Protocol Title:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Immunogenicity of ADM03820 in Adults
Protocol Number:	ADM03820-001
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Prepared by:	Xianmiao (Kelley) Qiu ICON GPHS Biostatistician
On behalf of:	Resilience Government Services 13200 NW Nano Court Alachua, FL 32615

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Signature Page

Prepared at ICON GPHS by:		
Xianmiao (Kelley) Qiu ICON GPHS Biostatistician	Kelley Qiu 11 Sep 2023 13:54:22 UTC (Z) REASON: I approve this document as author. b39bf162-0abc-4324-b5c9-b222ec615edc	
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Approved at ICON GPHS by:		
Tracey Mason Executive Director, Biostatistics	Tracey Mason 11 Sep 2023 13:55:25 UTC (Z) REASON: I approve this document cf861a83-89e0-46c8-be99-4c2d68b8479b	
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Approved at SPONSOR by:		
Angie Kimbler RGS Director, Regulatory and Clinical Operations	Angie Kimbler 11 Sep 2023 14:58:26 UTC (Z) REASON: I approve this document a1bd9fb3-22f9-48de-8319-5df19a9d0e18	
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Revision History

Version	Date	Revisions
0.1	03-NOV-2020	Initial draft.
0.2	11-NOV-2020	Revised draft after internal review.
1.0	25-NOV-2020	Finalized version after incorporating changes in protocol v2.0 and additional internal comments.
1.1	15-MAR-2021	Revised draft SAP incorporating changes in protocol v4.0.
2.0	16-MAR-2021	Finalized SAP after addressing minor comments from sponsor.
2.1	06-JUL-2022	Revised draft SAP incorporating changes in protocol v5.0 and PK populations.
3.0	13-JUL-2022	Final version
3.1	27-JUL-2023	Revised draft SAP incorporating changes in protocol v6.0. Section 1, Introduction: update the protocol version to 6.0. Section 3.0, Study design: update the total number of subjects to 50. Add cohort 5. Section 4.0, Study endpoints: update the primary endpoints, and secondary endpoints.
3.2	30-AUG-2023	Revised draft SAP incorporating changes in protocol v7.0: Change the company name to: Resilience Government Services Section 3.0, Study design: Add “for Cohorts 3 and 4” after “Discharge and outpatient follow-up (Day 2 to Day 540)”. Add “Discharge and outpatient follow-up (Day 2 to Day 379) for Cohort 5”. Change “Subjects in all cohorts” to “Subjects in cohorts 1-4”. Add “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.)” Add a footnote under Table 2 schedule of events: “19.TC visits will be conducted for only Cohorts 1-4 (Not applicable for Cohort 5).”
4.0	11-Sep-2023	Update Angie Kimbler’s title to “Director, Regulatory and Clinical Operations”.

Table of Contents

List of Abbreviations

Abbreviation	Explanation
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AV	Atrioventricular
BMI	Body mass index
BPM	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatine kinase
CRF	Case report form
CSR	Clinical study report
ECG	Electrocardiograms
ECLA	Electrochemiluminescence assay
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose and throat
HIV	Human immunodeficiency virus
IA	Interim Analysis
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IM	Intramuscular
INR	International normalized ratio
IQR	Interquartile range
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MN	Microneutralization
MPV	Mean platelet volume
PE	Physical examination
PI	Principal investigator
PK	Pharmacokinetics
PP	Per-protocol
PR	PR interval – standard ECG terminology
PT	Prothrombin time
PTT	Partial thromboplastin time
QRS	QRS interval – standard ECG terminology
QT	QT interval – standard ECG terminology
QTcF	QTc by Fridericia formula
RDW	Red cell distribution width
RT-PCR	Reverse transcription polymerase chain reaction

Abbreviation	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	Standard international
SOC	System organ class
SRC	Safety review committee
TLF	Table, listing and figure
WBC	White blood count

1.0 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for the study protocol ADM03820-001 Version 6.0 “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics, and Immunogenicity of ADM03820 in Adults” dated 14-JUL-2022 for final analysis. The table of contents and templates for the Table, Listing and Figure (TLF) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9 and Good Clinical Practice (GCP) guidelines.

