titer/Concentration
CPM	Clinical Project Manager
CROMS	Clinical Research Operations and Management Support
CTCAE	Common Terminology Criteria for Adverse Events version 5.0
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMP	Data Management Plan
DOD	Department of Defense
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
ECLA	Electrochemiluminescence Assay
ELISA	Enzyme-Linked Immunosorbent Assay

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FESAP	Federal Experts Advisory Panel
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Gm	Gram
gm/dL	Grams per Deciliter
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropic Hormone
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
Hr/hr	Hour
HRPO	Human Research Protections Office
HRSA	Health Resources and Services Administration
ICH	International Conference on Harmonisation
IDES	Internet Data Entry System
IEC	Independent or Institutional Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular
IND	Investigational New Drug
IP	Intraperitoneal
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat

IUDs	Intrauterine Contraceptive Device
IV	Intravenous
IVIG	Intravenous Immune Globulin
KG	Kilogram
LLN	Lower Limit of Normal
mAbs/mAb	Monoclonal Antibodies
MedDRA®	Medical Dictionary for Regulatory Activities
mEq/L	Milliequivalent per Liter
Mg/mg	Milligram/milligram
mg/dl	Milligram per Deciliter
ML	Medical Lead
Ml/mL	Milliliter
Mm/mm	Millimeter
mmHg	Millimeters of Mercury
MN	Microneutralization
MOP	Manual of Procedures
MPA	Mouse Potency Assay
MRSD	Maximum Recommended Starting Dose
N	Number
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NLM	National Library of Medicine
NOAEL	No-Observed-Adverse-Effect-Level
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OHRP	Office for Human Research Protections
OTC	Over the Counter
PE	Physical Examination
PI	Principal Investigator
PK	Pharmacokinetic(s)

PR	PR Interval-Standard ECG Terminology
PREP	Public Readiness and Emergency Preparedness
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PVG	Pharmacovigilance Group
PVSS	Pharmacovigilance Safety System
RBC/HPF	Red Blood Cells per High-Power Field
SAE	Serious Adverse Event
SRC	Safety Review Committee
SOP	Standard Operating Procedure
TIG	Tetanus Immune Globulin
T_{max}	Time to Maximum Concentration
TTD	Time to Death
µg	Microgram
ULN	Upper Limit of Normal
VZIG	Varicella Zoster Immune Globulin
WBC	White Blood Count

SUMMARY OF CHANGES FOR VERSION 7.0

Version 6.0 06 Jul 2022	Version 7.0 08 Aug 2023	Reason for Change
Ology Bioservices, Inc./Ology Bioservices/Ology Bio	Resilience Government Services, Inc./Resilience Government Services/RGS	Administrative change due to acquisition of Ology Bioservices, Inc. by Resilience Government Services, Inc.
Page 71: Protocol Summary: Study Duration Approximately 18 months	Page 74: Protocol Summary: Study Duration Approximately 18 months for cohorts 1-4 and 12 months for cohort 5	Reduction in study follow-up from 18-months to 12-months for cohort 5
Page 71: Protocol Summary: Subject Participation Subjects in all cohorts will participate approximately 554 days (up to a 14-day screening, overnight stay, up to 12-month outpatient follow-up visits and telephone visits at 15-months and 18-months.)	Page 74: Protocol Summary: Subject Participation Subjects in cohorts 1-4 will participate approximately 554 days (up to a 14-day screening, overnight stay, up to 12-month outpatient follow-up visits and telephone visits at 15-months and 18-months.) Subjects in cohort 5 will participate approximately 379 days (up to a 14-day screening, overnight stay, and up to 12-month outpatient follow-up visits.)	Reduction in study follow-up from 18-months to 12-months for cohort 5

Version 6.0 06 Jul 2022	Version 7.0 08 Aug 2023	Reason for Change
Page 73: Protocol Summary: Study Design Cohort 5 (600 mg IM injection) will enroll two sentinel subjects (one ADM03820 and one placebo) and each will be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365. Subjects will have follow-up telephone visits at Days 450 and 540. The study will consist of a fourteen-day screening period. The end of the study is defined as the date of the last visit of the last subject in the study (day 540)	Page 76-77: Protocol Summary: Study Design Cohort 5 (600 mg IM injection) will enroll two sentinel subjects (one ADM03820 and one placebo) and each will be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365. The study will consist of a fourteen-day screening period. The end of the study is defined as the date of the last visit of the last subject in the study (day 540 for cohorts 1-4 and day 365 for cohort 5)	Reduction in study follow-up from 18-months to 12-months for cohort 5

Version 6.0 06 Jul 2022	Version 7.0 08 Aug 2023	Reason for Change
Page 87: Study Design Subjects in all cohorts will participate in the study for approximately 554 days, including a 14-day screening period. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up outpatient visits will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, and 365 with telephone visits on Days 450 and 540. The last outpatient follow up visit is scheduled at Day 365. The end of the study is defined as the date of the last visit of the last subject in the study.	Page 90: Study Design Subjects in cohorts 1-4 will participate in the study for approximately 554 days, including a 14-day screening period. Subjects in cohort 5 will participate in the study for approximately 379 days, including a 14-day screening period. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up outpatient visits for all cohorts will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, and 365 with cohorts 1-4 having additional telephone visits on Days 450 and 540. The last outpatient follow up visit is scheduled at Day 365. The end of the study is defined as the date of the last visit of the last subject in the study.	Reduction in study follow-up from 18-months to 12-months for cohort 5
Page 129-131: Schedule of Events Visit 16 & 17 TC	Page 132-134: Schedule of Events Visit 16 & 17 TC for only Cohorts 1-4	Reduction in study follow-up from 18-months to 12-months for cohort 5

SUMMARY OF CHANGES FOR VERSION 6.0

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 3: Signature Page	Page 3: Signature Page Sponsor: Wael El-Amin, MD / Medical Lead	Updated Medical Lead
Page 12: List of Abbreviations	Page 11: List of Abbreviations ML: Medical Lead	Added Medical Lead abbreviation
Page 56: Protocol Summary A total of 40 healthy male and female subjects between 18 – 55 years of age	Page 70: Protocol Summary A total of 50 healthy male and female subjects between 18 – 55 years of age	Addition of Cohort 5
Page 57: Protocol Summary: Study Endpoints: Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3 and Cohort 4.	Page 71: Protocol Summary: Study Endpoints: Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3, Cohort 4, and Cohort 5.	Addition of Cohort 5

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Page 57: Protocol Summary: Study Design This study is a phase 1, randomized, double-blind, placebo-controlled study of four dose cohorts. The study will randomize a total of 40 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Dosing Cohorts: • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (8 active, 2 placebo) • Cohort 4 – 300 mg IM injection (8 active, 2 placebo)	Page 71: Protocol Summary: Study Design This study is a phase 1, randomized, double-blind, placebo-controlled study of five dose cohorts. The study will randomize a total of 50 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Dosing Cohorts: • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (8 active, 2 placebo) • Cohort 4 – 300 mg IM injection (8 active, 2 placebo) • Cohort 5 – 600 mg IM Injection (8 active, 2 placebo)	Addition of Cohort 5
Page 58: Protocol Summary: Study Design Dose escalation to Cohort 2 will not occur until safety data through day 8 for Cohort 1 is reviewed by the Safety Review Committee (SRC), which is composed of the Principal Investigator (PI), RGS Medical Monitor, and ICON Medical Monitor. Objective dose escalation criteria and safety evaluations will be utilized.	Page 72: Protocol Summary: Study Design Dose escalation to Cohort 2 will not occur until safety data through day 8 for Cohort 1 is reviewed by the Safety Review Committee (SRC), which is composed of the Principal Investigator (PI), RGS Medical Lead (ML), and ICON Medical Monitor. Objective dose escalation criteria and safety evaluations will be utilized.	Updated to include Medical Lead

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 58: Protocol Summary: Study Design	Page 72: Protocol Summary: Study Design Cohort 5 (600 mg IM injection) will enroll two sentinel subjects (one ADM03820 and one placebo) and each will be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365. Subjects will have follow-up telephone visits at Days 450 and 540.	Addition of Cohort 5

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 58: Protocol Summary: Study Design There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. There is also an interim clinical study report (CSR) planned after all subjects in all cohorts complete Day 90.	Page 73: Protocol Summary: Study Design There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. • A third interim analysis is planned to analyze safety and PK after all subjects in cohort 5 complete Day 60. There is also an interim clinical study report (CSR) planned after all subjects in Cohorts 1 through 4 complete Day 90.	Addition of third interim analysis and updated interim CSR to include Cohorts 1-4
Page 60: Protocol Summary: Exclusion Criteria 15. Positive serology results for SARS-CoV-2 antibodies	Page 74-75: Protocol Summary: Exclusion Criteria 15. Positive serology results for SARS-CoV-2 antibodies (Not applicable for Cohort 5).	Updated exclusion criteria to not applicable to Cohort 5

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Page 61: Protocol Summary: Exclusion Criteria 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit).	Page 75: Protocol Summary: Exclusion Criteria 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit). For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.	Updated exclusion criteria to not applicable to Cohort 5
Page 62: Assess Eligibility Figure	Page 76: Assess Eligibility Figure Cohort 5 N=10 (600 mg dose) Two 3 mL IM injection of ADM03820 (8 subjects) or Placebo (2 subjects)	Addition of Cohort 5 to figure
Page 63: Key Roles RGS Medical Monitor: John Abernethy, MD RGS, Inc. 13200 NW Nano Court Alachua, FL 32615 Telephone: 352-213-5757 Email: john.abernethy@resilience.com	Page 77: Key Roles RGS Medical Lead: Wael El-Amin, MD RGS, Inc. 13200 NW Nano Court Alachua, FL 32615 Telephone: 240-885-1221 Email: wael.el-amin@resilience.com	Updated Medical Lead
Page 65: Introduction As of August 10, 2020, 19.9 million cases and 6.3 million deaths attributed to COVID-19 have been reported globally, with 13 million cases and 65,000 deaths in the US.	Page 79: Introduction As of June 24, 2022, 539 million cases and 6.3 million deaths attributed to COVID-19 have been reported globally, with 85.5 million cases and 1 million deaths in the US.	Updated introduction

Page 66-67: Currently Available Treatments There are currently no FDA-approved treatments for or vaccines against COVID-19, nor are there any for SARS or MERS. On May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease. While there is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19, the investigational drug was shown in a clinical trial to shorten the time to recovery in some patients. On December 11, 2020 the FDA issued the first EUA for a vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the U.S. for use in individuals 16 years of age and older as a series of two doses that are given three weeks apart. The most commonly reported side effects, which typically lasted several days were pain at the injection site, tiredness, headache, muscle pain, joint pain, and fever. On December 18, 2020 the FDA issued an EUA for the second vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Moderna COVID-19 Vaccine to	Page 81: Currently Available Treatments At the initiation of this protocol, there were no FDA-approved treatments for or vaccines against COVID-19, nor were there any for SARS or MERS. On May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease. While there is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19, the investigational drug was shown in a clinical trial to shorten the time to recovery in some patients. Currently, there are multiple vaccines for the protection against and several mAbs available for the treatment and prophylaxis of COVID-19 that are available under emergency use authorization.	Updated currently available treatment

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be distributed in the U.S for use in individuals 18 years of age and older administered as a series of two doses that are given one month apart. The most commonly reported side effects, which typically lasted several days were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, swollen lymph nodes in the same arm as the injection, nausea and vomiting, and fever. A global push to identify potential treatments has resulted in registration of a significant number of clinical trials for COVID-19 worldwide. Per ClinicalTrials.gov, there are currently 1645 interventional studies, including chloroquine and hydroxychloroquine; antivirals (e.g., remdesivir); antibiotics (e.g., azithromycin); steroids (e.g., dexamethasone); non-steroidal anti-inflammatory drugs (e.g., naproxen); angiotensin II receptor blockers (e.g., losartan); small molecule inhibitors (e.g., baricitinib); dietary supplements (e.g., vitamin D); biological products, including various monoclonal antibodies, cell therapies, and blood products; other drugs (e.g., colchicine); and medical devices (e.g., hyperbaric oxygen therapy).		

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Page 68: ADM03820 Development A GLP repeat dose toxicity study is being performed to evaluate the safety of ADM03820 in rats when administered by intramuscular injection or intravenous infusion once weekly for three weeks and to evaluate toxicity and reversibility of effects after a 72-day recovery period.	Page 82: ADM03820 Development A GLP repeat dose toxicity study was performed to evaluate the safety of ADM03820 in rats when administered by intramuscular injection or intravenous infusion once weekly for three weeks and to evaluate toxicity and reversibility of effects after a 72-day recovery period.	Updated ADM03820 development
Page 69: Rationale for Use of ADM03820 The proposed starting dose for ADM03820 dose escalation (150 mg IM) is based on previous toxicology studies, known safety profile of mAbs, and the expected potency of ADM03820. Based on the expected potency of ADM03820, the doses proposed for evaluation are anticipated to support PK analysis with microneutralization values (TCID50) in therapeutic window for a prophylactic. Provided there are no safety concerns, dosing will escalate to 300 mg IM.	Page 84: Rationale for Use of ADM03820 The proposed starting dose for ADM03820 dose escalation (150 mg IM) is based on previous toxicology studies, known safety profile of mAbs, and the expected potency of ADM03820. Based on the expected potency of ADM03820, the doses proposed for evaluation are anticipated to support PK analysis with microneutralization values (TCID50) in therapeutic window for a prophylactic. Provided there are no safety concerns, dosing will escalate to 300 mg and 600 mg IM.	Updated rationale for use of ADM03820

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Page 71: Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3 and Cohort 4.	Page 84-85: Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3, Cohort 4, and Cohort 5.	Addition of Cohort 5

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Page 72: Study Design This is a Phase 1, randomized, double-blind, placebo-controlled study of four dose cohorts to evaluate the safety, tolerability, and immunogenicity of ADM03820 in healthy adults. This is a first-in-human study and each subject will receive a single dose of ADM03820 or placebo. The study will randomize a total of 40 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Table 1: Cohorts • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (8 active, 2 placebo) • Cohort 4 – 300 mg IM injection (8 active, 2 placebo)	Page 86: Study Design This is a Phase 1, randomized, double-blind, placebo-controlled study of five dose cohorts to evaluate the safety, tolerability, and immunogenicity of ADM03820 in healthy adults. This is a first-in-human study and each subject will receive a single dose of ADM03820 or placebo. The study will randomize a total of 50 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Table 1: Cohorts • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (8 active, 2 placebo) • Cohort 4 – 300 mg IM injection (8 active, 2 placebo) • Cohort 5 – 600 mg IM Injection (8 active, 2 placebo)	Addition of Cohort 5

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Page 72: Study Design There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 – 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. There is also an interim clinical study report (CSR) planned after all subjects complete Day 90.	Page 87: Study Design There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 – 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. A third interim analysis is planned to analyze safety and PK after all subjects in cohort 5 complete Day 60. There is also an interim clinical study report (CSR) planned after subjects in Cohorts 1 through 4 complete Day 90.	Addition of third interim analysis and updated interim CSR to include Cohorts 1-4

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Page 72-73: Study Design: Schedule for Cohorts Since this is a first-in-human study, administration of the study products to subjects in cohorts 1 and 2 will occur to allow careful observation of individuals for adverse events. Two sentinel subjects within each cohort will be admitted and administered a dose on Day 1 to remain in the clinic until Day 2. The randomization scheme will be designed to ensure that one subject will receive ADM03820 and the other will receive placebo. The IM dosing of the remaining subjects within cohorts 1 and 2 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in cohorts 1 and 2 will be dosed at least four hours apart until all subjects in the cohort have been dosed. An alternate subject will be admitted to the unit for each two-subject group. Dose escalation will not occur until safety data through Day 8 is reviewed by the SRC.	Page 87: Study Design: Schedule for Cohorts Since this is a first-in-human study, administration of the study products to subjects in cohorts 1, 2 and 5 will occur to allow careful observation of individuals for adverse events. Two sentinel subjects within each cohort will be admitted and administered a dose on Day 1 to remain in the clinic until Day 2. The randomization scheme will be designed to ensure that one subject will receive ADM03820 and the other will receive placebo. The IM dosing of the remaining subjects within cohorts 1, 2, and 5 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects within each specific cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. An alternate subject will be admitted to the unit for each two-subject group. Dose escalation will not occur until safety data through Day 8 is reviewed by the SRC.	Addition of Cohort 5

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 73: Study Design: Schedule for Cohorts	Page 88: Study Design: Schedule for Cohorts In Cohort 5 (600 mg IM injection of drug product concentrated at 100mg/mL), two sentinel subjects (one ADM03820 and one placebo) will each be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. The SRC will review safety data through day 8 for subjects in cohort 5 prior to the initiation of the phase 2 protocol.	Addition of Cohort 5
Page 73: Site Enrollment This study will enroll forty healthy male and female subjects ages 18 to 55 years old in four cohorts.	Page 88: Site Enrollment This study will enroll fifty healthy male and female subjects ages 18 to 55 years old in five cohorts.	Addition of Cohort 5
Page 73: Site Enrollment Exemptions may be granted on Inclusion/Exclusion Criteria pending Medical Director Approval.	Page 88: Site Enrollment Exemptions may be granted on Inclusion/Exclusion Criteria pending Medical Lead Approval.	Updated to Medical Lead

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 76: Protocol Summary: Exclusion Criteria 15. Positive serology results for SARS-CoV-2 antibodies	Page 90: Protocol Summary: Exclusion Criteria 15. Positive serology results for SARS-CoV-2 antibodies (Not applicable for Cohort 5).	Updated exclusion criteria to not applicable to Cohort 5
Page 77: Protocol Summary: Exclusion Criteria 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit).	Page 91: Protocol Summary: Exclusion Criteria 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit). For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.	Updated exclusion criteria to not applicable to Cohort 5
Page 77: Randomization Procedures This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within four dosing cohorts to either active or placebo. **Cohorts 1 and 2** For cohorts 1 and 2, the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control.	Page 91: Randomization Procedures This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within five dosing cohorts to either active or placebo. **Cohorts 1, 2, and 5** For cohorts 1, 2, and 5, the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control.	Addition of Cohort 5

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Page 77: Masking Procedures Whenever possible, the Investigator should first discuss the options with the ICON GPHS Medical Monitor and the RGS Medical Monitor or appropriately designated RGS personnel before unblinding the subject's treatment assignment.	Page 92: Masking Procedures Whenever possible, the Investigator should first discuss the options with the ICON GPHS Medical Monitor and the RGS ML or appropriately designated RGS personnel before unblinding the subject's treatment assignment.	Updated to include Medical Lead
Page 79: Formulation, Packaging, and Labeling: ADM03820 ADM03820 will be administered by intramuscular (IM) injection as follows: 150 mg (1 x 3 mL IM injection) or 300 mg (Group 3 as 2 x 3 mL IM injections or Group 4 as 1 x 3mL IM injection).	Page 94: Formulation, Packaging, and Labeling: ADM03820 ADM03820 will be administered by intramuscular (IM) injection as follows: 150 mg (Cohort 1 as 1 x 3 mL IM injection) or 300 mg (Cohorts 2 and 3 as 2 x 3 mL IM injections or Cohort 4 as 1 x 3mL IM injection) or 600 mg (Cohort 5 as 2 x 3 mL IM injections).	Addition of Cohort 5
Page 80: Formulation, Packaging, and Labeling: Placebo Placebo will be administered by intramuscular (IM) injection as follows: 150 mg (1 x 3 mL IM injection) or 300 mg (Group 3 as 2 x 3 mL IM injections or Group 4 as 1 x 3mL IM injection).	Page 95: Formulation, Packaging, and Labeling: Placebo Placebo will be administered by intramuscular (IM) injection as follows: 150 mg (Cohort 1 as 1 x 3 mL IM injection) or 300 mg (Cohorts 2 and 3 as 2 x 3 mL IM injections or Cohort 4 as 1 x 3mL IM injection) or 600 mg (Cohort 5 as 2 x 3 mL IM injections).	Addition of Cohort 5
Page 80: Product Storage and Stability **<u>Cohorts 4 Only</u>**	Page 95: Product Storage and Stability **<u>Cohorts 4 and 5 Only</u>**	Addition of Cohort 5

