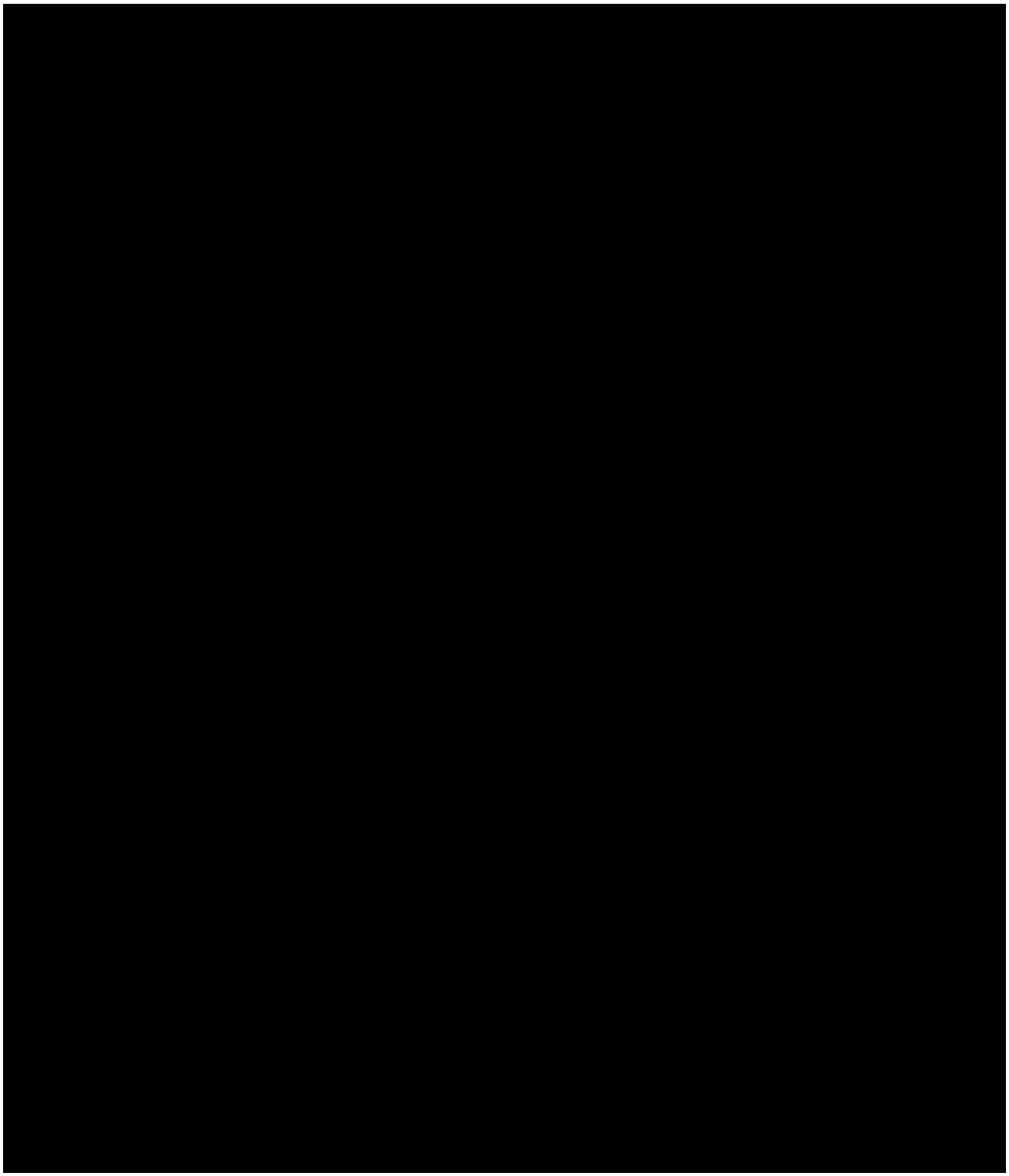