All data analyses and generation of TLFs will be performed using SAS 9.4® (or higher) and Phoenix WinNonLin 8.3.1 (or higher).

2.0 Study Objectives

Primary objective(s)

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

Secondary objective(s)

To assess the pharmacokinetics (PK) and immunogenicity (ADA) of different doses of ADM03820 in healthy adult subjects

Exploratory objective(s)

None.

Safety objective(s)

No additional safety objectives of current study besides the primary objective.

3.0 Study Design

General study design

This study is a phase 1, randomized, double-blind, placebo-controlled study of four dose cohorts. The study will enroll and randomize a total of 50 healthy subjects from five study sites to receive an intramuscular (IM) injection of either ADM03820 or placebo. Five dosing cohorts will be enrolled sequentially. Dose escalation will occur after the Safety Review Committee (SRC) reviews safety data and confirms that the dose escalation criteria are met. Within each cohort, 8 actives and 2 placebos will be included. The 5 dosing cohorts are

1. Cohort 1 –150 mg IM injection (8 active, 2 placebo)
2. Cohort 2 – 300 mg IM injection (8 active, 2 placebo)
3. Cohort 3 – 300 mg IM injection (8 active, 2 placebo)
4. Cohort 4 – 300 mg IM injection (8 active, 2 placebo)
5. Cohort 5 – 600 mg IM injection (8 active, 2 placebo)

All enrolled subjects in Cohorts 1 and 2 will follow the study schedule below:

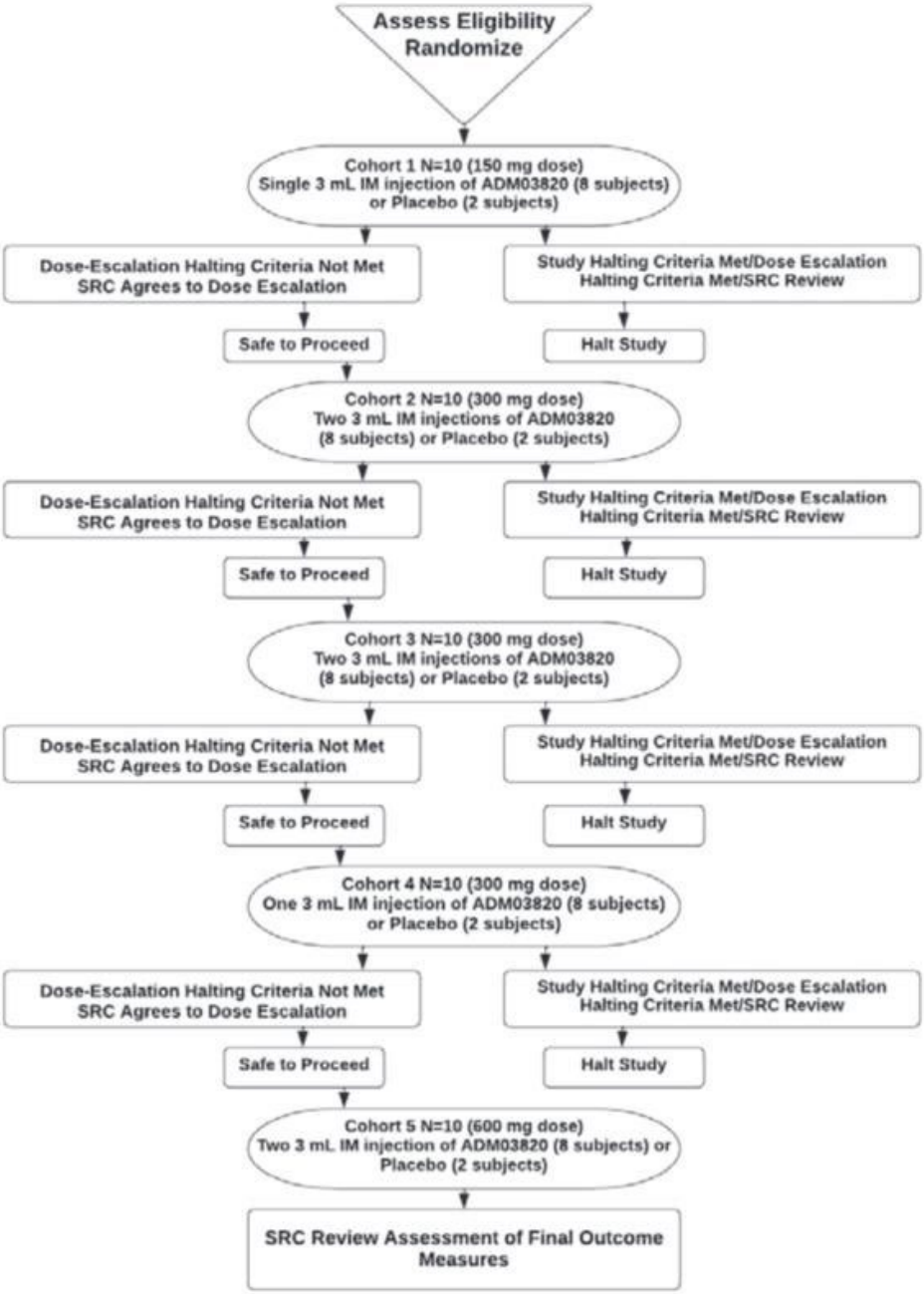
- Screening (Day -14 to Day -2)
- Baseline/admission to Unit (Day -1)
- Dosing (Day 1)
- Discharge and outpatient follow-up (Day 2 to Day 540)