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Page 82: Concomitant Medications • H1 antihistamines (PRN use of H1 antihistamines may be acceptable after Medical Director/Medical Monitor approval)	Page 96: Concomitant Medications • H1 antihistamines (PRN use of H1 antihistamines may be acceptable after Medical Lead/Medical Monitor approval)	Updated to Medical Lead
Page 88: Visit 1: Screening (Day -14 to Day -2) • Documentation that the subject has not received an FDA approved vaccine for COVID-19 (Subjects may receive an approved COVID-19 vaccine after completing their Day 90 visit).	Page 103: Visit 1: Screening (Day -14 to Day -2) • Documentation that the subject has not received an FDA approved vaccine for COVID-19 (Subjects may receive an approved COVID-19 vaccine after completing their Day 90 visit). For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.	Addition of Cohort 5
Page 96: Visit 14: Out-patient Follow-up (Day 180±5) • Counsel both men and women of childbearing potential on the avoidance of pregnancy (for subjects who withdraw from the study early)	Page 111: Visit 14: Out-patient Follow-up (Day 180±5) • Counsel both men and women of childbearing potential on the avoidance of pregnancy	Removed for subjects who withdraw from the study early
Page 100: Serious Adverse Events SAE Hotline: 352-213-5757	Page 115: Serious Adverse Events SAE Hotline: 240-885-1221	Updated SAE Hotline phone number

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 103: ICON Medical Monitor The ICON MM is responsible for liaising with RGS Medical Monitor to ensure that all medical concerns are communicated and will provide any potential pertinent medical communication update to the project team as needed.	Page 118: ICON Medical Monitor The ICON MM is responsible for liaising with RGS ML to ensure that all medical concerns are communicated and will provide any potential pertinent medical communication update to the project team as needed.	Updated to include Medical Lead
Page 103: RGS Medical Monitor The RGS Medical Monitor will be the main point of contact for the ICON MM and the DOD for any safety-related questions or concerns. The RGS MM will escalate any medical or safety concerns to the DOD as needed. The RGS MM will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.	Page 118: RGS Medical Lead The RGS ML will be the main point of contact for the ICON MM and the DOD for any safety-related questions or concerns. The RGS ML will escalate any medical or safety concerns to the DOD as needed. The RGS ML will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.	Updated to include Medical Lead
Page 103: Safety Review Committee (SRC) The SRC will be composed of: • PI, or designee • RGS ML • ICON Medical Monitor or designee;	Page 118: Safety Review Committee (SRC) The SRC will be composed of: • PI, or designee • RGS Medical Monitor • ICON Medical Monitor or designee;	Updated to include Medical Lead

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 104: Sample Size Consideration This is a Phase 1 study first in humans with four dosing cohorts and no formal sample size calculations based on testing a statistical hypothesis were constructed. Sample sizes are consistent with this type of early phase study. Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for each cohort are practical and provide sufficient information for a total sample size of 40 for a Phase 1 trial primarily designed to assess safety.	Page 119: Sample Size Consideration This is a Phase 1 study first in humans with five dosing cohorts and no formal sample size calculations based on testing a statistical hypothesis were constructed. Sample sizes are consistent with this type of early phase study. Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for each cohort are practical and provide sufficient information for a total sample size of 50 for a Phase 1 trial primarily designed to assess safety.	Addition of Cohort 5
Page 105: Planned Interim Analyses There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in cohorts 1-3 complete Day 60. There is also an interim clinical study report (CSR) planned after all subjects complete Day 90.	Page 119: Planned Interim Analyses There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in cohorts 1-3 complete Day 60. A third interim analysis is planned to analyze safety and PK after all subjects in cohort 5 complete Day 60. There is also an interim clinical study report (CSR) planned after subjects in Cohorts 1 through 4 complete Day 90.	Addition of third interim analysis and updated interim CSR to include Cohorts 1-4

Version 5.0 22 Jun 2022	Version 6.0 06 Jul 2022	Reason for Change
Page 116-117: Appendix A: Schedule of Events SARS-CoV-2 Antibodies	Page 131-132: Appendix A: Schedule of Events SARS-CoV-2 Antibodies[18] 18. SARS-CoV-2 antibodies will only be tested in Cohorts 1-4 (Not applicable for Cohort 5).	Updated to not applicable to Cohort 5
Page 119: Appendix C: Intramuscular (IM) Administration	Page 134: Appendix C: Intramuscular (IM) Administration **Cohort 5 Only**: IP is administered as two 3mL (600mg dose) IM injection within 30 minutes of removing from refrigerator.	Addition of Cohort 5

SUMMARY OF CHANGES FOR VERSION 5.0

Version 4.0 02 Mar 2021	Version 5.0 22 Jun 2021	Reason for Change
Page 51 Protocol Summary Study Population = 30	Page 56 Protocol Summary and Page 70 Study Design Study Population = 40	Increased number of subjects by adding a cohort
Page 51 Protocol Summary and Page 65 Study Outcome Measures <u>Secondary Endpoints</u> The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3.	Page 56 Protocol Summary and Page 70 Study Outcome Measures <u>Secondary Endpoints</u> The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3 and Cohort 4.	Performing testing on each of the monoclonal antibodies of ADM03820 for cohort 3 and cohort 4
Page 53 Protocol Summary Study Design and Page 66 Study Design	Page 57 Protocol Summary Study Design and Page 71 Study Design Cohort 4 –300 mg IM injection (8 active, 2 placebo) Cohort 4 (300 mg IM injection) will enroll ten subjects without delay using 100 mg/mL drug product.	Added cohort for 100mg/mL drug product

Version 4.0 02 Mar 2021	Version 5.0 22 Jun 2021	Reason for Change
Page 53 Protocol Summary Study Design There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK samples after all subjects in all cohorts complete Day 60.	Page 58 Protocol Summary Study Design and Page 71 Study Design There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60.	Specified the Day 60 interim analysis will analyze data for cohorts 1-3
Page 57 Key Roles ICON Medical Monitor Kelly Struble, DO	Page 62 Key Roles ICON Medical Monitor	Change in ICON MM

Version 4.0 02 Mar 2021	Version 5.0 22 Jun 2021	Reason for Change
Page 73 Study Products Description of Study Products ADM03820 is a 1:1 mixture of two human IgG1 non-competitive anti-SARS-CoV-2 antibodies [mAb2130 (YTE+LALA) and mAb2381 (YTE+LALA)] formulated in 141 mM L-arginine, 10 mM sodium succinate buffer, with 0.25% v/v Polysorbate 80, and filled as 1.2 mL at 50 mg/mL in a 2 mL vial. The drug product is a clear, colorless, sterile aqueous solution at pH 6.	Page 78 Study Products Description of Study Products ADM03820 is a 1:1 mixture of two human IgG1 non-competitive anti-SARS-CoV-2 antibodies formulated as 50 mg/mL or 100 mg/mL strength solutions in a 2 mL vial for IM administration. The drug product is a clear to opalescent, slightly colored, sterile aqueous solution at pH 6. ADM03820 is formulated in 141 mM L-arginine, 10 mM sodium succinate buffer, with 0.25% v/v Polysorbate 80 and is filled as 1.2 mL in a 2 mL vial (50 mg/mL) or 1.7 mL in a 2 mL vial (100 mg/mL).	Added a 100mg/mL formulation

Version 4.0 02 Mar 2021	Version 5.0 22 Jun 2021	Reason for Change
Page 74 Product Storage and Stability ADM03820 drug product will be shipped frozen and should be stored at -90°C to -70°C until time of preparation. If a vial is removed from the freezer it must be used within 1 hour of thawing. If not used, it must be quarantined and maintained for study product accountability as per Section 6.6. ADM03820 should be protected from direct sunlight. ADM03820 is not light sensitive under normal shipping and storage conditions. Avoid vigorous shaking or agitation.	Page 78 Product Storage and Stability **Cohorts 1-3** ADM03820 drug product (50mg/mL) will be shipped frozen and should be stored at -90°C to -70°C until time of preparation. If a vial is removed from the freezer it must be used within 1 hour of thawing. If not used, it must be quarantined and maintained for study product accountability as per Section 6.6. ADM03820 should be protected from direct sunlight. ADM03820 is not light sensitive under normal shipping and storage conditions. Avoid vigorous shaking or agitation. **Cohort 4 Only** ADM03820 (100mg/mL) drug product will be shipped and should be stored at 2°C to 8°C until time of preparation. If a vial is removed from the refrigerator it must be used within 30 minutes. If not used, it must be quarantined and maintained for study product accountability as per Section 10.5. ADM03820 should be protected from direct sunlight. ADM03820 is not light sensitive under normal shipping and storage conditions. Avoid vigorous shaking or agitation.	Added 100mg/mL drug product information

Version 4.0 02 Mar 2021	Version 5.0 22 Jun 2021	Reason for Change
Page 78 Drug Screen A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. A breathalyzer test or blood alcohol test will also be performed, and results must be negative for eligibility into the study.	Page 83 Drug Screen A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. A blood/saliva alcohol test will also be performed, and results must be negative for eligibility into the study.	Allowing for blood/saliva alcohol test

SUMMARY OF CHANGES FOR VERSION 4.0

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 45 Protocol Summary Study Population = 185	Page 51 Protocol Summary Study Population = 30	Decrease number of subjects in the study
Page 45 Protocol Summary Number of Site = 10 Study Duration = 12 months Subject Participation = 379 days	Page 51 Protocol Summary Number of Site = 5 Study Duration = 18 months Subject Participation = 554 days	Increase study participation duration to 18-months (554 days)
Page 45 Protocol Summary Secondary Endpoints The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) methods designed for total monoclonal antibody in the Drug Product.	Page 51 Protocol Summary Secondary Endpoints The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3.	Performing testing on each of the monoclonal antibodies of ADM03820 for cohort 3 only
Page 46 Protocol Summary Study Design Cohort 3 –300 mg IM injection (110 active, 55 placebo)	Page 48 Protocol Summary Study Design Cohort 3 –300 mg IM injection (8 active, 2 placebo)	Decreased the number of subjects in cohort 3
Page 47 Protocol Summary Study Design Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365.	Page 48 Protocol Summary Study Design Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365. Subjects will have follow-up telephone visits at Days 450 and 540.	Increase study participation duration to 18-months (554 days)

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 47 Protocol Summary Study Design • There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK and MN samples through Day 8 for all subjects in Cohorts 1 – 3. A second blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 30.	Page 49 Protocol Summary Study Design There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK and MN samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 60.	Revised plan for interim analysis
Page 48 Protocol Summary Inclusion Criteria 13. Breathalyzer test is negative and subject agrees to abstain from alcohol consumption for a period of 2 days prior to dosing and 2 days prior to any study visit.	Page 50 Protocol Summary Inclusion Criteria 13. Breathalyzer test or blood alcohol test is negative and subject agrees to abstain from alcohol consumption for a period of 2 days prior to dosing and 2 days prior to any study visit.	Added blood alcohol test as an option for testing alcohol consumption

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 59 Section 3.2.2 Secondary Endpoints The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) methods designed for total monoclonal antibody in the Drug Product.	Page 61 Section 3.2.2 Secondary Endpoints The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3.	Performing testing on each of the monoclonal antibodies of ADM03820 for cohort 3 only
Page 60, Section 4 Study Design The study will randomize a total of 185 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo.	Page 62, Section 4 Study Design The study will randomize a total of 30 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo.	Decreased the number of subjects in cohort 3
Page 60 Schedule for Subjects Follow-up visits will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, and 365.The last follow up visit is scheduled at Day 365.	Page 62 Schedule for Subjects Follow-up outpatient visits will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, and 365 with telephone visits on Days 450 and 540. The last outpatient follow-up visit is scheduled at Day 365.	Added telephone visits

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 60 Schedule for Subjects A blinded interim analysis is planned to analyze all PK and MN samples through Day 8 for all subjects in Cohorts 1 – 3. A second blinded interim analysis is planned to analyze all PK and MN samples after the first 100 subjects complete Day 30. A third blinded interim analysis is planned to analyze all PK and MD samples after all subjects in all cohorts complete Day 30.	Page 62 Schedule for Subjects A blinded interim analysis is planned to analyze all PK and MN samples through Day 30 for all subjects in Cohorts 1 – 2. A second blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 60.	Revised plan for interim analysis
Page 61 Section 5 Study Enrollment and Withdrawal No exemptions are granted on Inclusion/Exclusion Criteria.	Page 63 Section 5 Study Enrollment and Withdrawal Exemptions may be granted on Inclusion/Exclusion Criteria pending Medical Director Approval.	Allowed exceptions with approval
Page 66 Section 5.3.4 Handling of Withdrawals Subjects that withdraw from cohort 3 after dosing will not be replaced. Subjects who withdraw or are withdrawn from the study who received any amount of the study product will be encouraged to continue follow-up (with subjects' consent) for safety. Subjects withdrawing will be asked to complete a final termination visit if they do not wish to be followed per protocol.	Page 68 Section 5.3.4 Handling of Withdrawals Removed language specific to cohort 3	Withdrawal of subjects will be handled the same for all cohorts
Page 68 Section 6.5 Dosage, Preparation and Administration The subjects will be admitted to the Phase 1 unit the day before the planned dosing.	Page 70 Section 6.5 Dosage, Preparation and Administration The subjects will be admitted to the Phase 1 unit the day of the planned dosing.	Admittance to the Phase 1 unit prior to day of dosing is not necessary

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 69 Section 6.8 Concomitant Medications • H1 antihistamines	Page 71 Section 6.8 Concomitant Medications • H1 antihistamines (PRN use of H1 antihistamines may be acceptable after Medical Director/Medical Monitor approval)	Will allow PRN use of H1 antihistamines upon approval
No visit 16	Page 86 Section 8.16 Visit 16	Added telephone visit
No visit 17	Page 86 Section 8.17 Visit 17	Added telephone visit
Page 87 Section 9.2.1 Adverse Events Severity of adverse events will be graded as follows based on the Investigator's assessment unless otherwise specified by CTCAE v5.0 (Appendix B).: **Mild:** Events require minimal or no treatment and do not interfere with the subject's daily activities. **Moderate:** Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning. **Severe:** Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.	Page 88 Section 9.2.1 Adverse Events Severity of adverse events will be graded using CTCAE v5.0 (Appendix B).	Removed mild, moderate, severe rating for AEs and added the use of CTCAE v5.0 for grading AEs

Version 3.0 12 Jan 2021	Version 4.0 02 Mar 2021	Reason for Change
Page 93 Section 11.1 Sample Size Considerations Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for cohorts 1 and 2, and a dosing group of one hundred sixty-five participants in cohort 3, one hundred ten participants assigned to the active group and fifty-five assigned to the control group are practical and provide sufficient information for a total sample size of 185 for a Phase 1 trial primarily designed to assess safety.	Page 93 Section 11.1 Sample Size Considerations Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for each cohort are practical and provide sufficient information for a total sample size of 30 for a Phase 1 trial primarily designed to assess safety.	Decreased the number of subjects in cohort 3
Page 94 Section 11.3.4 PK Analysis Plan PK parameters will be estimated for total monoclonal antibodies using noncompartmental methods in WinNonlin or a similar software package.	Page 95 Section 11.3.4 PK Analysis Plan PK parameters will be estimated for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. PK parameters for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3 using noncompartmental methods in WinNonlin or a similar software package.	Performing testing on each of the monoclonal antibodies of ADM03820 for cohort 3 only
Page 103 Appendix A Schedule of Events	Page 104 Appendix A Schedule of Events	Added telephone visits 16 and 17

SUMMARY OF CHANGES FOR VERSION 3.0

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 9 List of abbreviations	Page 9 List of abbreviations – added CTCAE	Protocol is using the CTCAE to replace the toxicity grading scale
Page 25 Protocol Summary – Study Population = 40 subjects	Page 41 Protocol Summary – Study Population = 185 subjects	Increased number of subjects
Page 25 Protocol Summary – Number of Sites = 2	Page 41 Protocol Summary - Number of Site = 10	Increased number of sites to expedite enrollment
Page 25 Protocol Summary – Study Duration = 18 months	Page 41 Protocol Summary – Study Duration = 12 months	Reduced the subject participation from 18-months to 12-months
Page 25 Protocol Summary – Subject Participation Duration = Subjects in all cohorts will participate approximately 554 days (14 to a 14-day screening, overnight stay, up to 18-month outpatient follow)	Page 41 Protocol Summary – Subject Participation Duration Subjects in all cohorts will participate approximately 379 days (14 to a 14-day screening, overnight stay, up to 12-month outpatient follow)	Reduced the subject participation from 18-months to 12-months
Page 25 Protocol Summary – Route of Delivery = Subjects will receive IM injections in the buttocks or an IV infusion over 1 hour	Page 41 Protocol Summary – Route of Delivery = Subjects will receive IM injections in the buttocks	Removed IV infusion cohorts from this protocol
Page 25 Protocol Summary – Study Endpoints o Secondary Endpoints = Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Page 41 Protocol Summary – Study Endpoints o Secondary Endpoints = Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts	Reduced the subject participation from 18-months to 12-months

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 25 Protocol Summary – Study Endpoints • Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 360 and 540 for all cohorts	Page 41 Protocol Summary – Study Endpoints • Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts	Reduced subject participation from 18-months to 12-months
Page 25 Protocol Summary – Study Endpoints	Page 42 Protocol Summary – Study Endpoints • Incidence of the first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurring after dosing through Day 365 • Incidence of SARS-CoV-2 RT-PCR positive severe or critical symptomatic illness occurring after dosing through Day 365 • Incidence of COVID-19 related Emergency Department visits occurring after dosing through Day 365	Added secondary endpoints

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 26 Protocol Summary – Study Design – The study will randomize a total of 40 healthy subjects to receive either an intramuscular (IM) injection or intravenous (IV) infusion of either ADM03820 or placebo. Dosing Cohorts: • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –10 mg/kg IV infusion (8 active, 2 placebo) • Cohort 4 – 20 mg/kg IV infusion (8 active, 2 placebo)	Page 42 Protocol Summary – Study Design - The study will randomize a total of 185 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Dosing Cohorts: • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (110 active, 55 placebo) Dosing for Cohort 3 (300 mg IM injection) will not occur until safety data through day 8 for Cohort 2 is reviewed by the SRC. Objective safety evaluations will be utilized. Subjects in Cohort 3 will be scheduled based on the SRC recommendation and will each be administered two 3 mL IM injections without delay.	Removed IV cohorts and revised cohort 3 to be IM injection cohort and dosing for cohort 3 will not have the four-hour dosing restrictions that cohorts 1 and 2 have.