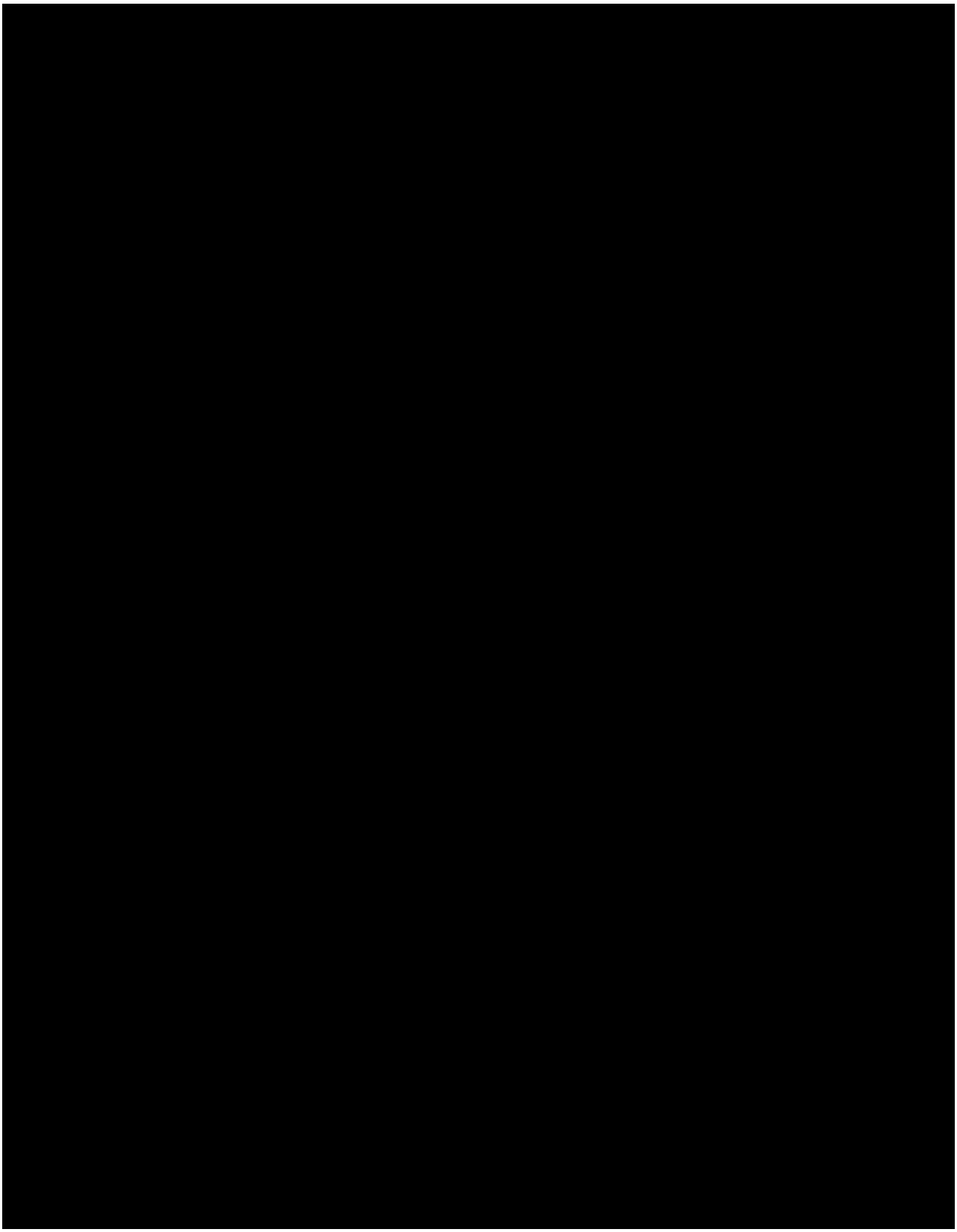
Statistical Analysis Plan