According to Protocol v7.0, subjects in Cohorts 3, 4 and 5 will be admitted to the unit the day of the planned dosing. Thus, study schedule is specified below:

- Screening (Day -14 to Day -2)
- Dosing (Day 1)
- Discharge and outpatient follow-up (Day 2 to Day 540) for Cohorts 3 and 4
- Discharge and outpatient follow-up (Day 2 to Day 379) for Cohort 5

A schematic of the study design is summarized in Figure 1.

Figure 1 – Schematic of Study Design



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.

For dosing 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 the 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 Cohorts 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.

The following rules apply in case of subject withdrawal:

- Subjects who are withdrawn prior to dosing must be replaced.
- Following dosing, one subjects 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 sites 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.

Study treatments and assessments

Subjects in cohorts 1-4 will participate for an approximate duration of 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 for approximately 379 days (up to a 14-day screening, overnight stay, and

up to 12-months of outpatient follow-up visits.) All eligible subjects in Cohorts 1, 2, and 5 will be admitted to clinical unit on Day -1, receive the randomized treatment on Day 1, and be discharged from unit on Day 2. All eligible subjects in Cohorts 3 and 4 will be admitted to clinical unit and receive the randomized treatment on Day 1, and to be discharged from unit on Day 2. Fourteen scheduled outpatient visits are planned for each subject, including the final study visit and two telephone visits.

Patients will be enrolled into 5 dosing cohorts (see Section 3.1) sequentially with interim review of safety data through Day 8 at current dosing level. Each dosing cohort consists of 8 subjects receiving active treatments and 2 receiving placebos. Refer to protocol Section 9.5 for Halting Rules, including halting criteria for the study, dose escalation halting criteria and evaluation of dose escalation.

A detailed description of procedures and assessments to be conducted during this study is summarized in the Schedule of Events in Table 1 below.

TABLE 2 - SCHEDULE OF EVENTS

Study Visit	Screening[1] 01	Baseline/Dosing 02	Discharge 03	04	05	06	07	08	09	10	11	12	13
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±**
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
Vital Signs[4]	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		
Serum β-HCG	X[7]												
Urine pregnancy test		X			X				X			X	X
Urine Dipstick[8]	X	X										X	X
Urine Toxicology	X	X											
Breathalyzer test	X	X											
Immunogenicity (ADA)[15]		X					X	X	X	X	X	X	X
PK samples[11]		X	X	X	X	X	X	X	X	X	X	X	X
MN Samples		X	X				X	X		X	X	X	X
Hypersensitivity Panel[16]		X											
12-lead ECG[9]	X	X											
Viral Serology[10]	X												
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
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
AE Review		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

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).