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 27 Protocol Summary – Study Design – A blinded interim safety and PK analysis is planned for this study to analyze all PK and MN samples through Day 30. This will include all subjects in all cohorts through Day 30.	Page 43 Protocol Summary – Study Design – There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK and MN samples through Day 8 for all subjects in Cohorts 1 – 3. A second blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 30. There is also an interim clinical study report (CSR) planned after all subjects complete Day 90.	Additional interim analysis added as well as an interim CSR
Page 28 Protocol Summary – Exclusion Criteria – 11.Donated blood within 56 days of enrollment	Page 45 Protocol Summary – Exclusion Criteria – 11.Donated blood or plasma within 56 days of enrollment	Added or plasma
Page 28 Protocol Summary – Exclusion Criteria –	Page 45 Protocol Summary – Exclusion Criteria – 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit)	Added exclusion
Page 30 Schematic of Study Design	Page 46 Schematic of Study Design	Revised to three cohorts and removed the IV cohorts

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 34 Section 2.1.2 Currently Available Treatments	Page 50 Section 2.1.2 Currently Available Treatments On December 11, 2020 the FDA issued the first EUA for a vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the U.S. for use in individuals 16 years of age and older as a series of two doses that are given three weeks apart. The most commonly reported side effects, which typically lasted several days were pain at the injection site, tiredness, headache, muscle pain, joint pain, and fever. On December 18, 2020 the FDA issued an EUA for the second vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Moderna COVID-19 Vaccine to be distributed in the U.S for use in individuals 18 years of age and older administered as a series of two doses that are given one month apart. The most commonly reported side effects, which typically lasted several days were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, swollen lymph nodes in the same arm as the injection, nausea and vomiting, and fever.	Added language to cover the approved Pfizer and Moderna COVID-19 vaccines

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 36 Section 2.2 Rationale for Use of ADM03820 – The proposed starting dose for ADM03820 dose escalation (150 mg IM) is based on previous toxicology studies, known safety profile of mAbs, and the expected potency of ADM03820. Based on the expected potency of ADM03820, the doses proposed for evaluation are anticipated to support PK analysis with microneutralization values ($TCID_{50}$) in therapeutic window for a prophylactic. Provided there are no safety concerns, dosing will escalate to 300 mg IM. Provided there are no safety concerns with the 300 mg IM dosing, dosing will then escalate to 10 mg/kg IV infusion. Provided there are no safety concerns, dosing will escalate to 20 mg/kg IV infusion.	Page 53 Section 2.2 Rationale for Use of ADM03820 – The proposed starting dose for ADM03820 dose escalation (150 mg IM) is based on previous toxicology studies, known safety profile of mAbs, and the expected potency of ADM03820. Based on the expected potency of ADM03820, the doses proposed for evaluation are anticipated to support PK analysis with microneutralization values ($TCID_{50}$) in therapeutic window for a prophylactic. Provided there are no safety concerns, dosing will escalate to 300 mg IM.	Removed IV dosing

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 37 Section 2.3.1 Potential Risks IV Infusion of mAbs An indwelling catheter may cause phlebitis with signs of redness and warmth at or near the IV insertion site. Thrombophlebitis is also a potential risk with a hard area palpable near the IV insertion site. These risks are minimal as the infusion time is around one hour. There is the potential for infiltration of the study product into the tissues surrounding the IV site. Careful inspection of the site, including visualization of blood return at the catheter site will minimize this risk. There is a risk of infection; however, this is a small risk as aseptic technique will be employed. Infusions of mAbs may be associated with infusion reactions, including anaphylaxis/ anaphylactoid type reaction, especially during a first exposure, and when administered rapidly. Fever, chills, and rigors, typically occurring within the first 2 hours following infusion, characterize these reactions. Other risks sometimes associated with infusion reactions include nausea, vomiting, rash, pruritus, bronchospasm or other acute pulmonary response, angioedema, hypotension, hypertension, cardiac arrhythmias, dizziness, dyspnea, headache, and malaise.	Page 54 Section 2.3.1 Potential Risks	Removed risks associated with IV infusion

Page 39 Section 3.2.2 Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) methods designed for total monoclonal antibody in the Drug Product. o Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360 and 540 for all cohorts o Samples will be tested by Microneutralization at pre-dose and Days 2, 15, 30, 60, 90, 120, 150, and 180 for all cohorts • Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Page 55 Section 3.2.2 Secondary Endpoints • The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) methods designed for total monoclonal antibody in the Drug Product. o Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts o Samples will be tested by Microneutralization at pre-dose and Days 2, 15, 30, 60, 90, 120, 150, and 180 for all cohorts • Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 365 for all cohorts • Incidence of the first case of SARS-SoV-2 RT-PCR positive symptomatic illness occurring after dosing through Day 365 • Incidence of SARS-CoV-2 RT-PCR positive severe or critical symptomatic illness occurring after dosing through Day 365 • Incidence of COVID-19 related Emergency	Revised timepoints that samples will be tested based on reducing the subject follow-up from 18-months to 12-months and added three secondary endpoints

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
	Department visits occurring after dosing through Day 365	
Page 40 Section 4 Study Design This is a Phase 1, randomized, double-blind, placebo-controlled study of four dose cohorts to evaluate the safety, tolerability, and immunogenicity of ADM03820 in healthy adults. The study will randomize a total of 40 healthy subjects to receive either an intramuscular (IM) injection or intravenous (IV) infusion of either ADM03820 or placebo.	Page 56 Section 4 Study Design This is a Phase 1, randomized, double-blind, placebo-controlled study of three dose cohorts to evaluate the safety, tolerability, and immunogenicity of ADM03820 in healthy adults. The study will randomize a total of 185 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo.	Revised number of cohorts from four to three. Revised number of total subjects from 40 to 185 Removed reference to IV cohorts
Page 40 Section 4 Study Design Schedule for Subjects A blinded interim safety and PK analysis is planned for this study to analyze all PK and MN sample through Day 30. This will include all subjects in all cohorts through Day 30.	Page 56 Section 4 Study Design Schedule for Subjects There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK and MN samples through Day 8 for all subjects in Cohorts 1 – 3. A second blinded interim analysis is planned to analyze all PK and MN samples after the first 100 subjects complete Day 30. A third blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 30. There is also an interim clinical study report (CSR) planned after all subjects complete Day 90.	Added additional interim analysis

Page 40 Section 4 Study Design Schedule for Cohorts	Page 56 Section 4 Study Design Schedule for Cohorts Cohort 1 (150 mg IM injection) will be dosed first. Two sentinel subjects (one ADM03820 and one placebo) will each be administered a single 3 mL IM injection. The dosing of the next subjects within Cohort 1 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Dose escalation to Cohort 2 will not occur until safety data through day 8 for Cohort 1 is reviewed by the SRC. Objective dose escalation criteria and safety evaluations will be utilized. In Cohort 2 (300 mg IM injection), two sentinel subjects (one ADM03820 and one placebo) will each be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 2 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed.	Added language to explain IM dosing for each cohort. Removed IV Dosing

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
	Dosing for Cohort 3 (300 mg IM injection) will not occur until safety data through day 8 for Cohort 2 is reviewed by the SRC. Objective safety evaluations will be utilized. Subjects in Cohort 3 will be scheduled based on the SRC recommendation and will each be administered two 3 mL IM injections without delay.	
Page 41 Section 5 Study Enrollment and Withdrawal This study will enroll forty healthy male and female subjects ages 18 to 55 years old in four cohorts. Alternates who meet all eligibility criteria for IM dosing cohorts may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 48 hours after the initial two subjects are dosed. Alternates who meet all eligibility criteria for IV dosing cohorts may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 24 hours after the initial two subjects are dosed. Alternates not enrolled into a dosing group within a cohort are eligible for enrollment into the next group for that cohort.	Page 57 Section 5 Study Enrollment and Withdrawal This study will enroll one hundred and eight-five healthy male and female subjects ages 18 to 55 years old in three cohorts. Alternates who meet all eligibility criteria may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until dosing for that cohort begins. Alternates not enrolled into the cohort are eligible for enrollment in subsequent cohorts but would have to undergo re-screening if more than 14 days have passed since their initial screening visit.	Revised number of subjects from 40 to 185 Clarified language for alternate subjects
Page 43 Section 5.2 Exclusion Criteria 11. Donated blood within 56 days of enrollment.	Page 59 Section 5.2 Exclusion Criteria 11. Donated blood or plasma within 56 days of enrollment.	Added or plasma

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 43 Section 5.2 Exclusion Criteria	Page 60 Section 5.2 Exclusion Criteria 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit.	Added exclusion for receiving the COVID-19 vaccine

Page 44 Section 5.3 Treatment Assignment Procedures For each dosing cohort the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control. An alternate subject will be admitted to the unit for each two-subject group. If one of the first two subjects is not randomized for any reason, then the alternate subject will receive the next consecutive randomization number. The product assignment of the remaining subjects in each cohort will follow a 7:1 randomization of active to placebo, respectively. The randomization list will be generated by the unblinded study biostatistician and transferred to the unblinded study pharmacist prior to start of the study.	Page 60 Section 5.3 Treatment Assignment Procedures For cohorts 1 and 2 the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control. An alternate subject will be admitted to the unit for each two-subject group. If one of the first two subjects is not randomized for any reason, then the alternate subject will receive the next consecutive randomization number. The product assignment of the remaining subjects in each cohort will follow a 7:1 randomization of active to placebo, respectively. The randomization list will be generated by the unblinded study biostatistician and uploaded to IRT system by vendor (4G Clinical). Upon confirming eligibility of subjects, site research personnel will randomize subjects then the unblinded study pharmacist will be notified of treatment allocation via system-generated email. Subjects in cohort 3 will be randomized in a 2:1 ratio of active to placebo. The randomization list will be generated by the unblinded study biostatistician and uploaded to IRT system by vendor (4G Clinical). Upon confirming eligibility of subjects, site research personnel will randomize subjects then the unblinded study pharmacist will be notified of treatment	Clarified language for randomization within each cohort

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
	allocation via system-generated email.	
Page 46 Section 5.3.4 Handling of Withdrawals Subjects who are withdrawn prior to dosing must be replaced. Following dosing one subject per cohort may withdraw prior to the completion of Visit 11 (day 60) or was noncompliant with all PK draws through Visit 6 (day 4) without being replaced.	Page 62 Section 5.3.4 Handling of Withdrawals Subjects who are withdrawn prior to dosing must be replaced. Following dosing in cohorts 1 and 2, one subject per cohort may withdraw prior to the completion of Visit 11 (day 60) or was noncompliant with all PK draws through Visit 6 (day 4) without being replaced. If 4 or more subjects withdraw, are lost to follow up or terminate prior to Day 8 within a cohort, at least one of those subjects need to be replaced to ensure that data for at least 7 subjects are available for review. If 4 or more subjects withdraw, are lost to follow up or terminate on or after Day 8 but prior to Day 60 or are not compliant with all PK draws through Day 15 within a cohort, they should be replaced. If more than 4 subjects withdraw, are lost to follow up or terminate following the Day 8 SRC review of safety data within a cohort, the site will attempt to replace those subjects in that dose group at the time of the next planned cohort. All replaced subjects will be assigned to the same treatment assignment as the subject they are replacing. This will be documented in the source documents and eCRFs. Subjects that withdraw from cohort 3 after dosing will not be replaced.	Added language to clarify replacement of subjects that withdraw from the study.

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 47 Section 6.3 Formulation, Packaging, and Labeling ADM03820 will be administered by intramuscular (IM) injection or intravenous (IV) infusion as follows: 150 mg (1 x 3 mL IM injection) or 300 mg (2 x 3 mL IM injections), 10mg/kg (~15 mL IV infusion), and 20 mg/kg (~30 mL IV infusion).	Page 63 Section 6.3 Formulation, Packaging, and Labeling ADM03820 will be administered by intramuscular (IM) injection as follows: 150 mg (1 x 3 mL IM injection) or 300 mg (2 x 3 mL IM injections).	Removed IV infusion
Page 48 Section 6.5 Dosage, Preparation, and Administration Administration of the IV dose of ADM03820 or placebo must be started within 30 minutes of preparation.	Page 64 Section 6.5 Dosage, Preparation, and Administration	Removed IV dosing preparation
Page 50 Section 7.3 Vital Signs During screening and follow-up, a measurement that is Grade 1 (as referenced in Appendix B Toxicity Grading) may be repeated once if the PI believes a transient condition led to the aberrant value.	Page 66 Section 7.3 Vital Signs During screening and follow-up, a measurement that is Grade 1 (as referenced in Appendix B CTCAE version 5.0) may be repeated once if the PI believes a transient condition led to the aberrant value.	Changed toxicity grading to use CTCAE version 5.0
Page 51 Section 7.5.1.4 Screening Laboratory Tests	Page 68 Section 7.5.1.4 Screening Laboratory Tests ○ FSH to confirm post-menopausal status for women ≥ 1 year without menses	Added FSH test
Page 54 Table 2 Laboratory Samples and Estimated Total Blood Volume	Page 70 Table 2 Laboratory Samples and Estimated Total Blood Volume	Revised table for reducing subject participation from 18-months to 12-months
Page 55 Section 8 Study Schedule	Page 71 Section 8 Study Schedule	Revised visit schedule for reducing the subject participation from 18-months to 12-months
Page 56 Section 8.2 Visit 2: Baseline / Admission to Unit (Day -1)	Page 72 Section 8.2 Visit 2: Baseline / Day of Dosing	Revised to remove the Day -1 visit and make baseline visit the day of dosing Removed reference to IV dosing
Page 71 Section 9.5.1 Halting Criteria for Infusion Dosing	Page 85 Section 9.5.1 Halting Criteria for Infusion Dosing	Removed IV dosing halting criteria

Version 2.0 16 Nov 2020	Version 3.0 12 Jan 2021	Reason for Change
Page 74Section 11.1 Sample Size Considerations Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group practical and provide sufficient information for a total sample size of 40 for a Phase 1 trial primarily designed to assess safety.	Page 87 Section 11.1 Sample Size Considerations Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for cohorts 1 and 2, and a dosing group of one hundred sixty-five participants in cohort 3, one hundred ten participants assigned to the active group and fifty-five assigned to the control group are practical and provide sufficient information for a total sample size of 185 for a Phase 1 trial primarily designed to assess safety.	Revised to reflect three cohorts and 185 subjects
Page 74 Section 11.2 Planned Interim Analysis A blinded interim safety and PK analysis is planned for this study to analyze all PK and MN samples through Day 30. This will include all subjects in all cohorts.	Page 87 Section 11.2 Planned Interim Analysis There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK and MN samples through Day 8 for all subjects in Cohorts 1 – 3. A second blinded interim analysis is planned to analyze all PK and MN samples after all subjects in all cohorts complete Day 30. There is also an interim clinical study report (CSR) planned after all subjects complete Day 90.	Added interim analysis and interim CSR
Page 84 Appendix A Schedule of Events	Page 97 Appendix A Schedule of Events	Revised to reduce subject participation from 18-months to 12-months
Page 86 Appendix B Toxicity Grading	Page 99 Appendix B CTCAE v5.0	Revised to use CTCAE v5.0

SUMMARY OF CHANGES FOR VERSION 2.0

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 13 Protocol Summary/Study Duration – Approximately 10 months	Page 25 Protocol Summary Study Duration – Approximately 18 months	Extended the length of subject follow-up to 18-months
Page 13 Protocol Summary/Subject Participation Duration Subjects in all cohorts will participate approximately 208 days (up to a 14-day screening, overnight stay, up to 180 days outpatient follow-up)	Page 25 Protocol Summary/Subject Participation Duration Subjects in all cohorts will participate approximately 554 days (up to a 14-day screening, overnight stay, up to 18-month outpatient follow-up)	Extended the length of subject follow-up to 18-months
Page 13 Protocol Summary/Secondary Endpoints Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150 and 180, for all cohorts	Page 25 Protocol Summary/Secondary Endpoints Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Extended the length of subject follow-up to 18-months
Page 14 Protocol Summary/Secondary Endpoints ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, and 180 for all cohorts	Page 26 Protocol Summary/Secondary Endpoints ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Extended the length of subject follow-up to 18-months

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 14 Protocol Summary/ Study Design The dosing of the next subjects within Cohort 1 will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed as scheduled without delay.	Page 26 Protocol Summary/ Study Design The dosing of the next subjects within Cohort 1 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed.	Added a longer delay of subsequent enrollment (48 hours) following sentinel cohort in subjects receiving the IM dose.
Page 14 Protocol Summary/ Study Design The dosing of the next subjects within Cohort 2 will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed as scheduled without delay.	Page 26 Protocol Summary/ Study Design The dosing of the next subjects within Cohort 2 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed.	Added a longer delay of subsequent enrollment (48 hours) following sentinel cohort in subjects receiving the IM dose.
Page 15 Protocol Summary/Study Design Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, and 180.	Page 27 Protocol Summary/Study Design Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 with telephone visits at Days 270 and 450.	Extended the length of subject follow-up to 18-months

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 17 Protocol Summary/Exclusion Criteria 20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period • Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents; any vaccine (licenses or investigational)	Page 29 Protocol Summary/Exclusion Criteria 20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period • Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents	Removed vaccine exclusion to allow subject to receive necessary vaccinations
Page 26 Section 2.3.1 Potential Risks/IM Injection An IM injection may cause some discomfort at the injection site. Other risks may include pain, redness, swelling, or warmth at the injection	Page 38 Potential Risks/IM Injection An IM injection may cause some discomfort at the injection site. Other risks may include pain, redness, swelling, or warmth at the injection site. These risks are minimal. An IM injection into the gluteus medius may cause sciatic nerve damage, bleeding, hematoma, or infection.	Revised location of the IM dose to the gluteus medius

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 27 Section 3.2.2 Study Outcome Measures/Secondary Endpoints Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150 and 180, for all cohorts	Page 39 Study Outcome Measures/Secondary Endpoints Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Extended the length of subject follow-up to 18-months
Page 27 Section 3.2.2 Study Outcome Measures/Secondary Endpoints ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, and 180 for all cohorts	Page 40 Study Outcome Measures/Secondary Endpoints ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540 for all cohorts	Extended the length of subject follow-up to 18-months
Page 28 Section 4 Study Design/Schedule for Subjects Subjects in all cohorts will participate in the study for approximately 180 days, including a 14-day screening period. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150 and 180. The last follow up visit is scheduled at Day 180.	Page 40 Study Design/Schedule for Subjects Subjects in all cohorts will participate in the study for approximately 554 days, including a 14-day screening period. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, 360, and 540 with telephone visits at Days 270 and 450. The last follow up visit is scheduled at Day 540.	Extended the length of subject follow-up to 18-months

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 28 Section 4 Study Design/Schedule for Cohorts The dosing of the remaining subjects within that cohort will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed without delay.	Page 41 Study Design/Schedule for Cohorts The IM dosing of the remaining subjects within cohorts 1 and 2 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in cohorts 1 and 2 will be dosed at least four hours apart until all subjects in the cohort have been dosed. The IV dosing of the remaining subjects in cohort 3 and 4 will not be initiated until at least 24 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred in the opinion of the investigator warrant further investigation. The remaining subjects in cohorts 3 and 4 will be dosed as scheduled without delay.	Added a longer delay of subsequent enrollment (48 hours) following sentinel cohort in subjects receiving the IM dose.