Study Endpoints

Primary endpoint(s)

- The occurrence of Serious Adverse Events following administration of ADM03820 to the final follow-up visit.
- The occurrence of adverse events (AEs) from administration of ADM03820 to the final follow-up 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 endpoint(s)

- 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-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

Exploratory endpoint(s)

None.

Safety endpoint(s)

No additional safety endpoints besides those specified in Section 4.1.

4.0 Sample Size and Power

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.

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.

5.0 Analysis Populations

Full Analysis Set (FAS)/Intention-To-Treat population (ITT)

An intent-to-treat population will consist of all subjects randomized and will be analyzed as randomized.

Safety population (Safety)

All subjects who received study product will be included in the safety population and analyzed as treated.

Per-Protocol population (PP)

The Per-protocol population will consist of all subjects in the ITT population who were free from major protocol violations. Patients will be included in the analysis according to the treatment group they are randomized to.

Pharmacokinetics (PK) population

The PK population will consist of all subjects who complete ADM03820 injection and have sufficient evaluable PK samples for the estimation of PK parameters. Subjects in the PK population will be analyzed in the dose cohort and treatment group corresponding to the study drug that they have received.

Protocol deviations

Protocol deviation data will be captured in the clinical trial management system. Extracts of all protocol deviations will be reviewed periodically and prior to any interim or final analyses. All protocol deviations and the exclusion of participants from analysis sets will be identified prior to unblinding through clinical review and input provided by the sponsor using supportive participant listings provided by the ICON GPHS statistician based upon data recorded in the clinical trial management system.

Further, deviations from the protocol will be classified as major or minor. Classification of major and minor protocol deviations is determined prior to participant enrollment and is outlined in detail in the protocol deviation criteria documentation managed by the clinical trial management team.

6.0 Statistical Considerations and Analysis

Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, baseline derivation and other important derivations applicable for this study.

Table 3: Derived Variables

Variables	Formula
Demographic and Baseline Characteristics	
Age at informed consent (in years)	Integer ((date of informed consent – date of birth + 1) / 365.25)
Body Mass Index	Weight (kg) / [height (m)]^2
Derivation of Durations	
Study day at any visit	Date of interest – date of first dose of vaccine. One day is added if the difference is ≥ 0.
Duration of any events	End date of event – start date of event + 1
Baseline Derivations	
Laboratory results/vital signs baseline	The baseline value is defined as the last observation prior to or on the date of dosing.
Derivations of Changes	
Change from baseline	Post baseline value – baseline
Change from previous visit	Current value – previous value
Change after dosing from before dosing	Value after dose – value before dose
Pharmacokinetic Parameters (PK) (Plasma/Serum)	

Variables	Formula
C_{max}	Maximum observed concentration, occurring at time $T_{max.}$
T_{max}	Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. If the maximum observed concentration is not unique, then the first maximum is used.
$AUC_{(0-t)}$	Area under the concentration time-curve from the time of dosing to the time of the last measurable (positive) concentration
λ_z	First-order rate constant associated with the terminal (log-linear) portion of the curve, estimated by linear regression of time vs. log concentration during steady-state elimination
$AUC_{(0-\infty)}$	Area under the concentration time-curve from time of dosing extrapolated to infinity, based on the last observed concentration or last predicted concentration defined as $AUC_{(0-t)} + (C_{(0-t)}/\lambda_z)$
$t_{1/2}$	Terminal half-life defined as $\ln(2)/ \lambda_z$ as measured during steady-state
CL	Total body clearance for extravascular administration defined as Dose/ $AUC_{(0-\infty)}$
V_Z	Volume of distribution based on the terminal phase. For non-steady-state data defined as Dose/[λ_z $(AUC_{(0-\infty)})$]

Handling of missing data and outliers

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

Missing data analysis methods

Imputation rules for missing or partial adverse event start/stop dates

- If the AE start date day is missing (month and year provided) then set the date to the first of the month unless the month and year are the same as the first dose of study drug. In this case, set the date to the date of first dose.
- If the AE start date month is missing (year is provided) then set the month and day to January 1, unless the year is the same as the year of the first dose. In this case, set the date to the date of first dose.
- If the AE end date day is missing (month and year provided) then set the date to the last day of the month.
- If the AE end date month is missing (year is provided) then set the date to December 31.

- If the year of the AE start date or AE end date are missing, then a query to the site must be made to gather additional information. If the end date and start date are both missing, then no imputation will be done. If the stat date remains missing but the end date is before first dose date, then the AE will be considered before treatment. If the end date is after the first dose, then the AE will be considered to have been treatment emergent.

Imputation rules for missing or partial medication start/stop dates

Start Date:

- If only day is missing, use the first day of the month.
- If day and month are missing, use the first day of the year.
- If day, month, and year are missing use the first day of the year with the same year as the first dose.

End Date:

- If only day is missing, use the last day of the month.
- If day and month are missing, use the last day of the year.
- If day, month, and year are missing assign 'continuing' status to the stop date.

7.0 Statistical Methods

General statistical conventions

All statistical procedures will be completed using SAS version 9.4 (or higher), R version 4.0.0 (or higher), or Phoenix WinNonLin 8.3.1 (or higher).

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), interquartile ranges (IQR), minimum, and maximum.

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last available pre-dose value. All summaries will be presented by treatment group, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by subject ID, date/time and visit. The treatment group will be stated on each listing. Unless otherwise stated, data listings will be based on FAS.

Unscheduled data points will not be used in any summary tables separated by visit but will be presented in each listing as appropriate.

Subject disposition

Subject disposition information will be summarized by dosing cohort, treatment group and overall. The number and percentage of subjects who are enrolled, who complete the study, and who withdraw early from the study will be presented.

The primary reasons for early withdrawal will also be tabulated, including withdrawal by subject, physician decision, lost to follow-up, major protocol deviation or other.

The number of subjects enrolled will be used as the denominator for the percentage calculation. Subject disposition will be listed.

The number and percent of subjects in each analysis set will also be tabulated. A listing of each subject excluded from an analysis population will be listed as well as the reason why they were excluded from the population.

Treatment Misallocations: if a subject is

- Randomized but withdrawn prior to dosing, then they will be replaced and will not be included in any analysis.
- Randomized but receive incorrect treatment, they will be reported under the treatment they actually have received for all safety analysis and PK analysis.

Protocol deviations

The number of patients excluded from FAS/ITT, Safety, and Per-protocol analysis sets and reasons for exclusion will be summarized by treatment group and overall.

Population membership details will be listed, including reason for exclusion from each population.

Protocol deviation data are not captured in the clinical database and therefore will not be reported individually within the scope of the SAP. Protocol deviations will be summarized in the final clinical study report.

Demographics and baseline characteristics

8.4.1 Demographics

Age at consent, height, weight, BMI and other continuous demographic variables at baseline will be summarized descriptively. Sex, race, ethnicity and other categorical variables will be summarized using the ITT/FAS population.

8.4.2 Baseline and disease characteristics

The baseline continuous characteristics (vital signs) will be summarized descriptively for the ITT population. The baseline categorical characteristics (results of physical exams, ECG, serum chemistry, hematology and urinalysis, serology) will be summarized using frequency counts and percentages for the safety population.

8.4.3 Medical history

A summary of medical history and defined high-risk comorbidities will be presented by system organ class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Medical history will be graded for severity.

8.4.4 Prior and concomitant medications

Medications used in this study will be coded by using MedDRA version 23.0.

Prior medications are defined as those medications with a start date 28 days prior to the initial screening.

Concomitant medications are defined as those medications with a start state later than 28 days prior to the initial screening and will be recorded at screening visit. 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 Principal Investigator (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. Per protocol section 5.2 exclusion criteria #20, subjects using any of the prohibited medications within 28 days prior to screening or planned use during the study period will be excluded from the study. However, if any prohibited medication is used during study period by any enrolled subject, it would be captured as a protocol deviation at local sites.

Prior and concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) class and preferred name by treatment group on the ITT population and presented separately for the following groups:

- Medications prior to 28 days before the initial screening.
- Concomitant medications continued after initial screening.
- Concomitant medications started at or after the initial screening.
- Prior and concomitant use of any restricted medications as described in protocol exclusion criteria.

Details for imputing missing or partial start and/or stop dates of medication are described in section 7.3.

Extent of exposure

A single dose of study product will be administered on-site by research personnel at Day 1 (Visit 2 per protocol v7.0) for all subjects. All study products will be administered via IM injection. Thus, treatment compliance will not be applicable.