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 29 Section 5 Study Enrollment and Withdrawal Alternates who meet all eligibility criteria may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 24 hours after the initial two subjects are dosed.	Page 41 Study Enrollment and Withdrawal Alternates who meet all eligibility criteria for IM dosing cohorts may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 48 hours after the initial two subjects are dosed. Alternates who meet all eligibility criteria for IV dosing cohorts may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until 24 hours after the initial two subjects are dosed.	Added a longer delay of subsequent enrollment (48 hours) following sentinel cohort in subjects receiving the IM dose.
Page 31 Section 5.2 Subject Exclusion Criteria 20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period • Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents; any vaccine (licenses or investigational)	Page 44 Section 5.2 Subject Exclusion Criteria 20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents	Removed vaccine exclusion to allow subject to receive necessary vaccinations

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 36 Section 6.5 Dosage, Preparation and Administration Administration of the IM dose of ADM03820 or placebo should be injected into the gluteus maximus and must be completed within 30 minutes of preparation.	Page 48 Section 6.5 Dosage, Preparation and Administration Administration of the IM dose of ADM03820 or placebo should be injected into the gluteus medius (see Appendix C) and must be completed within 30 minutes of preparation.	Revised location of IM dose to the gluteus medius
Page 37 Section 6.8 Concomitant Medications Subjects will be instructed to refrain from the receipt of any of the following during study participation unless medically indicated and deemed immediately necessary by their private physician: • Blood or blood products, • Any antibody (e.g. TIG, VZIG, IVIG, IM gamma globulin) • Any vaccine (licensed or investigational) • Monoclonal antibody • H1 antihistamines • Beta-blockers • Immunosuppressives (except NSAIDS) • Oral corticosteroids (topical/intranasal steroids are acceptable) • Anti-neoplastic agents	Page 49 Section 6.8 Concomitant Medications Subjects will be instructed to refrain from the receipt of any of the following during study participation unless medically indicated and deemed immediately necessary by their private physician: • Blood or blood products, • Any antibody (e.g. TIG, VZIG, IVIG, IM gamma globulin) • Monoclonal antibody • H1 antihistamines • Beta-blockers • Immunosuppressives (except NSAIDS) • Oral corticosteroids (topical/intranasal steroids are acceptable) • Anti-neoplastic agents	Removed vaccinations as an excluded medication to allow subject to receive necessary vaccinations

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 37 Section 7.1 Medical History and COVID-19 Instruction	Page 50 Section 7.1 Medical History and COVID-19 Instruction If a subject acquires COVID-19 during their participation in the study, they should seek and obtain the appropriate treatment.	Added language to ensure that subjects are permitted to seek and obtain treatment of COVID-19, if acquired
Page 39 Section 7.5.1.3 Pregnancy Testing A urine pregnancy test will be repeated on Day 4, Day 45, Day 120, 150, and Day 180 (end of study).	Page 51 Section 7.5.1.3 Pregnancy Testing A urine pregnancy test will be repeated on Day 4, Day 45, Day 120, 150, Day 180, 360, and 540 (end of study).	Extended the length of subject follow-up to 18-months
Page 39 Section 7.5.2 Safety Laboratory Tests The following laboratory tests will be performed at Days 8, 15, 30, 90, and end of study.	Page 52 Section 7.5.2 Safety Laboratory Tests The following laboratory tests will be performed at Days 8, 15, 30, 90, and 180, 360 and end of study.	Extended the length of subject follow-up to 18-months
Page 40 Section 7.6.1 Pharmacokinetic Assay PK samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150 and 180.	Page 52 Section 7.6.1 Pharmacokinetic Assay PK samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, 360, and 540.	Extended the length of subject follow-up to 18-months
Page 40 Section 7.6.3 Immunogenicity / Anti-Drug Antibody Assay Six-mL samples of blood will be drawn at pre-dose and on Days 15, 30,45,60, 90, 120, 150, and 180	Page 53 Section 7.6.3 Immunogenicity / Anti-Drug Antibody Assay Six-mL samples of blood will be drawn at pre-dose and on Days 15, 30,45,60, 90, 120, 150, 180, 360, and 540	Extended the length of subject follow-up to 18-months

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
Page 41 Section 7.6.4 RT-PCR Testing for SARS-CoV-2	Page 53 Section 7.6.4 RT-PCR Testing for SARS-CoV-2 If a subject acquires COVID-19 during their participation in the study, they should seek and obtain the appropriate treatment.	Added language
Page 42 Table 2 Laboratory Samples and Estimated Total Blood Volume (mL)	Page 54 Table 2 Laboratory Samples and Estimated Total Blood Volume (mL)	Updated table to include additional blood volumes for additional visits
Page 45 Section 8.3 Visit 3: Day of Dosing (Day 1) IM Cohorts-During Dosing Study product should be injected into the gluteus maximus.	Page 57 Section 8.3 Visit 3: Day of Dosing (Day 1) IM Cohorts-During Dosing Study product should be injected into the gluteus medius (see Appendix C).	Revised location of IM dosing to the gluteus medius
Page 47 Section 8.4 Visit 4: Discharge from Unit (Day 2) Remind the subject not to receive any routine vaccines or drugs listed in section 6.8 for the duration of the study unless clinically indicated. If subjects receive vaccines that are clinically indicated (e.g. tetanus after an open wound injury), they will be instructed to contact study staff immediately. If study activities overlap with influenza season, subjects will be instructed to delay influenza vaccination until after Day 60 (Visit 11).	Page 60 Section 8.4 Visit 4: Discharge from Unit (Day 2) Remind the subject not to receive any drugs listed in section 6.8 for the duration of the study unless clinically indicated. If subjects receive necessary vaccines that are clinically indicated (e.g. tetanus after an open wound injury, influenza), they will be instructed to contact study staff immediately.	Removed vaccinations as an excluded medication to allow subject to receive necessary vaccinations
Page 52 Section 8.15 Visit 15: Final Visit / Early Termination Visit (day 180±3)	Page 64 Section 8.15 Visit 15: Out-Patient Follow-Up Visit (day 180±3)	Day 180 is no longer the end of study
N/A	Page 64 Section 8.16 Visit 16: Telephone Visit (Day 270±3)	Added visits to extend length of subject follow up

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
N/A	Page 64 Section 8.17 Visit 17: Out-Patient Follow-Up (Day 360±3)	Added visits to extend length of subject follow up
N/A	Page 65 Section 8.18 Visit 18: Telephone Visit (Day 450±3)	Added visits to extend length of subject follow up
N/A	Page 65 Section 8.19 Visit 19: Final Visit / Early Termination (Day 540±3)	Added visit to extend length of subject follow up
Page 52 Section 8.16 Unscheduled Visit	Page 66 Section 8.20 Unscheduled Visit	Added visits to extend length of subject follow up
Page 53 Section 9 Assessment of Safety	Page 66 Section 9 Assessment of Safety have emergency staff and medications such as epinephrine, corticosteroids, bronchodilators, and emergency tool kits for emergent intubation and initial acute cardiopulmonary resuscitative care are available at all clinical sites in the event they are needed during and immediately after IM injections or IV infusions.	Additional safety language added
Page 57 Section 9.4 Type and Duration of Follow-up of Subjects after Adverse Events Subjects who experience AEs consistent with COVID-19 through Day 180 will be evaluated either by the site or by a health care provider to which the subject may be referred.	Page 70 Section 9.4 Type and Duration of Follow-up of Subjects after Adverse Events Subjects who experience AEs consistent with COVID-19 through Day 540 will be evaluated either by the site or by a health care provider to which the subject may be referred.	Extended the length of subject follow-up to 18-months

Page 57 Section 9.5.1 Halting Criteria for the Study	Page 71 Section 9.5.1 Halting Criteria for Infusion Dosing Study dosing can be halted at any time if medically indicated. Intravenous infusion dosing should be immediately stopped should any of the following occur: • Profound hypotension (systolic blood pressure < 85 mmHg) • Tachycardia with an increase in resting heart rate to ≥ 130 beats per minute (bpm); or development of a ventricular dysrhythmia; or bradycardia <45 bpm (or <40 bpm in subjects with a baseline of <60bpm) that is associated with complaints of dizziness, nausea or feeling faint • Shortness of breath, wheezing, or sustained (i.e. ≥10 seconds) oxygen saturation < 92% on room air • Severe (Grade ≥3) local infusion site reactions, including pain, tenderness, erythema, or swelling as defined in the toxicity grading scale (Appendix B) • Body core temperature exceeding 1.5°C above baseline • Suspected sepsis • Severe chest pain	Added language for halting criteria for IV dosing

Version 1.0 07 Oct 2020	Version 2.0 16 Nov 2020	Reason for Change
	• Suspected anaphylaxis	
Page 70 Appendix A: Schedule of Events	Page 84 Appendix A: Schedule of Events	Added visits to extend length of subject follow up
N/A	Page 89 Appendix C: Intramuscular (IM) Administration	Added appendix for IM injection instructions

PROTOCOL SUMMARY

Protocol Element	Description
Study Title	Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Immunogenicity of ADM03820 in Adults.
Clinical Phase	Phase 1
Study Population	A total of 50 healthy male and female subjects between 18 – 55 years of age
Number of Sites	Approximately 5
Study Duration	Approximately 18 months for cohorts 1-4 and 12 months for cohort 5
Subject Participation Duration	Subjects in cohorts 1-4 will participate approximately 554 days (up to a 14-day screening, overnight stay, up to 12-month outpatient follow-up visits and telephone visits at 15-months and 18-months.) Subjects in cohort 5 will participate approximately 379 days (up to a 14-day screening, overnight stay, and up to 12-month outpatient follow-up visits.)
Description of Study Product	ADM03820 is a 1:1 mixture of two human IgG1 non-competitive binding anti-SARS-CoV-2 antibodies, mAb2130 (YTE+LALA) and mAb2381 (YTE+LALA), individually expressed in a Chinese hamster ovary (CHO) cell line.
Route of Delivery	Subjects will receive IM injections in the buttocks
Study Objectives	Primary Objective • To assess the safety and tolerability of different doses of ADM03820 in healthy adult subjects Secondary Objective • To assess the pharmacokinetics (PK) and immunogenicity (ADA) of different doses of ADM03820 in healthy adult subjects
Study Endpoints	Primary Endpoints • The occurrence of Serious Adverse Events following administration of ADM03820 to the final visit • The occurrence of AEs from administration of ADM03820 to the final visit • The occurrence of changes from baseline in physical examination, vital signs, and clinical safety laboratory values following administration of ADM03820 to the final follow up visit Secondary Endpoints

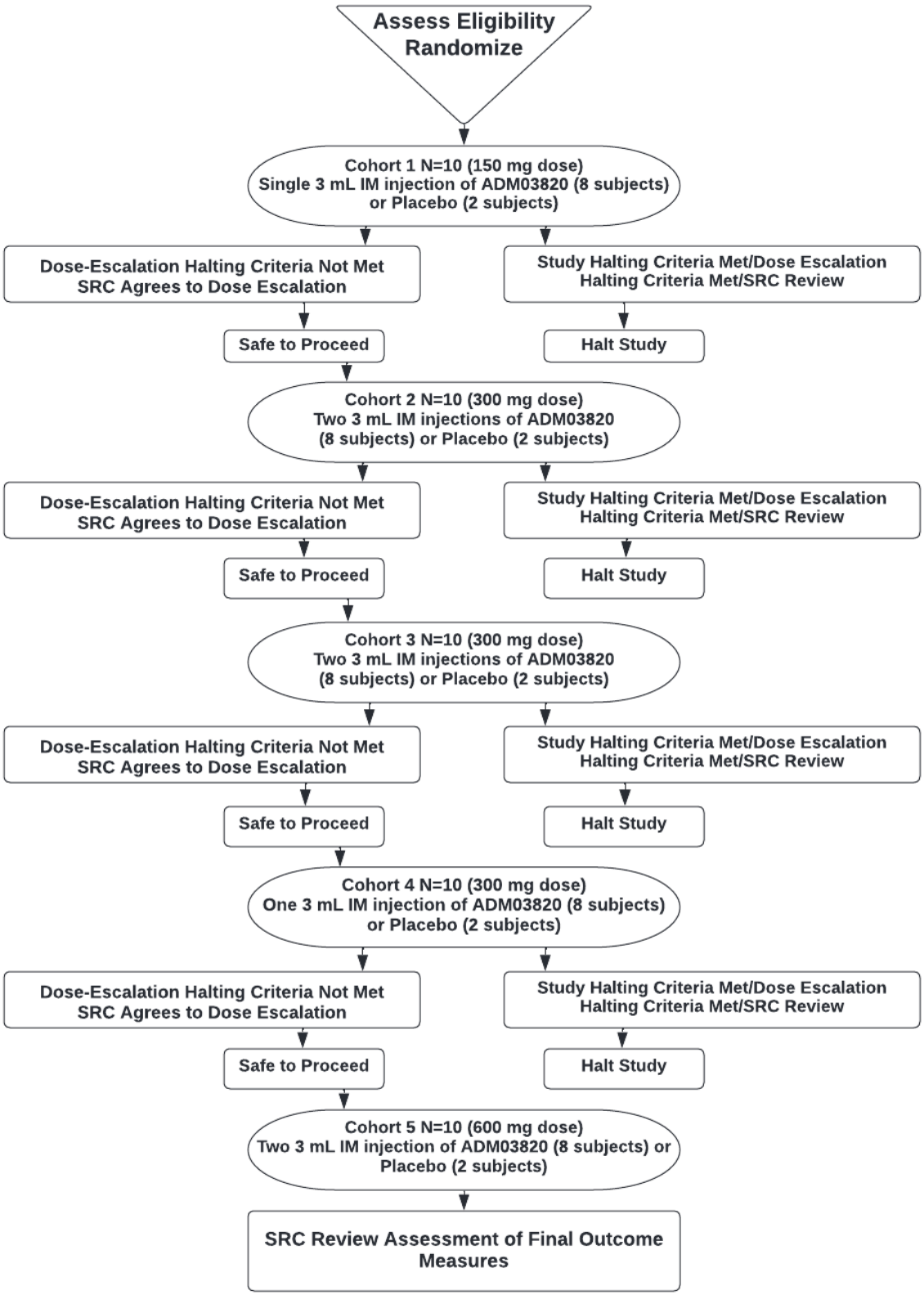
	• The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3, Cohort 4, and Cohort 5. o Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts o Samples will be tested by Microneutralization at pre-dose and Days 2, 15, 30, 60, 90, 120, 150, and 180 for all cohorts • Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts. o ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts • Incidence of the first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurring after dosing through Day 365 • Incidence of SARS-CoV-2 RT-PCR positive severe or critical symptomatic illness occurring after dosing through Day 365 • Incidence of COVID-19 related Emergency Department visits occurring after dosing through Day 365
Study Design	This study is a phase 1, randomized, double-blind, placebo-controlled study of five dose cohorts. The study will randomize a total of 50 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo. Dosing Cohorts: • Cohort 1 –150 mg IM injection (8 active, 2 placebo) • Cohort 2 – 300 mg IM injection (8 active, 2 placebo) • Cohort 3 –300 mg IM injection (8 active, 2 placebo) • Cohort 4 – 300 mg IM injection (8 active, 2 placebo) • Cohort 5 – 600 mg IM Injection (8 active, 2 placebo) Cohort 1 (150 mg IM injection) will be dosed first. Two sentinel subjects (one ADM03820 and one placebo) will each be administered a single 3 mL IM injection. The dosing of the next subjects within Cohort 1 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in

	the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Dose escalation to Cohort 2 will not occur until safety data through day 8 for Cohort 1 is reviewed by the Safety Review Committee (SRC), which is composed of the Principal Investigator (PI), Resilience Government Services (RGS) Medical Lead (ML), and ICON Medical Monitor. Objective dose escalation criteria and safety evaluations will be utilized. In Cohort 2 (300 mg IM injection), two sentinel subjects (one ADM03820 and one placebo) will each be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 2 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Dosing for Cohort 3 (300 mg IM injection) will not occur until safety data through day 8 for Cohort 2 is reviewed by the SRC. Objective safety evaluations will be utilized. Subjects in Cohort 3 will be scheduled based on the SRC recommendation and will each be administered two 3 mL IM injections without delay. Cohort 4 (300 mg IM injection) will enroll ten subjects without delay using 100 mg/mL drug product. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365. Subjects will have follow-up telephone visits at Days 450 and 540. Cohort 5 (600 mg IM injection) will enroll two sentinel subjects (one ADM03820 and one placebo) and each will be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. Follow-up visits will occur on Days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365.

	The study will consist of a fourteen-day screening period. The end of the study is defined as the date of the last visit of the last subject in the study (day 540 for cohorts 1-4 and day 365 for cohort 5) There are several blinded interim analyses planned for this study. • A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. • A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. • A third interim analysis is planned to analyze safety and PK after all subjects in cohort 5 complete Day 60. There is also an interim clinical study report (CSR) planned after subjects in Cohorts 1 through 4 complete Day 90.
Inclusion Criteria	1. Informed consent understood and signed 2. Healthy male or healthy, non-pregnant, non-lactating female 3. Willingness to comply and be available for all protocol procedures for the duration of the study 4. Between the ages of 18 and 55, inclusive on the day of dosing 5. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2 6. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1 prior to dosing. • Note: A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses without other known or suspected cause and appropriately elevated FSH) or surgically sterilized via bilateral oophorectomy or hysterectomy 7. Females of childbearing potential and males agree to use acceptable contraception for the duration of the study • Note: These include progestin implants, intrauterine devices (IUDs), surgical (hysterectomy or tubal ligation; vasectomy) or abstinence. Use of methods such as progestin injectables, combined oral hormonal contraceptives, condoms, and diaphragms will not be acceptable when used alone, but they could be considered, if used in combination with another method (for example, a female using combined oral contraceptives if her male partner is sterile, or if she and her non-sterile male partner use a double-barrier method), after consultation with the RGS ML. All males will be required to use a barrier method (condoms) for the duration of the study 8. Screening laboratory tests are within normal ranges or outside the normal ranges and considered not clinically significant by the Principal Investigator 9. If urinalysis by dipstick is abnormal, a complete urinalysis with

	microscopic evaluation will be performed and the results will supersede the results of the dipstick for blood, glucose, and protein. 10. Menstruating females failing inclusion criteria due to a positive blood on urine test may be retested following cessation of menses. 11. Other laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or collection or laboratory error may be repeated once. 12. The urine drug screen is negative 13. Breathalyzer test or blood/saliva alcohol test is negative and subject agrees to abstain from alcohol consumption for a period of 2 days prior to dosing and 2 days prior to any study visit. 14. Agree to minimize risk of SARS-CoV-2 infection.
Exclusion Criteria	1. History of chronic medical condition that would either interfere with the accurate assessment of the objectives of the study or increase the risk profile of the subject. 2. Subjects with cardiovascular disease 3. Subjects with diabetes 4. Subjects with pulmonary diseases such as COPD or asthma 5. History of severe allergic reactions of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobins. 6. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds) 7. Clinically significant abnormal electrocardiogram at screening. • Note: Clinically significant abnormal ECG results include but not limited to: complete left or right bundle branch block; other ventricular conduction block; 2nd degree or 3rd degree atrioventricular (AV) block; sustained ventricular arrhythmia; sustained atrial arrhythmia; two Premature Ventricular Contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; or any condition deemed clinically significant by a study investigator • Incomplete right bundle branch block is not exclusionary if there are no abnormal ECG findings and there is no clinical history or evidence on physical examination to indicate cardiac disease. 8. Positive serology results for HIV, HBsAg, or HCV antibodies 9. Febrile illness with temperature ≥38°C within 7 days of dosing 10. Female subject who is pregnant or breastfeeding 11. Donated blood or plasma within 56 days of enrollment 12. Known allergic reactions to any of the study product components present in the formulation or in the processing, as listed in the Investigator Brochure 13. Treatment with another investigational drug within 28 days of dosing

	14. Treatment with a monoclonal antibody within 3 months of enrollment 15. Positive serology results for SARS-CoV-2 antibodies (Not applicable for Cohort 5). 16. Positive results from a reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 17. Receipt of antibody (e.g. TIG, VZIG, IVIG, IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given 18. Active drug or alcohol use disorder or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements 19. Use of H1 antihistamines or beta-blockers within 5 days of dosing 20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period • Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents 21. Any specific condition that in the judgment of the investigator precludes participation because it could affect subject safety 22. Plans to enroll or is already enrolled in another clinical trial that could interfere with safety assessment of the investigational product at any time during the study period • Note: Includes trials that have a study intervention such as a drug, biologic, or device 23. Is a study site employee or staff • Note: Site employees or staff include the PIs and sub-investigators or staff who are supervised by the PI or Sub-Investigators 24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit). For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.


Assess Eligibility
Randomize
Cohort 1 N=10 (150 mg dose)
Single 3 mL IM injection of ADM03820 (8 subjects)
or Placebo (2 subjects)
Dose-Escalation Halting Criteria Not Met
SRC Agrees to Dose Escalation
Study Halting Criteria Met/Dose Escalation
Halting Criteria Met/SRC Review
Safe to Proceed
Halt Study
Cohort 2 N=10 (300 mg dose)
Two 3 mL IM injections of ADM03820
(8 subjects) or Placebo (2 subjects)
Dose-Escalation Halting Criteria Not Met
SRC Agrees to Dose Escalation
Study Halting Criteria Met/Dose Escalation
Halting Criteria Met/SRC Review
Safe to Proceed
Halt Study
Cohort 3 N=10 (300 mg dose)
Two 3 mL IM injections of ADM03820
(8 subjects) or Placebo (2 subjects)
Dose-Escalation Halting Criteria Not Met
SRC Agrees to Dose Escalation
Study Halting Criteria Met/Dose Escalation
Halting Criteria Met/SRC Review
Safe to Proceed
Halt Study
Cohort 4 N=10 (300 mg dose)
One 3 mL IM injection of ADM03820 (8 subjects)
or Placebo (2 subjects)
Dose-Escalation Halting Criteria Not Met
SRC Agrees to Dose Escalation
Study Halting Criteria Met/Dose Escalation
Halting Criteria Met/SRC Review
Safe to Proceed
Halt Study
Cohort 5 N=10 (600 mg dose)
Two 3 mL IM injection of ADM03820 (8 subjects) or
Placebo (2 subjects)
SRC Review Assessment of Final Outcome
Measures

1. KEY ROLES

ICON Medical Monitor:	Priyumvada Naik, MD ICON, Plc. 320 Seven Springs Way Suite 500 Brentwood, TN Telephone: 616-309-3831 Email: priyumvada.naik@iconplc.com
Resilience Government Services Medical Lead:	Wael El-Amin, MD Resilience Government Services, Inc. 13200 NW Nano Court Alachua, FL 32615 Telephone: 240-885-1221 Email: wael.el-amin@resilience.com
CRO Safety and Pharmacovigilance Contractor:	ICON Pharmacovigilance & Safety Services Unit 2, Globeside Business Park Marlow SL7 1HZ United Kingdom PV email: ICON-Safety-CentralReceipt@iconplc.com

Laboratory for Safety Testing:	Local laboratories to be used for safety testing
COVID-19 Testing	Local laboratories to be used for safety testing
Research Laboratory for PK and ADA Samples:	Resilience Government Services, Inc. 2061 Challenger Drive, Suite 101 Alameda, CA 94501
Laboratory for Microneutralization Samples:	Battelle Biomedical Research Center 1425 State Route 142 West Jefferson, OH 43162

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by infection with a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan city, Hubei province, China in 2019. As of June 24, 2022, 539 million cases and 6.3 million deaths attributed to COVID-19 have been reported globally, with 85.5 million cases and 1 million deaths in the US. SARS-CoV-2 is transmitted primarily via respiratory droplets and contact with infectious individuals or fomites[1]. COVID-19 commonly manifests with fever, cough, or fatigue, and illness severity ranges from mild (including mild pneumonia) to critical (including acute respiratory distress syndrome [ARDS] and multiorgan dysfunction), with older adults and patients with serious chronic medical conditions at higher risk of adverse outcomes[2]. The mean incubation time from exposure to onset of symptoms is approximately 5 days[3]. Viral load in posterior oropharyngeal saliva samples is highest in the first week after symptom onset, declining gradually thereafter and remaining detectable for at least 20 days in some patients[4]. It has been observed that the viral load can increase for up to 12 days in naïve patients[5]. SARS-CoV-2 transmission may occur from asymptomatic or pre-symptomatic individuals and is associated with younger age[2]. In addition, high SARS-CoV-2 titers have been detected in oropharyngeal samples early in the disease course[5],[6]. The current estimated basic reproduction number is 2.2, so SARS-CoV-2 is expected to continue spreading.[7]

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[1] WHO, 2020. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. Accessed 2022 June 24. https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.

[2] CDC, 2020. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Accessed 2020 April 3. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

[3] Zhang et al. Evolving epidemiology and transmission dynamics of coronavirus disease 2019 outside Hubei province, China: a descriptive and modelling study. *Lancet Infect Dis*. 2020 Apr 2. [Epub ahead of print]

[4] To et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* 2020 Mar 23. [Epub ahead of print]

[5] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020 Mar 5;382(10):929-936.

[6] Zou L, Ruan F, Huang M, Liang L, Huang H, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 2020 Mar 19;382(12):1177-1179.

[7] Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med*. 2020 Mar 26;382(13):1268-1269.

SARS-CoV-2 belongs to the *Betacoronavirus* genus of single-stranded RNA viruses along with SARS-CoV, which caused the global epidemic of SARS that originated in Guangdong province, China in 2002; Middle East respiratory syndrome coronavirus (MERS-CoV), which has been recognized as causing outbreaks in and near the Arabian peninsula since 2012; and various SARS-related coronaviruses (SARSr-CoV) in humans, bats, and other animals[8,9,10]. *Betacoronaviruses* are subdivided into A, B, C, and D lineages. SARS-CoV and SARS-CoV-2 belong to the B lineage and MERS-CoV to the C lineage[11]. The natural reservoir for SARS-CoV is the horseshoe bat, with civets and racoon dogs acting as intermediate hosts[12]. For MERS-CoV, the dromedary camel is the reservoir host, although bats may have been the original reservoir[13]. For SARS-CoV-2, the bat is a likely natural reservoir, with pangolins potentially serving as intermediate hosts[14]. Horseshoe bat coronavirus (RaTG13) found in Yunnan province, China bears 96.2% sequence identity to SARS-CoV-2 isolated from patients in Wuhan city based on genome-wide comparison[11]; however, pangolin coronaviruses found in Guangdong are more similar in their receptor-binding domains[14]. Thus, while wet markets were implicated in the SARS epidemic[10] and suspected in the current pandemic[14]the illegal market for pangolins may be the proximal origin of COVID-19[15,14].

2.1.2. Currently Available Treatments

At the initiation of this protocol, there were no FDA-approved treatments for or vaccines against COVID-19, nor were there any for SARS or MERS. On May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized

[8] Lan J, Ge J, Yu J, Shan S, Zhou H, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020 Mar 30. doi: 10.1038/s41586-020-2180-5. [Epub ahead of print]

[9] WHO, 2020. Middle East respiratory syndrome coronavirus (MERS-CoV). Accessed 2020 April 3. https://www.who.int/emergencies/mers-cov/en/

[10] Xu RH, He JF, Evans MR, Peng GW, Field HE, et al. Epidemiologic clues to SARS origin in China. *Emerg Infect Dis*. 2004 Jun;10(6):1030-7.

[11] Zhou P, Yang XL, Wang XG, Hu B1, Zhang L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020 Mar;579(7798):270-273.

[12] Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*. 2003 Oct 10;302(5643):276-8.

[13] Kandeil A, Gomaa M, Nageh A, Shehata MM, Kayed AE, et al. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in dromedary camels in Africa and Middle East. *Viruses*. 2019 Aug 5;11(8). pii: E717.

[14] Lam TT, Shum MH, Zhu HC, Tong YG, Ni XB, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. *Nature*. 2020 Mar 26. doi: 10.1038/s41586-020-2169-0. [Epub ahead of print]

[15] Andersen KG, Rambaut A, Liplin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med.* 2020 Mar 17. https://doi.org/10.1038/s41591-020-0820-9. [Epub ahead of print]

with severe disease. While there is limited information known about the safety and effectiveness of using remdesivir to treat people in the hospital with COVID-19, the investigational drug was shown in a clinical trial to shorten the time to recovery in some patients.

Currently, there are multiple vaccines for the protection against and several mAbs available for the treatment and prophylaxis of COVID-19 that are available under emergency use authorization.

2.1.3. ADM03820 Development

ADM03820 drug product is being investigated for the treatment and prevention of COVID-19 in adults. ADM03820 is a 1:1 mixture of two human IgG1 non-competitive binding anti-SARS-CoV-2 antibodies, mAb2130 (YTE+LALA) and mAb2381 (YTE+LALA), individually expressed in a Chinese hamster ovary (CHO) cell line. Several amino acid changes in the Fc region have been incorporated into mAb2130 (YTE+LALA)and mAb2381 (YTE+LALA) to silence or reduce the effector function of antibodies. The LALA variant eliminates complement binding and fixation as well as Fc-γ dependent antibody-dependent cell-mediated cytotoxicity (ADCC) in both murine IgG2a and human IgG1[16]. The YTE mutation was also incorporated to extend circulating half-life of the antibodies[17]. RGS worked with Vanderbilt University Medical Center (VUMC), Just-Evotec, ATUM, and Seromyx to develop the ADM03820 anti-SARS-CoV-2 mAbs.

A GLP repeat dose toxicity study was performed to evaluate the safety of ADM03820 in rats when administered by intramuscular injection or intravenous infusion once weekly for three weeks and to evaluate toxicity and reversibility of effects after a 72-day recovery period.

2.1.4. Public Readiness and Emergency Preparedness Act

This protocol and the study product tested are covered under the Public Readiness and Emergency Preparedness (PREP) act. The PREP Act provides compensation to participants in the event of serious physical injury or death caused by covered drugs and vaccines, and liability protection for persons conducting the clinical trial and the manufacturer of the drug or vaccine.

The PREP act provides immunity for covered persons (such as Manufacturers, Distributers, Program planners and other qualified persons who prescribe, administer or dispense the study product) from tort liability, unless the injury was caused by willful misconduct.

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[16] Lo M, Kim HS, Tong RK, Bainbridge TW, Vernes J-M, Zhang Y, Lin YL, Chung S, Dennis MS, Zuchero YJY, Watts RJ, Couch JA, Meng YG, Atwal JK, Brezski RJ, Spiess C, Ernst JA. 2017. Effector-attenuating substitutions that maintain antibody stability and reduce toxicity in mice. *J Biol Chem* 292:3900 –3908. https://doi.org/10.1074/jbc.M116.767749.

[17] Yu XQ, Robbie GJ, Wu Y, Esser MT, Jensen K, Schwartz HI, et al. Safety, tolerability, and pharmacokinetics of MEDI4893, an investigational, extended-half-life, anti-staphylococcus aureus alpha-toxin human monoclonal antibody, in healthy adults. *Antimicrob Agents Chemother*. (2017) 61:e01020-16. doi: 10.1128/AAC.01020-16.

The PREP Act also authorized a "Covered Countermeasures Process Fund" to provide compensation to eligible individuals who suffer specified injuries from administration or use of a countermeasure pursuant to the declaration. Any requests for compensation must be filed within one year of administration or use of the countermeasure. Requests would go to the HRSA Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp). Compensation may then be available for medical benefits, lost wages and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from the administration and use of the study product must first seek compensation from the Covered Countermeasures Process Fund. A serious physical injury means an injury that is life threatening, results in, or requires medical or surgical intervention to prevent, permanent impairment of a body function or permanent damage to body structure. Any compensation will be reduced by public or private insurance or worker's compensation available to the injured individual.

If no funds have been appropriated to the compensation program, the Secretary does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the US District Court for the District of Columbia, but only if the claim involves willful misconduct, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, the individual does not have a tort claim that can be filed in a US Federal or a State court.

2.2. Rationale for Use of ADM03820

Antibodies from convalescent patients have been shown to lower or mediate the infectivity of the virus[18], and their presence in respiratory mucosa may also protect ACE2 receptor-presenting cells. Studies performed at VUMC showed that antibodies that block attachment of the virus to Hace2-presenting host cells by binding to the region of the receptor-binding domain of the S protein (SRBD) demonstrated neutralizing activity in a rapid screening assay with authentic SARS-CoV-2[19]. Further analysis demonstrated that the SARS-CoV-2 SRBD contained three major antigenic sites. By utilizing antibodies non-competitively binding to different antigenic

[18] Ou et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun.* 2020 Mar 27;11(1):1620.
[19] Crowe JE, Carnahan RH, Zost SJ, Gilchuk P, et al. Potently neutralizing human antibodies that block SARS-CoV-2 receptor binding and protect animals. *bioRxiv*. 2020 May 22. https://doi.org/10.1101/2020.05.22.111005. [Epub ahead of print]

sites the researchers were able to demonstrate synergistic response potentially lowering the dose of each mAb three-fold[19]. The long mean incubation time of the disease also provides a prolonged time for inactivation by circulating systemic antibodies. Therefore, there is a strong rationale for developing monoclonal antibodies (mAbs) derived from convalescent COVID-19 patient sera directed against S proteins, and perhaps a combination of multiple antibodies, some directed to the S1/S2 site.

ADM03820 is a 1:1 mixture of two human IgG1 non-competitive binding anti-SARS-CoV-2 antibodies, mAb2130 (YTE+LALA) and mAb2381 (YTE+LALA), individually expressed in a Chinese hamster ovary (CHO) cell line. Several amino acid changes in the Fc region have been incorporated into mAb2130 (YTE+LALA) and mAb2381 (YTE+LALA) to silence or reduce the effector function of antibodies. The LALA variant eliminates complement binding and fixation as well as Fc-γ dependent antibody-dependent cell-mediated cytotoxicity (ADCC) in both murine IgG2a and human IgG1.[16] The YTE mutation was also incorporated to extend circulating half-life of the antibodies.[17]

The proposed starting dose for ADM03820 dose escalation (150 mg IM) is based on previous toxicology studies, known safety profile of mAbs, and the expected potency of ADM03820. Based on the expected potency of ADM03820, the doses proposed for evaluation are anticipated to support PK analysis with microneutralization values ($TCID_{50}$) in therapeutic window for a prophylactic. Provided there are no safety concerns, dosing will escalate to 300 mg and 600 mg IM.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The potential risks to the subjects due to participation in the study are those related to venipuncture, the IM injection, the administration of ADM03820, and a theoretical possibility of enhanced disease by antibody-dependent enhancement (ADE).

Venipuncture

Venipuncture causes transient discomfort and may cause fainting. Bruising at the site of the venipuncture may occur but can be prevented or lessened by applying pressure for several minutes. Infection at the site is possible but highly unlikely as aseptic technique must be employed.

IM Injection

An IM injection may cause some discomfort at the injection site. Other risks may include pain, redness, swelling, or warmth at the injection site. These risks are minimal.

An IM injection into the gluteus medius may cause sciatic nerve damage, bleeding, hematoma, or infection.

Effects of ADM03820

As ADM03820 has not been administered to humans, the potential risks are primarily based on adverse events associated with administration of other antibody products, especially infusion reactions.

Immunogenicity, the elicitation of antibodies directed against ADM03820 may occur following injection. ADM03820 is a combination of two human IgG1 antibodies, which based on experience with other humanized or chimeric mAbs, reduces the immunogenic potential.

ADE of virus infection of cells or disease in animal models occurs with other coronaviruses. Low levels of antibody directed against SARS-CoV-2 may increase virus infection of human cells cultured in the laboratory. Some studies have shown that administration of antibodies directed against SARS-CoV-2 can increase the severity of disease or levels of the virus in challenged animals. Although ADE of SARS-CoV-2 infection or COVID-19 has not been shown to occur in humans, the LALA mutation in ADM03820, by reducing potential Fc-receptor binding of ADM03820-SARS-CoV-2 complexes, may mitigate this potential risk.[20]

2.3.2. Known Potential Benefits

This trial has no benefit for the subjects participating in the trial. The knowledge gained in this trial may help society, especially those exposed to, or at risk of being exposed to COVID-19.

3. OBJECTIVES

3.1. Study Objectives

Primary Objective:

- To assess the safety and tolerability of different doses of ADM03820 in healthy adult subjects.

Secondary Objective:

- To assess the pharmacokinetic (PK) and immunogenicity of different doses of ADM03820 in healthy adult subjects.

3.2. Study Outcome Measures

3.2.1. Primary Endpoints

- The occurrence of Serious Adverse Events following administration of ADM03820 to the final follow-up visit.
- The occurrence of Adverse Events from administration of ADM03820 to the final follow-up visit.

[20] Eroshenko, N., Gill, T., Keaveney, M. Church, et al. , Implications of Antibody-Dependent Enhancement of Infection for SARA-CoV-2 Countermeasures. *Nature biotechnology.* 05 June 2020. https://www.nature.com/articles/s41587-020-0577-1

- The occurrence of changes from baseline in physical examination, vital signs and clinical safety laboratory values following administration of ADM03820 to the final follow-up visit.

3.2.2. Secondary Endpoints

- The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. The assessment of C_{max}, T_{max} and $AUC_{(0-t)}$ for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3, Cohort 4, and Cohort 5.
  - Pharmacokinetic samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose, and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts
  - Samples will be tested by Microneutralization at pre-dose and Days 2, 15, 30, 60, 90, 120, 150, and 180 for all cohorts
- Samples will be tested by Electrochemiluminescence Assay (ECLA) to evaluate presence of anti-drug antibodies (ADA) collected for all cohorts.
  - ADA samples will be tested at pre-dose, and Day 15, 30, 45, 60, 90, 120, 150, 180, 365 for all cohorts
- Incidence of the first case of SARS-SoV-2 RT-PCR positive symptomatic illness occurring after dosing through Day 365
- Incidence of SARS-CoV-2 RT-PCR positive severe or critical symptomatic illness occurring after dosing through Day 365
- Incidence of COVID-19 related Emergency Department visits occurring after dosing through Day 365

4. STUDY DESIGN

This is a Phase 1, randomized, double-blind, placebo-controlled study of five dose cohorts to evaluate the safety, tolerability, and immunogenicity of ADM03820 in healthy adults. This is a first-in-human study and each subject will receive a single dose of ADM03820 or placebo.

The study will randomize a total of 50 healthy subjects to receive an intramuscular (IM) injection of either ADM03820 or placebo.

Table 1: Cohorts

Cohort	Dose of ADM03820	Number of Subjects
1	150 mg IM injection	10 subjects (8 active, 2 placebo)
2	300 mg IM injection	10 subjects (8 active, 2 placebo)

3	300 mg IM injection	10 subjects (8 active, 2 placebo)
4	300 mg IM injection	10 subjects (8 active, 2 placebo)
5	600 mg IM injection	10 subjects (8 active, 2 placebo)

Schedule for Subjects

Subjects in cohorts 1-4 will participate in the study for approximately 554 days, including a 14-day screening period. Subjects in cohort 5 will participate in the study for approximately 379 days, including a 14-day screening period. All subjects in the study will have a 24-hour stay in the clinic after dosing is complete to ensure that no hypersensitivities or safety signals occur. Follow-up outpatient visits for all cohorts will occur on Days 3, 4, 8, 15, 30, 45, 60, 90,120, 150, 180, and 365 with cohorts 1-4 having additional telephone visits on Days 450 and 540. The last outpatient follow up visit is scheduled at Day 365. The end of the study is defined as the date of the last visit of the last subject in the study.

There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 – 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in Cohorts 1-3 complete Day 60. A third interim analysis is planned to analyze safety and PK after all subjects in cohort 5 complete Day 60.

There is also an interim clinical study report (CSR) planned after subjects in Cohorts 1 through 4 complete Day 90.

Schedule for Cohorts

Since this is a first-in-human study, administration of the study products to subjects in cohorts 1, 2 and 5 will occur to allow careful observation of individuals for adverse events. Two sentinel subjects within each cohort will be admitted and administered a dose on Day 1 to remain in the clinic until Day 2. The randomization scheme will be designed to ensure that one subject will receive ADM03820 and the other will receive placebo. The IM dosing of the remaining subjects within cohorts 1, 2, and 5 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria, and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects within each specific cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. An alternate subject will be admitted to the unit for each two-subject group. Dose escalation will not occur until safety data through Day 8 is reviewed by the SRC.

Cohort 1 (150 mg IM injection) will be dosed first. Two sentinel subjects (one ADM03820 and one placebo) will each be administered a single 3 mL IM injection. The dosing of the next subjects within Cohort 1 will not be initiated until at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the

opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed.

Dose escalation to Cohort 2 will not occur until safety data through day 8 for Cohort 1 is reviewed by the SRC. Objective dose escalation criteria and safety evaluations will be utilized.

In Cohort 2 (300 mg IM injection), two sentinel subjects (one ADM03820 and one placebo) will each be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 2 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed.

Dosing for Cohort 3 (300 mg IM injection) will not occur until safety data through day 8 for Cohort 2 is reviewed by the SRC. Objective safety evaluations will be utilized. Subjects in Cohort 3 will be scheduled based on the SRC recommendation and will each be administered two 3 mL IM injections without delay.

Dosing for Cohort 4 (300mg IM injection of drug product concentrated at 100mg/mL) will occur without delay. Subjects in Cohort 4 will be administered a single 3mL IM injection.