Efficacy analysis

Efficacy analysis is only applicable to the secondary endpoints regarding immunogenicity described in section 4.2 and analysis methods are described in section 8.6.5 below.

8.6.1 Analysis methods

Refer to section 8.6.5 for analysis methods for secondary endpoints regarding immunogenicity.

8.6.2 Multiplicity

Each immunogenicity endpoint will be analyzed separately, and no multiplicity will be corrected.

8.6.3 Treatment by center interaction analysis (multi-center study)

Five study centers will be involved in the study; however, all subjects will be pooled for secondary efficacy analysis and no treatment by center interaction will be examined.

8.6.4 Analysis of primary efficacy endpoint(s)

Not applicable.

8.6.5 Analysis of secondary efficacy endpoint(s)

Secondary efficacy analysis will be based on microneutralization assay and immunogenicity/ADA assay using blood samples drawn at various predetermined visit days using per-protocol population.

Pharmacokinetic (PK) and Log-Transformed Pharmacokinetic (PK) Parameters will be summarized descriptively by treatment group.

Microneutralization titers will be summarized descriptively by treatment group and compared among treatment groups using Kruskal-Wallis test on log scale. GMT of ADA and GMFR over the initial GMT at baseline will be summarized descriptively by treatment group and compared using Kruskal-Wallis test among cohorts at each study visits. Exploratory pairwise comparisons will also be conducted using Wilcoxon rank sum test; however, resulting p-values will not be corrected for multiplicity. Microneutralization titers on log scale and GMTs for ADA will be plotted by treatment group over study days.

Incidence of the first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurring after dosing through Day 365 will be summarized descriptively by treatment group. Incidence of SARS-CoV-2 RT-PCR

positive severe or critical symptomatic illness occurring after dosing through Day 365 will be summarized descriptively by treatment group.

Incidence of COVID-19 related Emergency Department visits occurring after dosing through Day 365 will be summarized descriptively by treatment group.

Due to the small number of subjects in this study, negative hypothesis tests should be interpreted carefully as the study has not been powered to detect differences between groups.

8.6.6 Analysis of exploratory endpoint(s)

Not applicable.

Safety analysis

This section describes the safety analyses that will be conducted on the treatment and follow-up periods (i.e., the safety analyses on all data collected during the treatment and follow-up periods and all data collected in subjects who dropped-out during the treatment and follow-up periods).

All definitions relative to safety endpoints (primary endpoints) are detailed in section 4.1.

Safety analyses will be conducted on the safety population and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group.

The safety analyses of changes from baseline to a specific time point in safety variables (e.g., laboratory parameters, physical examinations, vital signs) will only include subjects from the safety population who have data available for both the baseline and the time point under considerations unless otherwise specified.

No statistical tests will be performed on the safety endpoints.

8.7.1 Adverse events

All AEs will be classified by Primary SOC and Preferred Term according to the MedDRA Version 23.0 or higher. The occurrence of AEs and SAEs following administration of ADM03820 to the final follow-up visit will be categorized as solicited adverse events, unsolicited adverse events and lab abnormalities. A summary table will be provided to summarize the frequencies and percentages of each category and overall by treatment group. Subsequent analyses will be conducted for each category, respectively, by severity, relationship to study medication, and by MedDRA level hierarchy (SOC and Preferred Term).

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 will be summarized descriptively by treatment group. AEs 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 will be recorded

as an AE. Severity and relationship to the treatment will be assessed by investigator: severity is graded according CTCAE v5.0; relationship to the treatment is categorized as not related, possibly related, and definitely related.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in the treatment period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables. Where a subject has multiple adverse events within the same system organ class in the treatment period, the subject will only be counted once at the system organ class level in adverse event frequency tables. Under both scenarios, the event of the worst severity or the worst-case relationship assessment will be used for summarizing safety endpoints.

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 and will be presented using individual patient listings.

Details for imputing missing or partial start dates of adverse events are described in section 7.2.2.

In summaries by SOC and Preferred Term, adverse events will be sorted by descending frequency within each SOC and Preferred Term according to the total number of events. In summaries by Preferred Term, AEs will be sorted by decreasing frequency according to the total number of events.