In Cohort 5 (600 mg IM injection of drug product concentrated at 100mg/mL), two sentinel subjects (one ADM03820 and one placebo) will each be administered two 3 mL IM injections. Dosing for the remaining subjects in Cohort 5 will be initiated after at least 48 hours have passed and no adverse events have occurred that meet halting criteria and no safety signals have occurred that in the opinion of the investigator warrant further investigation. The remaining subjects in the cohort will be dosed at least four hours apart until all subjects in the cohort have been dosed. The SRC will review safety data through day 8 for subjects in cohort 5 prior to the initiation of the phase 2 protocol.

5. STUDY ENROLLMENT AND WITHDRAWAL

Only subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study. Exemptions may be granted on Inclusion/Exclusion Criteria pending Medical Lead Approval.

This study will enroll fifty healthy male and female subjects ages 18 to 55 years old in five cohorts.

Alternates who meet all eligibility criteria may effectively have their check-in at the same time as the lead two subjects and be rolled over into the next group within that cohort but will not be dosed until dosing for that cohort begins. Alternates not enrolled into the cohort are eligible for enrollment in subsequent cohorts but would have to undergo re-screening if more than 14 days have passed since their initial screening visit.

5.1. Subject Inclusion Criteria

All must be answered yes for the subject to be eligible for study participation

1. Informed consent understood and signed
2. Healthy male or healthy, non-pregnant, non-lactating female
3. Willingness to comply and be available for all protocol procedures for the duration of the study
4. Between 18 and 55 years of age on the day of dosing
5. Body Mass Index (BMI) of ≥18.5 and ≤35 kg/m^2
6. Female subjects of childbearing potential must have a negative serum pregnancy test at screening and negative urine test on Day 1 prior to dosing
    - Note: A woman is considered of childbearing potential unless post-menopausal (≥ 1 year without menses or without other known or suspected cause and appropriately elevated FSH) or surgically sterilized via bilateral oophorectomy or hysterectomy
7. Females of childbearing potential and males agree to use acceptable contraception for the duration of the study.
    - Note: These include progestin implants, intrauterine devices (IUDs), surgical (hysterectomy or tubal ligation; vasectomy) or abstinence. Use of methods such as progestin injectables, combined oral hormonal contraceptives, condoms, and diaphragms will not be acceptable when used alone, but they could be considered, if used in combination with another method (for example, a female using combined oral contraceptives if her male partner is sterile, or if she and her non-sterile male partner use a double-barrier method), after consultation with the RGS ML. All males will be required to use a barrier method (condoms) for the duration of the study
8. Screening laboratory tests are within normal ranges or outside the normal ranges and considered not clinically significant by the Principal Investigator
    - If urinalysis by dipstick is abnormal, a complete urinalysis with microscopic evaluation will be performed and the results will supersede the results of the dipstick for blood, glucose, and protein.
    - Menstruating females failing inclusion criteria due to positive blood on urine test may be retested following cessation of menses.
    - Other laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or collection or laboratory error may be repeated once.
9. The urine drug screen is negative
10. Breathalyzer test or blood/saliva alcohol test is negative and subjects agrees to abstain from alcohol consumption for a period of 2 days prior to dosing and 2 days prior to any study visit
11. Agree to minimize risk of SARS-CoV-2 infection

5.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for participation.

All must be answered no for the subject to be eligible for study participation

1. History of a chronic medical condition that would either interfere with the accurate assessment of the objectives of the study or increase the risk profile of the subject.
2. Subjects with cardiovascular disease
3. Subjects with diabetes
4. Subjects with pulmonary diseases such as COPD or asthma
5. History of severe allergic reaction of any type to medications, bee stings, food, or environmental factors or hypersensitivity or reaction to immunoglobulins.
6. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds)
7. Clinically significant abnormal electrocardiogram at screening.
    - Note: Clinically significant abnormal ECG results include but not limited to: complete left or right bundle branch block; other ventricular conduction block; 2nd degree or 3rd degree atrioventricular (AV) block; sustained ventricular arrhythmia; sustained atrial arrhythmia; two Premature Ventricular Contractions in a row; pattern of ST elevation felt consistent with cardiac ischemia; or any condition deemed clinically significant by a study investigator
    - Incomplete right bundle branch block is not exclusionary if there are no abnormal ECG findings and there is no clinical history or evidence on physical examination to indicate cardiac disease.
8. Positive serology results for HIV, HbsAg, or HCV antibodies
9. Febrile illness with temperature ≥38°C within 7 days of dosing
10. Female subject is pregnant or breastfeeding
11. Donated blood or plasma within 56 days of enrollment
12. Known allergic reactions to any of the study product components present in the formulation or in the processing, as listed in the Investigator Brochure
13. Treatment with another investigational drug within 28 days of dosing
14. Treatment with a monoclonal antibody within 3 months of enrollment.
15. Positive serology results for SARS-CoV-2 antibodies (Not applicable for Cohort 5).
16. Positive results from a reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-Co-V-2

17. Receipt of antibody (e.g. TIG, VZIG, IVIG, IM gamma globulin) or blood transfusion within 6 months or within 5 half-lives of the specific product given
18. Active drug or alcohol use disorder or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements
19. Use of H1 antihistamines or beta-blockers within 5 days of dosing
20. Use of any prohibited medication within 28 days prior to screening or planned use during the study period
    - Note: Prohibited medications include immunosuppressives (except Nonsteroidal Anti-Inflammatory Drugs [NSAIDS]); immune modulators; oral corticosteroids (topical/intranasal steroids are acceptable); anti-neoplastic agents
21. Any specific condition that in the judgment of the investigator precludes participation because it could affect subject safety
22. Plans to enroll or is already enrolled in another clinical trial* that could interfere with safety assessment of the investigational product at any time during the study period
    - Note: Includes trials that have a study intervention such as a drug, biologic, or device
23. Is a study site employee or staff
    - Note: Site employees or staff include the Pis and sub-investigators or staff who are supervised by the PI or Sub-Investigators
24. Received an approved COVID-19 vaccine (subjects can receive an approved COVID-19 vaccine after completing their Day 90 visit. For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

Randomized treatment assignments will be generated by a statistician at ICON. Randomization will occur following admittance to the unit and confirmation of eligibility is confirmed.

This is a Phase 1 double-blinded, placebo-controlled trial that will randomize subjects within five dosing cohorts to either active or placebo.

Cohorts 1, 2, and 5

For cohorts 1, 2, and 5, the first two subjects will be randomized in a 1:1 fashion to active and placebo to ensure that one of the first two subjects receives active treatment and the other control. An alternate subject will be admitted to the unit for each two-subject group. If one of the first two subjects is not randomized for any reason, then the alternate subject will receive the next consecutive randomization number. The product assignment of the remaining subjects in each cohort will follow a 7:1 randomization of active to placebo, respectively. The randomization list will be generated by the unblinded study biostatistician and uploaded to IRT

system by vendor (4G Clinical). Upon confirming eligibility of subjects, site research personnel will randomize subjects then the unblinded study pharmacist will be notified of treatment allocation via system-generated email.

Cohort 3 and 4

Subjects in cohort 3 and 4 will be randomized in a 4:1 ratio of active to placebo. The randomization list will be generated by the unblinded study biostatistician and uploaded to IRT system by vendor (4G Clinical). Upon confirming eligibility of subjects, site research personnel will randomize subjects then the unblinded study pharmacist will be notified of treatment allocation via system-generated email.

5.3.2. Masking Procedures

The study staff participating in the administration of study product and assessment of the subjects will not be aware of the contents of the vial. The ADM03820 and placebo will look identical, so the study staff and the subject will not be able to determine whether placebo or ADM03820 is being injected.

The Investigator may unblind a subject's treatment assignment only in the case of an emergency or SAE, when knowledge of the study treatment is essential to the appropriate clinical management or welfare of the subject. Whenever possible, the Investigator should first discuss the options with the ICON GPHS Medical Monitor and the RGS ML or appropriately designated RGS personnel before unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify the ICON GPHS Medical Monitor and RGS as soon as possible but without revealing the subject's treatment assignment. The date and reason for unblinding must be recorded on the SAE form.

5.3.3. Reasons for Withdrawal

A subject may withdraw from the study at any time for any reason, without any consequence.

A study subject will be discontinued from participation in the study if any of the following reasons occur prior to dosing:

- Development of any exclusion criteria;
- Request by the subject to terminate participation;
- Requirement for prohibited concomitant medication or treatment;

A subject may be removed from the study for the following reasons post dosing; however, whenever possible the subject should be followed for safety per protocol:

- Failure to adhere to the protocol requirements
- Lost to follow-up;
- Request of primary care provider;

- At the request of the Institutional Review Board (IRB)/Ethics committee, Food and Drug Administration (FDA), or DOD;
- The subject's well-being based on the opinion of the investigator;
- The occurrence of a Serious Adverse Event (SAE) or (AE warranting withdrawal).

5.3.4. Handling of Withdrawals

Subjects who are withdrawn prior to dosing must be replaced.

Following dosing, one subject per cohort may withdraw prior to the completion of Visit 11 (day 60) or was noncompliant with all PK draws through Visit 6 (day 4) without being replaced.

If 4 or more subjects withdraw, are lost to follow up or terminate prior to Day 8 within a cohort, at least one of those subjects need to be replaced to ensure that data for at least 7 subjects are available for review.

If 4 or more subjects withdraw, are lost to follow up or terminate on or after Day 8 but prior to Day 60 or are not compliant with all PK draws through Day 15 within a cohort, they should be replaced.

If more than 4 subjects withdraw, are lost to follow up or terminate following the Day 8 SRC review of safety data within a cohort, the site will attempt to replace those subjects in that dose group at the time of the next planned cohort.

All replaced subjects will be assigned to the same treatment assignment as the subject they are replacing. This will be documented in the source documents and eCRFs.

5.3.5. Lost to Follow-up

In the case of subjects who fail to appear for a follow-up assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mail, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subjects' records.

5.3.6. Termination of Study

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

6. STUDY PRODUCTS

6.1. Description of Study Products

ADM03820 is a 1:1 mixture of two human IgG1 non-competitive anti-SARS-CoV-2 antibodies formulated as 50 mg/mL or 100 mg/mL strength solutions in a 2 mL vial for IM administration. The drug product is a clear to opalescent, slightly colored, sterile aqueous solution at Ph 6. ADM03820 is formulated in 141 Mm L-arginine, 10 Mm sodium succinate buffer, with 0.25% v/v Polysorbate 80 and is filled as 1.2 mL in a 2 mL vial (50 mg/mL) or 1.7 mL in a 2 mL vial (100 mg/mL).

Placebo is 0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection.

6.2. Acquisition

The ADM03820 will be supplied by Resilience Government Services (Previously Ology Bioservices, Inc.) Study product will be shipped to the site.

The normal saline for injection will be supplied by the study site.

6.3. Formulation, Packaging, and Labeling

ADM03820

ADM03820 is a 1:1 mixture of two human IgG1 non-competitive anti-SARS-CoV-2 antibodies formulated as 50 mg/mL or 100 mg/mL strength solutions in a 2 mL vial for IM administration. The drug product is a clear to opalescent, slightly colored, sterile aqueous solution at Ph 6. ADM03820 is formulated in 141 Mm L-arginine, 10 Mm sodium succinate buffer, with 0.25% v/v Polysorbate 80 and is filled as 1.2 mL in a 2 mL vial (50 mg/mL) or 1.7 mL in a 2 mL vial (100 mg/mL).

The drug product will be supplied in 2-mL, pyrogen-free, Type 1 glass vials fitted with Teflon-coated butyl rubber stoppers and flip-up aluminum seals.

ADM03820 will be administered by intramuscular (IM) injection as follows: 150 mg (Cohort 1 as 1 x 3 mL IM injection) or 300 mg (Cohorts 2 and 3 as 2 x 3 mL IM injections or Cohort 4 as 1 x 3mL IM injection) or 600 mg (Cohort 5 as 2 x 3 mL IM injections).

Placebo (Normal Saline, 0.9% Sodium Chloride, USP)

0.9% Sodium Chloride Injection, USP is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. Each mL contains sodium chloride 9 mg and contains no preservatives, bacteriostatic, antimicrobial agent, or added buffer. The solution is clear in appearance with a Ph range of 4.5 to 7.0.

Placebo will be administered by intramuscular (IM) injection as follows: 150 mg (Cohort 1 as 1 x 3 mL IM injection) or 300 mg (Cohorts 2 and 3 as 2 x 3 mL IM injections or Cohort 4 as 1 x 3mL IM injection) or 600 mg (Cohort 5 as 2 x 3 mL IM injections).

6.4. Product Storage and Stability

ADM03820

Cohorts 1-3

ADM03820 drug product (50mg/mL) will be shipped frozen and should be stored at -90°C to -70°C until time of preparation. If a vial is removed from the freezer it must be used within 1 hour of thawing. If not used, it must be quarantined and maintained for study product accountability as per Section 6.6. ADM03820 should be protected from direct sunlight.

ADM03820 is not light sensitive under normal shipping and storage conditions. Avoid vigorous shaking or agitation.

Cohorts 4 and 5 Only

ADM03820 (100mg/mL) drug product will be shipped and should be stored at 2°C to 8°C until time of preparation. If a vial is removed from the refrigerator it must be used within 30 minutes. If not used, it must be quarantined and maintained for study product accountability as per Section 10.5. ADM03820 should be protected from direct sunlight. ADM03820 is not light sensitive under normal shipping and storage conditions. Avoid vigorous shaking or agitation.

Placebo (Normal Saline, 0.9% Sodium Chloride, USP)

Store at 20ºC to 25ºC (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°F and 86°F) are permitted]. Protect from freezing.

6.5. Dosage, Preparation and Administration

The unblinded site Research Pharmacist will prepare the study drug on the same day as administration. Prior to using any of the parenteral products, inspect for discoloration or particulate matter before use. Any product that fails inspection should be quarantined at 2-8°C for inspection by the Sponsor. Preparation of the product will be performed using aseptic technique under a sterile environment (e.g., Biologic Safety Cabinet or laminar flow hood). Based on the subject assigned cohort randomization, the appropriate ADM03820 dose will be calculated, and the appropriate number of vials will be removed from storage to prepare for dosing. Vials containing ADM03820 should not be vigorously shaken. Any unused portion left in the vial should be retained for study product accountability as per Section 6.6. The placebo will be normal saline, 0.9% sodium chloride.

The subjects will be admitted to the Phase 1 unit the day of the planned dosing. Verification that the subject still meets all inclusion criteria and does not have any exclusion criteria must be made prior to randomization. The unblinded site Research Pharmacist will prepare the dose as described. Administration of the IM dose of ADM03820 or placebo should be injected into the gluteus medius (see Appendix C) and must be completed within 30 minutes of preparation.

6.6. Accountability Procedures for the Study Products

The Site Principal Investigator is responsible for the distribution and disposition of study product (both ADM03820 and placebo) and has ultimate responsibility for accountability. The site Principal Investigator may delegate this responsibility to the unblinded site Research Pharmacist. If delegated, the site Research Pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, temperature monitoring, and storage conditions, and final disposition of the study product.

All study products, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. Used and unused ADM03820 vials and placebo vials will be retained until monitored and released for disposition as per requirements.

Upon completion of the study and after the final monitoring visit, any remaining unused study product will either be returned or destroyed appropriately at the clinical site as per sponsor requirements and instructions, or in accordance with disposition plans.

6.7. Assessment of Subject Compliance with Study Product

Because each dose of ADM03820 will be administered by site personnel, subject compliance is not anticipated to be an issue.

6.8. Concomitant Medications

Concomitant medication information will be recorded at Screening for the prior 28 days. At each subsequent study visit each new concomitant medication and changes to existing medications will be recorded. Subjects will be required not to utilize non-study medication or herbal supplements during the study except those deemed necessary by the site PI or sub investigator. Any drug (e.g., over-the-counter herbal supplement, vitamins or prescription) used by the subject during the course of the trial will be recorded in the subject's source documents and on the appropriate Ecrf.

Subjects will be instructed to refrain from the receipt of any of the following during study participation unless medically indicated and deemed immediately necessary by their private physician:

- Blood or blood products,
- Any antibody (e.g. TIG, VZIG, IVIG, IM gamma globulin)
- Monoclonal antibody
- H1 antihistamines (PRN use of H1 antihistamines may be acceptable after Medical Lead/Medical Monitor approval)
- Beta-blockers
- Immunosuppressives (except NSAIDS)
- Oral corticosteroids (topical/intranasal steroids are acceptable)
- Anti-neoplastic agents

7. STUDY PROCEDURES

7.1. Medical History and COVID-19 Instruction

Medical history will be obtained by direct interview. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat (HEENT), mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, and autoimmune disease will be solicited. The medical history will include current and past medical diagnoses, hospitalizations and major surgical procedures.

Demographic information (date of birth, gender, race, ethnicity) will be obtained as part of the medical history assessment. The medical history will be obtained at screening, updated upon admittance to the unit on Day 1, and entered appropriately into the EDC using the CTCAE grading scale.

Because ADE is still being studied, subjects will be instructed to minimize the risk of SARS-CoV-2 infection. A printed fact sheet from the Centers for Disease Control website "How to Protect Yourself & Others" (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) will be distributed to all study participants and its content reviewed with them by study staff. If a subject acquires COVID-19 during their participation in the study, they should seek and obtain the appropriate treatment.

7.2. Physical Examination

An abbreviated physical examination (PE) will be conducted at the screening visit and Day 1. Height and weight will be obtained at screening. An abbreviated PE is distinguished from a complete PE as all body system assessments are not required (e.g., pelvic, rectal, etc.). On Day 1, the PE will focus assessment for the presence of the following in order to detect signs of a hypersensitivity reaction:

- General appearance including alertness, diaphoresis, chills, and any difficulty breathing.
- HEENT (confirm no swelling of lips/tongue/uvula)
- Chest (confirm no stridor or wheezing)
- Heart (assess regularity of rhythm)
- Skin (confirm no hives, examine for any eruptions)
- Joints (confirm no swelling, warmth, or tenderness)

A symptom- directed PE will be performed at all other in-clinic study visits. Refer to the MOP for further details on the symptom directed PE. Any new findings on examination post dosing or worsening of existing conditions are to be reported as Aes.

7.3. Vital Signs

Vital sign assessments including systolic and diastolic blood pressure (BP) [measured after sitting for at least 10 minutes], heart rate (HR), respiratory rate, and oral temperature will be performed at each in-clinic study visit. Vital signs that are thought to be aberrant due to an error in measurement may be repeated. During screening and follow-up, a measurement that is a Grade 1 (as referenced in Appendix B by CTCAE version 5.0) may be repeated once if the PI believes a transient condition led to the aberrant value.

Vital signs obtained at screening will serve as baseline values for the subject. Grade 1 values are allowable unless deemed clinically significant by the study investigator.

7.4. Electrocardiogram

A 12-lead ECG will be performed at screening and reviewed by the study PI or a co-Investigator to assess the cardiac status of a subject for eligibility for enrollment. ECGs will be performed after the subject rests quietly in a supine position for at least 10 minutes. To be eligible for participation, the QT interval should be ≤450ms, and there must be no clinically significant ECG abnormalities according to the study investigators and may be repeated once. A 12-lead ECG will also be performed after a subject has been dosed.

7.5. Laboratory Evaluations

Venipuncture schedule and volumes are displayed in Table 2.

7.5.1. Screening Laboratory Tests

7.5.1.1. Viral Serology Testing

Subjects will be screened for HIV, HbsAg, and antibody to HCV. These tests must be negative for eligibility into the study. In cases where a false positive result is suspected, confirmatory testing may be performed (e.g., Polymerase Chain Reaction).

Subjects will be screened for SARS-CoV-2 antibodies as well as a reverse transcriptase polymerase chain reaction test for SARS-Co-V-2. These tests must be negative for eligibility into the study.

7.5.1.2. Drug Screen

A urine toxicology screen will be performed to detect for the presence of the following: cocaine (and metabolite), barbiturates, benzodiazepines, opiates, THC, methamphetamine/amphetamine, methadone and PCP. The results must be negative for eligibility into the study. A breathalyzer test or blood/saliva alcohol test will also be performed, and results must be negative for eligibility into the study.