8.7.2 Clinical laboratory evaluations

Clinical laboratory evaluations include serum chemistry, hematology, and urinalysis. For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier; but will be listed as is in the listings. Severity of abnormal laboratory results will be graded according to CTCAE v5.0.

All laboratory data obtained between screening visit and the end of study will be used for the laboratory safety analysis. Laboratory summaries will be provided including values measured during the follow-up period, where appropriate.

Visit value and change and from baseline during the treatment period will be summarized by treatment group using descriptive statistics for all laboratory parameters.

Abnormal clinical laboratory results will be summarized by treatment group and severity at subsequent visits following screening when clinical safety labs are performed. Abnormality will be determined according to the pre-specified criteria at each site (which may vary by sites) and flagged in EDC.

Subjects with graded laboratory values will be identified in listings, including patient information, visit date, severity of abnormality, relationship to study product along with specifics of the abnormal laboratory results and corresponding normal ranges (when applicable).

8.7.3 Vital signs

Visit values and changes from baseline for vital sign measurements (blood pressure, oral temperature, heart rate and respiratory rate) will be summarized by treatment group at each visit or timepoint using descriptive statistics. Visit values will be calculated as the mean of all available measurements per parameter. Subjects with vital signs will be listed and summarized by treatment group.

8.7.4 Physical examinations

An abbreviated physical examination (PE) will be conducted at the screening visit and Day -1. Symptom-directed PEs will be performed at all other subsequent visits. Any new findings on PE post dosing or worsening of existing conditions will be reported as AEs, which will be summarized descriptively by treatment group using frequencies and percentages. Subjects with documented AEs based on PEs will be identified using listings and summarized by treatment group and study day. Abnormal physical exams will be summarized by treatment group.

8.7.5 Electrocardiograms

12-lead ECG will be performed at screening and on dosing day (30±10 minutes after injection) while subject is in supine position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (QTcF), intervals. Results will be categorized as normal sinus rhythm, normal variant and abnormal. Results at each study day will be summarized using frequency tables. Any changes after injection from baseline will be summarized using shift tables and subjects with abnormal ECG results after dosing will be identified using listings.

8.7.6 Other safety assessments

A hypersensitivity panel includes cytokine and complement panels, IgE and tryptase. A blood sample will be drawn prior to dosing and additional two blood samples will be drawn during and after the event if a subject develops anaphylaxis or anaphylactoid reaction. The samples will only be processed if the subject has a hypersensitivity reaction. Subjects with hypersensitivity reaction will be identified using listings and summarized descriptively by treatment group.

A nasopharyngeal swab specimen will be collected for RT-PCR testing for SARS-CoV-2 at screening and upon presentation of COVID-19 symptoms. Subjects with positive testing results will be identified using listings and summarized descriptively by treatment group.

8.8.1 Subgroup analysis

No planned subgroup analysis will be conducted.

8.8.2 PK analysis

PK parameters will be estimated for total antibodies of ADM03820 as measured by ELISA for samples from Cohorts 1 and 2. PK parameters for each monoclonal antibodies of ADM03820 as measured by ELISA for

samples from Cohorts 3-4 using noncompartmental methods. All analysis will be conducted 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:

- $AUC_{(0-t)}$: 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
- λ_z: Elimination rate constant
- $AUC_{(0-\infty)}$: 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.

Interim analysis (IA)

Two blinded interim analyses are planned for this study. See Table 4 below for their schedule and scope. No adjustment for multiplicity will be made at these interim analyses.

Table 4: Schedule and scope of IAs

IA Number	Time	Cohorts	Scope
1	Day 30	Cohorts 1 and 2	Safety, PK
2	Day 60	Cohorts 1-3	PK
3	Day 60	Cohort 5	Safety, PK
4	Day 90	Cohort 1-4	Safety

Refer to Section 8.6.5 and Section 8.8.2 for analysis methods. An interim CSR will be generated after all subjects complete Day 90.

8.0 Changes to Planned Analysis from Study Protocol

Added per-protocol population in protocol section 11.3.1.

9.0 References

None.

10.0 Appendices

None.