7.5.1.3. Pregnancy Testing

For women of child-bearing potential, a serum pregnancy test will be done at screening and must be negative. A urine pregnancy test will be done at Visit 2 (Day 1), which must be reported as negative before dosing. A urine pregnancy test will be repeated on Day 4, Day 45, Day 120, 150, Day 180, and 365.

7.5.1.4. Screening Laboratory Tests

The following laboratory tests will be performed at screening:

- Hematology: hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded.

- Chemistry: serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
- Urinalysis: dipstick: Urine protein, blood and glucose must be negative or trace. Menstruating females failing with a positive blood on urine dipstick may be retested following cessation of menses. If dipstick is abnormal, a complete urinalysis with microscopic will be performed. When a urine dipstick is more than trace positive for blood (whether a menstruating female or other subject), that subject would not be excluded if the urine microscopic exam shows <5 RBC/HPF.
- FSH to confirm post-menopausal status for women ≥ 1 year without menses

Laboratory values that are outside the range of eligibility but are thought to be due to an acute condition or due to laboratory error may be repeated once. Laboratory values will be entered in the Clinical Labs Ecrf.

7.5.2. Safety Laboratory Tests

The following laboratory tests will be performed at Days 8, 15, 30, 90, 180, and 365.

Safety labs with a mild Grade 1 value will not exclude a subject from participation but will serve as their baseline value.

- Hematology: hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded.
- Chemistry: serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
- Urinalysis: dipstick: Urine protein, blood and glucose must be negative or trace. Menstruating females failing with positive blood on urine dipstick may be retested following cessation of menses.

7.5.3. Hypersensitivity Panel

A hypersensitivity panel includes cytokine and complement panels, IgE and tryptase. This 14 mL sample will be drawn on Day 1 prior to dosing. The sample will be processed only if the subject has a hypersensitivity reaction. If a subject develops anaphylaxis or anaphylactoid reaction, an additional 10 mL sample will be drawn during the event and another will be drawn after the event. Refer to the Manual of Procedures for further details.

7.6. Special Assays or Procedures

7.6.1. Pharmacokinetic Assay

Six-mL of blood will be drawn for the analysis of levels of monoclonal antibodies in serum using a validated ELISA. For each timepoint, aliquot at least 0.50 mL each of serum into three 1.8 mL sterile cryogenic vials, freeze and store serum samples at ≤ -70°C until shipment.

PK samples will be tested by ELISA at pre-dose, 2, 4, 8, and 24 hours post dose and on Days 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365.

7.6.2. Microneutralization Assay

Three ten-mL samples of blood will be drawn to be analyzed for neutralizing antibody concentration using the validated Battelle microneutralization assay. For each timepoint, aliquot 2.5 mL each of serum into six sterile cryogenic vials, freeze and store serum samples at ≤ -70°C until shipment.

Samples will be tested by Microneutralization at pre-dose and Days 2, 15, 30, 60, 90, 120, 150, and Day 180 for all cohorts.

7.6.3. Immunogenicity / Anti-Drug Antibody Assay

Six-mL samples of blood will be drawn at pre-dose and on Days 15, 30,45,60, 90, 120, 150, 180, and 365 for determining the presence of ADA using validated ECLA methods that detect anti-mAb2130 and anti-mAb2381 antibodies in serum. This will be done to assess immunogenicity. For each timepoint, aliquot at least 0.50 mL each of serum into three 1.8 mL sterile cryogenic vials, freeze and store serum samples at ≤ -70°C until shipment

7.6.4. RT-PCR Testing for SARS-CoV-2

A nasopharyngeal swab specimen will be collected for RT-PCR testing for SARS-CoV-2 at screening and upon presentation of COVID-19 symptoms. If a subject acquires COVID-19 during their participation in the study, they should seek and obtain the appropriate treatment.

7.6.5. Future Use

Five-mL samples of blood will be drawn for subjects who consent to have samples stored for future use. These samples will be collected at Days 1, 2, 8 and 30. For each timepoint, aliquot at least 0.25mL each of serum into two (2) 1.8mL sterile cryogenic vials, freeze and store serum samples at ≤ -70°C until shipment.

This blood sample may be used in new or different laboratory tests, to provide information for the development of new drug products, or for the studies of SARS-Co-V-2 or other infections.

7.6.6. Specimen Preparation, Handling, and Shipping

Details regarding the specimen preparation, handling, storage, and shipping are described in the MOP.

Table 2: Laboratory Samples and Estimated Total Blood Volume (mL)

Study Visit	Screen 01	Baseline/ Dose 02	Discharge 03	04	05	06	07	08	09	10	11	12	13	14	Last outpatient visit 15	Total
Study Day	-14 to -2	1	2	3	4	8 ±2	15 ±2	30 ±2	45 ±3	60 ±3	90 ±3	120 ±3	150 ±3	180 ±3	365 ±3	
Dosing		X														
HIV, HBV,HCV Serum β-HCG	4															4
Screening Labs	9															9
Safety Labs						9	9	9			9			9	9	54
PK		24[a]	6	6	6	6	6	6	6	6	6	6	6	6	6	102
MN		30	30				30	30		30	30	30	30	30		270
SARS-CoV-2 antibodies	2															2
ADA		6					6	6	6	6	6	6	6	6	6	60
Future Use[c]		10	5			5		5								25
Hypersen-sitivity panel		14[b]														14
Total Volume/ Visit	15	84	41	6	6	20	51	56	12	42	51	42	42	51	21	540
Cumulative Total[d]	15	99	140	146	152	172	223	279	291	333	384	426	468	519	540	

[a] PK serum samples taken prior to injection and 2hr, 4hr, 8hr

[b] If a subject develops anaphylaxis or anaphylactoid reaction, an additional 14mL will be drawn during the event and after the event. In this instance an additional 30 mL may be drawn from a subject than is reflected in the table totals.

[c] For subjects consenting to future use

[d] Total estimated volume drawn will vary slightly depending on future use consent and need for additional draws for the occurrence of hypersensitivity

8. STUDY SCHEDULE

The Schedule of Events is included as Appendix A.

8.1. Visit 1: Screening (Day -14 to Day -2)

After providing written informed consent, each subject will be assigned a Subject ID number (840-XXX-XXX) and undergo an eligibility assessment. The following will be done during the screening period (within 14 days prior to administration of study product). Results of screening tests and procedures will be evaluated by the investigator to determine eligibility prior to enrollment and randomization. The following procedures will be performed.

- Record demographics including age, gender, race and ethnicity. Obtain contact information.
- Obtain medical history. The medical history will include the following:
  - current medical diagnoses
  - past medical diagnoses
  - hospitalizations
  - major surgical procedures
  - blood transfusions or immunoglobulin within the last 6 months
  - live vaccines within the last 28 days
  - killed vaccines within the last 28 days
  - blood or plasma donation within the last 56 days
  - allergic reactions
  - drug and/or alcohol use disorder or dependence
  - receipt of investigational drug within the last 28 days
  - Receipt of monoclonal antibody in the past
- Documentation that the subject has not received an FDA approved vaccine for COVID-19 (Subjects may receive an approved COVID-19 vaccine after completing their Day 90 visit). For Cohort 5, subjects who received a COVID-19 vaccine within 14 days prior to enrollment are excluded.
- Review concomitant medication history, including all medications taken within the last 28 days
- Review current use of contraceptive methods and recent menstrual history (female subjects only)

- Perform abbreviated PE by licensed clinician listed on the Form FDA 1572 [examples include Medical Doctor, Nurse Practitioner and Physician's Assistant]
- Obtain height and weight and calculate BMI
- Take vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature)
- Obtain fasting blood samples for viral serology, clinical laboratory screening tests including SARS-CoV-2 antibodies and RT-PCR for SARS-Co-V-2
- Obtain blood sample for serum pregnancy test for women of childbearing potential
- Obtain urine sample for dipstick urinalysis and urine toxicology
- Obtain 12-lead ECG
- Perform Breathalyzer test or blood/saliva alcohol test for recent alcohol use
- Counsel both men and women of childbearing potential on the avoidance of pregnancy
- Distribute fact sheet from the Centers for Disease Control website "How to Protect Yourself & Others" (https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html) and review its content with the subject
- If screening occurs during influenza season, encourage subject to obtain licensed (nonliving) influenza vaccine at least 14 days prior to scheduled dosing or after Day 60 on study. Of note, the subject is not prohibited from receiving an influenza vaccine while on study, however the above restrictions are highly encouraged.

8.2. Visit 2: Baseline / Day of Dosing (Day 1)

Subjects meeting inclusion/exclusion criteria will be admitted to the clinical unit the day of injection and the following procedures will be performed prior to the study drug administration:

Prior to Dosing

- Review inclusion/exclusion to confirm eligibility
- Review CDC fact sheet on prevention of COVID-19 with subject
- Review and update concomitant medications and medical history
- Obtain vital signs
- Perform abbreviated physical examination with focused assessment for the presence of the following in order to detect signs of a hypersensitivity reaction:
  - General appearance including alertness, diaphoresis, chills, and any difficulty breathing.

  - HEENT (confirm no swelling of lips/tongue/uvula)
  - Chest (confirm no stridor or wheezing)
  - Heart (assess regularity of rhythm)
  - Skin (confirm no hives, examine for any eruptions)
  - Joints (confirm no swelling, warmth, or tenderness)
- Perform Breathalyzer test or blood/saliva alcohol test to detect recent alcohol use
- Obtain urine sample for toxicology
- For women, a urine Hcg test will be done. The results must be confirmed to be negative before dosing
- Obtain blood samples for baseline serum PK and future use (for subjects who consent)
- Obtain blood sample for ADA
- Obtain blood sample for MN
- Obtain blood sample for RT-PCR testing
- Obtain blood sample for hypersensitivity panel
- Randomize the subject
- Obtain study product from the pharmacy
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

<u>During Dosing</u>

- Study product should be injected into the gluteus medius (see Appendix C). First divide the buttock in half from top to bottom and then in half from side to side. The injection should be given in the upper outer quarter.
- A study physician should be present at the time of study drug administration and the subject will be under direct observation during at least the initial 30 minutes after the injection by clinical study staff. The study staff should observe the subject closely for signs and symptoms of anaphylaxis and anaphylactoid type reactions. Should an adverse reaction of this type occur, the subject will be treated using the standard protocol at the site
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) 15 (±3) minutes after the injection is completed.
- Perform an abbreviated PE at 30 (±5) minutes post injection or in response to subject symptoms focusing on signs of anaphylaxis as follows:

  - General appearance including alertness, diaphoresis, chills, and any difficulty breathing.
  - HEENT (confirm no swelling of lips/tongue/uvula)
  - Chest (confirm no stridor or wheezing)
  - Heart (assess regularity of rhythm)
  - Skin (confirm no hives, examine for any eruptions)
  - Joints (confirm no swelling, warmth, or tenderness)
- Assessment of Aes and SAEs

Post Dosing

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature) every hour (±10 min) for the first 2 hours after the completion of the injection and then every 2 hours (±10 min) for the next 4 hours. More frequent monitoring will be at the discretion of the PI based on the clinical presentation of the subject.
- Obtain blood samples for PK measurements at 2 h (±10 min), 4 h (±15 min), 8 h (±15 min) post injection.
- Obtain serum samples for future use (if consent given) at the following times after the end of injection, 2 h (±15 min), and 4 h (±15 min).
- Obtain a 12-lead ECG 30 minutes (±10 minutes) after completion of the injection.
- Assessment of Aes and SAEs

8.3. Visit 3: Discharge from Unit (Day 2)

The subject is eligible for discharge 24 hours after the IM dosing is complete and after the following assessments have been performed and no signs of anaphylaxis have developed:

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform a symptom directed PE
- Obtain blood samples for the following:
  - PK measurement at 24 hours (± 2 hours)
  - MN
  - Serum sample to store for future use (if subject gave consent)
- Assessment of Aes and SAEs

- Remind the subject not to receive any drugs listed in section 6.8 for the duration of the study unless clinically indicated. If subjects receive necessary vaccines that are clinically indicated (e.g. tetanus after an open wound injury, influenza), they will be instructed to contact study staff immediately. Subjects may receive an approved COVID-19 vaccine after completing their Day 90 visit
- Counsel both men and women of childbearing potential on the avoidance of pregnancy
- Counsel all subjects on prevention of COVID-19
- Discharge subject and instruct on the next scheduled visit

8.4. Visit 4: Out-patient Follow-up (Day 3)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for PK at 48 hours (± 2 hours) post dosing completion
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy
- Counsel all subjects on prevention of COVID-19
- Assessment of Aes and SAEs

8.5. Visit 5: Out-patient Follow-up (Day 4)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for PK at 72 hours (± 2 hours) post dosing completion
- Obtain urine sample urine HCG for women of childbearing potential
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy
- Counsel all subjects on prevention of COVID-19
- Assessment of Aes and SAEs

8.6. Visit 6: Out-patient Follow-up (Day 8± 2)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications

- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety Labs
  - PK measurement
  - Serum sample to store for future use (if subject gave consent)
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy
- Counsel all subjects on prevention of COVID-19
- Assessment of Aes and SAEs

8.7. Visit 7: Out-patient Follow-up (Day 15± 2)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety Labs
  - PK measurement
  - ADA
  - MN
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.8. Visit 8: Out-patient Follow-up (Day 30 ± 2)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety Labs
  - PK measurement

  - ADA
  - MN
  - Serum sample to store for future use (if subject gave consent)
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.9. Visit 9: Out-patient Follow-up (Day 45± 3)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - PK measurement
  - ADA
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.10. Visit 10: Out-patient Follow-up (Day 60 ± 3)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - PK measurement
  - ADA
  - MN
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19

- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.11. Visit 11: Out-patient Follow-up (Day 90±3)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety labs
  - PK measurement
  - ADA
  - MN
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.12. Visit 12: Out-patient Follow-Up (Day 120±5)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - PK measurement
  - ADA
  - MN
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.13. Visit 13: Out-patient Follow-Up (Day 150±5)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - PK measurement
  - ADA
  - MN
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.14. Visit 14: Out-patient Follow-Up (Day 180±5)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety labs
  - PK measurement
  - ADA
  - MN
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.15. Visit 15: Day 365 ±5 / Early Termination

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Review and update concomitant medications
- Perform symptom directed PE
- Obtain blood samples for the following:
  - Clinical Safety labs
  - PK measurement
  - ADA
- Obtain urine sample for dipstick analysis
- Perform urine pregnancy test on women of child-bearing potential
- Assessment of Aes and SAEs
- Counsel all subjects on prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy (for subjects who withdraw from the study early)

8.16. Visit 16: Telephone Visit (Day 450 ±5) for Cohorts 1-4

- Review and update concomitant medications
- Assessment of Aes and SAEs
- Counsel all subjects on the prevention of COVID-19
- Counsel both men and women of child-bearing potential on the avoidance of pregnancy

8.17. Visit 17: Telephone Visit (Day 540 ±5) for Cohorts 1-4

- Review and update concomitant medications
- Assessment of Aes and SAEs
- Counsel all subjects on the prevention of COVID-19

8.18. Unscheduled Visit

A subject may return to the clinic for an unscheduled visit at any time. The following activities at a minimum should be performed:

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and oral temperature)
- Perform symptom directed PE as appropriate

- Review and update concomitant medications
- Assessment of Aes and SAEs

9. ASSESSMENT OF SAFETY

Regulatory requirements including the FDA regulations and ICH Guidelines for GCP set forth safety monitoring and reporting responsibilities of sponsors and investigators to ensure the safety and protection of human subjects participating in clinical trials.

Responsibilities

Investigators participating in this clinical trial are responsible for and will:

- evaluate subject safety including assessment of Aes for seriousness, severity, and causality;
- notify the sponsor (RGS) of SAEs immediately;
- provide detailed written reports, including necessary documentation requested by the sponsor or IRB/Independent Ethics Committee (IEC), promptly following immediate initial reports, and;
- inform the IRB/IEC of Aes as required by applicable regulatory requirements.
- have emergency staff and medications such as epinephrine, corticosteroids, bronchodilators, and emergency tool kits for emergent intubation and initial acute cardiopulmonary resuscitative care are available at all clinical sites in the event they are needed during and immediately after IM injections.

9.1. Specification of Safety Parameters

Definitions

Adverse events

ICH E6(R2) defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Events

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

- Results in death,

- Is life-threatening*,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Congenital anomaly/birth defect;
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Important Medical Event

**Life-threatening adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event, had it occurred in a more severe form, that might have caused death.*

Unexpected

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

Adverse events will be collected at Day 1 during and after dosing. Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if the condition increases in severity or frequency at any time during the study, it should be recorded as an AE.

All Aes must be graded for severity and relationship to study product based on the Investigator's assessment.

Severity of adverse events will be graded using CTCAE v5.0 (Appendix B).

9.2.2. Relationship to Study Product

Aes and SAEs must be assessed by the investigator to determine relationship to study product. All Aes must have their relationship to study product assessed using the following terms. In a clinical trial the study product must always be suspect.

- **Definitely Related:** There is a definite probability that the study product caused the adverse event.
- **Possibly Related:** There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event

- **Not Related**: There is not a reasonable possibility that the administration of the study product caused the event

To help assess, the following factors may be considered:

- Temporal relationship of the event to the administration of study product;
- Whether an alternative etiology has been identified;
- Biological plausibility;
- Existing therapy and/or concomitant medications.

9.3. Reporting Procedures

9.3.1. Adverse Events:

Aes not meeting the criteria for "SAEs," will be captured on the appropriate case report form. Information to be collected for Aes includes event description, date of onset, investigator assessment of severity, relationship to study product, date of resolution of the event, seriousness, and outcome.

All Aes will be followed until resolved or considered stable by the investigator.

9.3.2. Serious Adverse Events

The following procedures will apply to all serious adverse events:

- The Principal Investigator will report any SAE to ICON PVSS within 24 hours of awareness.
- ICON PVSS will perform an initial check of the SAE and contact the site for any missing elements and then inform the ICON MM, and the ISM of the SAE.
- ICON PVSS will record the information on the appropriate serious adverse event report form and send to RGS
- Each SAE will be reviewed and followed to resolution or stability by a study physician
- SAEs will be collected on each subject up to 60 days after his/her last study visit.

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to RGS at the following address:

ICON PVSS

ICON plc PVSS

3rd Floor Marlow International, Parkway, Marlow,

Buckinghamshire, SL7 1YL, United Kingdom

SAE Email Address: **ICON-Safety-CentralReceipt@iconplc.com**

SAE Fax Number (in case email is not available):

+44 (0) 208-100-5005

ICON PVSS will send AE/SAE information to Resilience Government Services, Inc.

Resilience Government Services

Resilience Government Services, Inc.
13200 NW Nano Court
Alachua, FL 32615, USA
SAE Hotline: 240-885-1221
SAE Fax Number: 888-551-1691
SAE Email Address: **olo.safety@resilience.com**

Other supporting documentation of the event may be requested by RGS and should be provided as soon as possible.

ICON plc PVSS will send SAEs with the ICON Drug Safety Physician assessment of causality, expectedness, and any impact on the benefit-risk ratio of the IMP to RGS. The DOD will be notified of the SAE by RGS.

If the investigator becomes aware of an SAE that is suspected to be related to study product up to 60 days after the subject completes the study, the investigator will report the event to ICON PVSS.

9.3.3. Regulatory Reporting

Following notification from the investigator, RGS, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected to the FDA. RGS will report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE. RGS will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. RGS will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, RGS will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

9.3.4. Reporting of Pregnancy

Pregnancies that occur during the study period will be reported to the Sponsor on the Pregnancy Report form within five days of site awareness.

Efforts will be made to follow all pregnancies occurring prior to 56 days post product administration through to outcome, as described in the Safety Management Plan (e.g. delivery, spontaneous abortion or therapeutic abortion).

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be followed until resolution or stability even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the subject's case report forms.

Subjects who experience AEs consistent with COVID-19 through Day 540 for cohorts 1-4 and Day 365 for cohort 5 will be evaluated either by the site or by a health care provider to which the subject may be referred. Clinical specimens for SARS-CoV-2 RNA and serum for immunology (e.g., pro-inflammatory cytokine levels) assessments will be collected or requested to be collected using standardized methods. Assays of these specimens will be conducted at a central laboratory. Subjects will ideally be followed for as long as they continue to shed viral RNA. If feasible, other samples for concurrent or retrospective virologic assessments (e.g., the quantification of viral RNA in blood, rectal swabs, lower respiratory tract samples) will also be collected and analyzed.

9.5. Halting Rules

9.5.1. Halting Criteria for the Study

Study dosing can be halted at any time if medically indicated. Study dosing must be stopped, and a review of available safety data will be conducted by the SRC if any of the following occur:

1. Death of a dosed subject following injection and prior to the subject's last visit that was not the result of trauma or accident, and possibly related to study product.
2. Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis) in any subject, manifested by bronchospasm with or without urticaria or angioedema or requiring hemodynamic support with pressor medications or mechanical ventilation.
3. One subject with an SAE that is considered possibly related or definitely related to study product.
4. Two or more subjects with a Grade 3 AE in the same organ class (systemic toxicity, clinical laboratory tests or vital signs) regardless of relatedness to study drug. An

exception to this includes scenarios where there are obvious and acceptable physiological explanations for a Grade 3 abnormality (e.g., Grade 3 hematuria in a menstruating female).

9.5.2. Dose Escalation Halting Criteria

If any of the following criteria are met, escalation to the next planned dose cohort will not proceed until all available study data have been reviewed by the SRC.

- More than 25% of the subjects in the cohort experience an AE, grade 2 or above in the same organ class
- A specific AE increases in severity from one cohort to the next AND the number of subjects reporting that AE (at the higher severity level) in the cohort is the same or greater. An exception would be headaches going from a grade 1 to a grade 2.

9.5.3. Evaluation of Dose Escalation

The SRC must agree unanimously on the following criteria prior to dose escalation:

- A review of all available unmonitored and uncoded safety data from at least 7 subjects per cohort to Day 8, at a minimum, demonstrate that study halting criteria as outlined in Section 9.5.2 have not been met.
- A review of all available unmonitored and uncoded safety data from at least 7 subjects per cohort to Day 8, at a minimum, demonstrate that no safety signals of any nature were observed.

9.6. Safety Oversight

9.6.1. Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. The ISM will review SAEs and other AEs as needed and provide an independent assessment.

9.6.2. ICON Medical Monitor

The ICON Medical Monitor (MM) is the clinical site's primary point of contact for eligibility or safety related questions. The ICON MM is responsible for liaising with RGS ML to ensure that all medical concerns are communicated and will provide any potential pertinent medical communication update to the project team as needed. The ICON MM will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.

9.6.3. Resilience Government Services Medical Lead

The RGS ML will be the main point of contact for the ICON MM and the DOD for any safety-related questions or concerns. The RGS ML will escalate any medical or safety concerns to the DOD as needed. The RGS ML will participate in the planned SRC meetings and can make a recommendation that the SRC be convened to review any safety concerns.

9.6.4. Safety Review Committee (SRC)

The SRC will be composed of:

- PI, or designee
- RGS ML
- ICON Medical Monitor or designee;

Objective dose-escalation criteria and safety evaluations will be utilized. Prior to dose escalation, the SRC will evaluate unmonitored and uncoded safety and tolerability data for at least 7 subjects out to Day 8 to determine whether dose escalation can occur. If none of the events described in 9.5.1 Study Halting Criteria or in 9.5.2 Dose Escalation Halting Criteria are observed, dose escalation will proceed. Should any of the study halting criteria or dose escalation halting criteria be met, the SRC will meet to evaluate the data and recommend appropriateness of further dosing. The SRC recommendation to advance to the next level will be documented and provided to all the appropriate parties (PI, RGS, and ICON) involved with the study.

If 4 or more subjects withdraw prior to Day 8, those subjects need to be replaced to ensure that data for at least 7 subjects are available for review.

If 4 or more subjects withdraw prior to Day 60 or are not compliant with all PK draws through Day 15, they may be replaced.

If more than 2 subjects withdraw following the Day 8 SRC review of safety data, the site will attempt to replace those subjects in that dose group at the time of the next planned cohort.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protection, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH and, when appropriate, regulatory guidelines. Site visits may be conducted by an authorized representative of ICON, the IRB, HRPO, other regulatory or government agencies to inspect study data, subjects' medical records, and eCRFs in accordance with ICH guidelines, GCP and the respective local and national government regulations and guidelines.

The investigator will permit authorized representatives of ICON and the respective local and national health authorities to inspect facilities and records relevant to this study, if needed.

A separate monitoring plan, to be developed by ICON, will describe protocol-specific items to be monitored.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Considerations

This is a Phase 1 study first in humans with five dosing cohorts and no formal sample size calculations based on testing a statistical hypothesis were constructed. Sample sizes are consistent with this type of early phase study. Dosing groups of ten participants each, eight participants assigned the active group and two assigned to the control group for each cohort are practical and provide sufficient information for a total sample size of 50 for a Phase 1 trial primarily designed to assess safety.

The dosing groups of eight participants in the active group has a probability of at least one subject experiencing an event of toxicity ranges from 0.728 to 0.996 assuming true event rates are between 0.15 and 0.5.

Additionally, if no events are observed in each scenario described above, the upper bound of an exact 95% confidence interval for the true proportion is 0.369.

11.2. Planned Interim Analyses

There are several blinded interim analyses planned for this study. A blinded interim analysis is planned to analyze all PK samples through Day 30 for all subjects in Cohorts 1 and 2. A second blinded interim analysis is planned to analyze all PK samples after all subjects in cohorts 1-3 complete Day 60. A third interim analysis is planned to analyze safety and PK data after all subjects in cohort 5 complete Day 60.

There is also an interim clinical study report (CSR) planned after subjects in Cohorts 1 through 4 complete Day 90.

Stopping criteria are for safety and are defined in section 9.5. No adjustments for multiplicity will be made at these interim analyses.

11.3. Final Analysis Plan

A formal statistical analysis plan will be developed with mock tables, listings, and figures. The ICH Guidance Document E9 (Statistical Principles for Clinical Trials) will be followed for all statistical content. For categorical data, summaries of frequencies and percentages will be presented. Summaries for continuous data will include minimum, lower quartile, median, mean, standard deviation, upper quartile, and maximum.

11.3.1. Analysis Populations

An intent-to-treat population will consist of all subjects randomized and will be analyzed as randomized All subjects who received study product will be included in the safety population and analyzed as treated. The PK analysis population will consist of all subjects who complete

ADM03820 injection and have sufficient evaluable PK samples for the estimation of PK parameters.

11.3.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by dose cohort and control group.

11.3.3. Safety Analysis Plan

11.3.3.1. Adverse and Serious Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities® (MedDRA). All AEs that occur after the initiation of study medication will be summarized using frequency counts and percentages. Summaries will be presented by dose cohort and control group. The following summaries will be presented for AEs and SAEs:

- Overall (i.e., regardless of severity or relationship to treatment)
- By CTCAE v5.0
- By relationship to study medication
- By MedDRA level hierarchy (system organ class and preferred term)

Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AEs, a subject will be counted once if the subject reported one or more events. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

11.3.3.2. Additional Safety Analyses

Vital signs, physical examinations, and clinical laboratory values, including change from baseline, will be summarized by dose cohort and control group.

Descriptive summary statistics for laboratory data at admission (baseline value) and each applicable post-dose visit, including change from the baseline value, will be calculated. Descriptive summary statistics for vital signs at screening (baseline value) and each applicable post-dose visit, including change from the baseline value, will be calculated. Shift tables, showing individual subject changes from baseline will be presented for laboratory parameters using toxicity grading. Subjects with Graded values of vital sign and laboratory parameters will be identified in listings.

11.3.4. PK Analysis Plan

PK parameters will be estimated for total antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohorts 1 and 2. PK parameters for each of the monoclonal antibodies of ADM03820 as measured by enzyme-linked immunosorbent assay (ELISA) for samples from Cohort 3 and 4 using noncompartmental methods in WinNonlin or a similar software package. Parameters will be estimated by dose cohort. Summary statistics

will include the mean, median, coefficient of variation, and range. When evaluable, estimated PK parameters will include:

- $AUC_{(0\text{-}t)}$: Area under the concentration time-curve to the last concentration above the lower limit of quantitation
- C_{max}: Maximum observed concentration
- T_{max}: Time of maximum observed concentration
- Kel: Elimination rate constant
- $AUC_{(0\text{-}\infty)}$: Area under the concentration time-curve extrapolated to infinity
- $t_{1/2}$: Terminal elimination half-life
- CL: Total clearance
- V_Z: Volume of distribution

Additionally, multi-compartmental models will be considered based on inspection of concentration-time curves. If models are fit, base models will assume first-order elimination from the central compartment, and models will be parameterized in terms of clearance, volume of distribution and inter-compartmental rates. Standard objective goodness of fit measures will be used to determine the final model.

11.3.5. Immunogenicity

Immunogenicity will be measured by the development of antibody titers. The presence of ADA will be measured over the course of the post-injection period.

11.3.6. Missing values and outliers

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Outliers identified during the PK analysis will be discussed in the analysis report.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a DOD-affiliated, or manufacturer-sponsored study, the site will permit authorized representatives of the sponsor(s), DOD, and regulatory agencies to review (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Forms for use as source documents will be derived from the electronic CRFs and will be provided by ICON. Additional source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. If data is recorded directly into the eCRF with no paper source, then that data should be listed as being a direct electronic data entry with no paper source available.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DOD-accepted site quality management plan, the investigational site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The PI will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

Clinical monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to RGS.

ICON will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of

Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6(R2); 62 Federal Regulations 25691 (1997), if applicable. The investigator's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection for federally funded research.

14.2. Institutional Review Board

ICON will provide for the review and approval of this protocol and the associated informed consent documents, by an appropriate ethics review committee or IRB listed on the FWA. Any amendments to the protocol or consent materials must also be approved before they are placed into use unless change is for the safety of the subject. Only those IRB members who are independent of the investigators and the sponsor should provide an opinion on study related matters. Verification of IRB approval of the protocol and the written informed consent will be transmitted by the investigator or designee prior to the shipment of study product. No deviations from or changes to the protocol will be initiated without prior approval of an appropriate amendment unless change is for the safety of the subject.

14.3. Informed Consent Process

14.3.1. Informed Consent

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonized Tripartite Guideline for Good Clinical Practice. Informed consent should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46. Information should be presented both orally and in written form.

An investigator or designee will describe the protocol to potential subjects face-to-face. The investigator shall give the subjects ample opportunity to read the Subject Information and Consent Form and to inquire about details of the study and ask any questions before the signing and dating the consent form.

Study staff must inform subjects that the trial involves research, and explain the purpose of the trial, those aspects of the trial that are experimental, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, the procedures of the research study, including all invasive procedures, and the probability for random assignment to treatment groups. Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available, and the important potential benefits and risks of these available alternative procedures. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.

Subjects must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in the trial. The extent of the confidentiality of the subjects' records must be defined, and subjects must be informed that applicable data protection legislation will be followed. Subjects must be informed that the monitor(s), auditors(s), IRB, DOD, RGS, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access. Subjects must be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

Consent forms must be in a language fully comprehensible to the prospective subjects. Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject and the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been provided and all questions have been answered to the prospective participant's satisfaction. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the sponsor and Regulatory Compliance persons. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

Pregnant women, lactating women and children are excluded for safety reasons.

14.5. Subject Confidentiality

Subject confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval from the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

14.6. Study Discontinuation

RGS has the right to terminate this study or the site's participation at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of adverse events indicates a potential health hazard;
- Data recording is inaccurate or incomplete;
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

14.7. Future Use of Stored Specimens

Samples will be collected as outlined in the protocol. Subjects will be given a choice during the informed consent process to have their residual linked samples stored indefinitely by the Sponsor for future research, have their residual samples de-linked from any subject information and stored indefinitely, or have their residual linked samples destroyed at completion of the study. The use of long-term stored linked samples will be conducted under the restrictions regarding confidentiality, as outlined in the preceding paragraphs.

Only coded specimens will be sent to the sponsor with the code identifiers maintained by the principal investigator. Any future research studies will utilize only the residual long-term stored specimens from subjects consenting to future use.

15. DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **Do not erase, overwrite, or use correction fluid or tape on the original.**

Copies of the electronic CRF (eCRF) will be provided to the site to create source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained.

RGS and/or its designee will provide guidance to investigators on making corrections to the data collection forms/source documents and eCRFs.

15.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality, and reviewed by the site Principal Investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. During the study, the investigator must maintain complete and accurate documentation for the study.

ICON will serve as the Statistical and DCC for this study, and will be responsible for data management, quality review, analysis, and reporting of the study data.

15.2. Data Capture Methods

Clinical data (including AEs, concomitant medications, and reactogenicity data) and clinical laboratory data will be entered into a 21CFR part 11-compliant Internet Data Entry System provided by ICON. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.3. Types of Data

Data for this study will include clinical safety assessments, safety laboratory assessments, immunology, PK, and MNA.

15.4. Timing/Reports

A final report will be prepared following the availability of all the safety and immunogenicity data.

15.5. Study Records Retention

Study files (except for future use consent forms) must be maintained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in and ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Consent forms for future use will be maintained as long as the sample exists.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6(R2):

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to ICON and /RGS.

All protocol deviations, as defined above, must be addressed in study subject source documents and entered into a database. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File per clinical site(s) SOP, as well as in the subject's source document. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

16. PUBLICATION POLICY

All manuscripts resulting from this trial will be reviewed by representatives from the sites, DOD and the product manufacturer. Each institution will have at least thirty days to review the publication prior to submission.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine (NLM). Other biomedical journals are considering adopting similar policies. This trial will be registered in NLM in accordance with the new NLM requirements under the Food and Drug Administration Amendments Act (FDAAA).

*Journal Citation :

De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351:1250-1.

APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Study Visit	Screening[1] 01	Baseline/Dosing 02	Discharge 03	04	05	06	07	08	09	10	11	12	13	14	Final Outpatient Visit / ET 15	TC[19] 16	TC[19] 17
Study Day (Window)	**-14 to -2**	**1**	**2**	**3**	**4**	**8±2**	**15±2**	**30±2**	**45±3**	**60±3**	**90±3**	**120±5**	**150±5**	**180±5**	**365±5**	**450±5**	**540±5**
Review Inc/ ExcI Criteria	X	X															
Review Medical History	X	X															
Review Contraception/menses	X																
Perform Abbreviated PE[3]	X																
Perform Symptom-Directed PE[14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Screening Labs[5]	X																
Clinical Safety Labs[6]						X	X	X			X			X	X		
Serum β-HCG[7]	X[7]																
Urine pregnancy test		X			X				X			X	X	X	X		
Urine Dipstick[8]	X	X										X	X	X	X		
Urine Toxicology	X	X															
Breathalyzer test	X	X															
Immunogenicity (ADA)[15]		X					X	X	X	X	X	X	X	X	X		
PK samples[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MN Samples		X	X				X	X		X	X	X	X	X			
Hypersensitivity Panel[16]		X															
12-lead ECG[9]	X	X															
Viral Serology[10]	X																

Study Visit	Screening[1] 01	Baseline/Dosing 02	Discharge 03	04	05	06	07	08	09	10	11	12	13	14	Final Outpatient Visit / ET 15	TC[19] 16	TC[19] 17
Study Day (Window)	**-14 to -2**	**1**	**2**	**3**	**4**	**8±2**	**15±2**	**30±2**	**45±3**	**60±3**	**90±3**	**120±5**	**150±5**	**180±5**	**365±5**	**450±5**	**540±5**
SARS-CoV-2 Antibodies[18]	X																
RT-PCR[17]	X	X															
Concomitant Medications[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X															
Study Drug Administration		X															
Future Use Sample[12]		X	X			X		X									
Counsel on the avoidance of pregnancy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening will be completed within 14 days prior to administration of study drug and may require more than one visit.
2. Concomitant medications including all of the following: prescription drugs, over-the–counter drugs, herbs, vitamins, nutritional supplements, illicit and recreational substance use, birth control
3. PE includes height and weight at screening.
4. Vital Signs to include sitting diastolic and systolic blood pressure, heart rate, respiratory rate, and oral temperature. See section 8 for a schedule of when vital signs are to be obtained.
5. Screening Laboratory Tests that will include hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded, serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK. Include FSH at screening to confirm post-menopausal status for women ≥ 1 year without menses
6. Clinical Safety Laboratory Tests that will include hemoglobin, WBC with differential, absolute neutrophil count and platelet count. MCV, MCH, MCHC, RDW, MPV, which are included in a complete blood count with differential, will not be graded, serum creatinine, BUN, calcium, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, PT, PTT, INR, ALT, AST, sodium, potassium, and total CK.
7. A serum pregnancy test will be obtained for all women of reproductive capacity. Results must be confirmed as negative before study product is dosed.
8. A urine dipstick will be done to evaluate for presence of protein, glucose or blood in urine. If dipstick is abnormal, a complete urinalysis with microscopic will be performed.
9. A 12-lead ECG will be performed during screening and post dose performed 30 minutes (±10 minutes) after completion of dosing.
10. Viral Serology includes HIV, HBsAg and antibody to HCV.
11. PK samples will be taken at the following times: pre-dose, 2, 4, 8, and 24 hours post injection and on days 2, 3, 4, 8, 15, 30, 45, 60, 90, 120, 150, 180, and 365 for all cohorts
12. Serum from subjects who give consent for future use samples will be collected at 2 hr and 4 hr post dose and on days 2, 8, and 30
13. Vital signs (sitting for at least 10 minutes) will be checked just before injection and every visit.
14. The subject will be under direct observation during at least the initial 30 minutes of dosing. A physical examination will be performed at approximately 30 minutes post injection or in response to subject symptoms which will include the following: General appearance including alertness, diaphoresis, chills, and any difficulty breathing, HEENT, Chest, Heart, Skin and Joints
15. Draw prior to dosing at baseline
16. The Hypersensitivity Panel includes cytokine and complement panels, IgE, and tryptase. Draw 14ml prior to dosing. If a subject develops anaphylaxis or anaphylactoid reaction, an additional 10 mL sample will be drawn during the event and another will be drawn after the event

17. Subjects in all cohorts will receive RT-PCR testing at screening, Day 1 prior to dosing, and at presentation of symptoms.
18. SARS-CoV-2 antibodies will only be tested in Cohorts 1-4 (Not applicable for Cohort 5).
19. TC visits will be conducted for only Cohorts 1-4 (Not applicable for Cohort 5).

APPENDIX B: CTCAE V5.0

The CTCAE version 5.0 can be found at the following address:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_60

APPENDIX C: INTRAMUSCULAR (IM) ADMINISTRATION

Cohorts 1-3 Only: IP is administered as one 3mL (150mg dose) or two 3mL (300mg dose) IM injection(s) within 1 hour of thawing.

Cohort 4 Only: IP is administered as one 3mL (300mg dose) IM injection within 30 minutes of removing from refrigerator.

Cohort 5 Only: IP is administered as two 3mL (600mg dose) IM injection within 30 minutes of removing from refrigerator.

Instruct subject to lay prone (on abdomen) with toes pointing inward and heels apart (to relax gluteal muscles). Visually divide the buttock in half from top to bottom and then in half from side to side. The injection should be given in the upper outer quarter to avoid the sciatic nerve and gluteal artery. Intramuscular (IM) injections are administered into the gluteus medius muscle of the buttocks using a 1 ½ inch 20 or 22 gauge needle. Inject entire contents of syringe and remove needle. Do not rub the injected area. Gentle pressure is allowable if bleeding is noted.