Study Title	An Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of HM15912 in Subjects with Renal Impairment and Matched Control Subjects with Normal Renal Function
Protocol No	HM-GLP2-102
Version	V1.0





Revision History

Approval Date	Version	Prepared by	Comment
05 Sep 2023	V1.0	[redacted]	Initial document

Table of Contents

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
anti-PEG	Anti-polyethylene glycol
ATC	Anatomic Therapeutic Chemical
AUC	Area under the serum concentration-time profile
$AUC_{\%Extrap}$	Percentage of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinite time
AUC_{last}	AUC from time zero to the last observable concentration
BLQ	Below the limit of quantification
BMI	Body mass index
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Clearance
CM	Concomitant medication
C_{max}	Maximum serum concentration
CRU	Clinical research unit
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMR	Geometric mean ratio
HR	Heart rate
ICH	International Conference on Harmonisation
IP	Investigational product

IPD	Important protocol deviation
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not available
NAb	Neutralizing antibody
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Protocol deviation
PK	Pharmacokinetics
PT	Preferred term
QTcF	QT interval corrected using Fridericia's correction
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
$t_{½}$	Elimination half life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{max}	Time to maximum serum concentration
TRAE	Treatment-related adverse event
Vd/F	Volume of distribution
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve

1 INTRODUCTION

This Statistical Analysis Plan (SAP) has been developed based on following study documents:

- Protocol: Version 1.0 (05 Aug 2022)
- Protocol Clarification Letter (05 Sep 2022, 18 Nov 2022, and 27 Jun 2023)
- Electronic Case Report Form (eCRF): Version 2.0 (06 Jan 2023)

This SAP describes the statistical analysis to be conducted for the above mentioned protocol, and has been developed and finalized prior to database lock of the clinical database.

This SAP is being written with consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials”, the most recent ICH E9(R1) Guideline entitled “Addendum on Estimands and Sensitivity Analysis in Clinical Trials” and the most recent ICH E3 Guideline entitled “Guidance for Industry: Structure and Content of Clinical Study Reports”.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part 1: To evaluate the effect of severe renal impairment on the pharmacokinetics (PK) of HM15912 following single SC dose	• Maximum serum concentration (C_{max}) • Area under the concentration-time curve from extrapolated to infinity ($AUC_{0-\infty}$)
Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the pharmacokinetics of HM15912 following single SC dose	
Secondary	
To evaluate the safety and tolerability of a single SC dose of HM15912 in subjects between mild, moderate and severe renal impairment and normal renal function subjects	• Incidence of adverse events (AEs), treatment emergent AEs (TEAEs) and serious AEs (SAEs) • Changes from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters
Exploratory	
To assess the immunogenicity of HM15912 after single SC dose in subjects with renal impairment and in subjects with normal renal function	• Anti-drug antibody (ADA) • Neutralizing antibody (NAb) • Anti-polyethylene glycol (anti-PEG) antibody
To assess the additional PK parameters of HM15912 in subjects	• Time to maximum serum concentration (t_{max}) • Elimination half-life ($t_{1/2}$)

with renal impairment and in subjects with normal renal function	• Volume of distribution (Vd/F) • Clearance (CL/F) • First order rate constant associated with the terminal (log-linear) portion of the curve (λ_Z) • Area under the concentration-time curve from time zero to the last observable concentration (AUC_{last}) • Percentage of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity ($AUC_{\%Extrap}$)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is a phase 1, open-label, single-dose, parallel-group study to investigate the effect of renal impairment on the PK of HM15912 in subjects with severe renal impairment and subjects without renal impairment as a control group (Part 1), and in subjects with moderate and mild renal impairment (Part 2).

At Screening, subjects will be enrolled to the appropriate groups based on the classification as defined in the Food and Drug Administration (FDA) draft guidance for industry, "Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling" (2020). Subjects with normal renal function and subjects with renal impairment will be classified based on the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021).

Subject screening for participation in this study will be conducted within 28 days prior to investigational product (IP) dosing on Day 1. The mean of the eGFR obtained from two screening visits will be used for group assignment. Second baseline eGFR sample will be taken during the screening period, that are greater than 3 days (72 hours) but no more than 14 days apart from the first eGFR assessment. All subjects must have stable renal function to enter the study which is defined as ≤25% difference between 2 measurements of eGFR during the screening period. Subjects will be selected and categorized according to their eGFR as shown in Table 1.

Table 1 Renal Function Categories by eGFR ranges

Cohort	Renal Impairment	eGFR ($mL/min/1.73m^2$)	Number of Subjects
1	Normal	≥ 90	8
2	Severe	< 30	8
3	Moderate	≥ 30 to < 60	8
4	Mild	≥ 60 to < 90	8

Approximately 16 subjects will be enrolled in Part 1; 8 subjects with severe renal impairment (Cohort 2) and 8 with normal renal function (Cohort 1). The 8 subjects of Cohort 2 will be recruited first. After the end of recruitment of Cohort 2, the demographics will be pooled to determine an average value for age and weight which will be used as a reference value for Cohort 1. The subjects with normal renal function in Cohort 1 will be recruited later such that each subject's age is within ±10 years and weight is within ±15 kg of the mean of the Cohort 2. An attempt will be made to maintain a similar male/female ratio between Cohort 1 and Cohort 2. Care will be taken when recruiting the subjects with normal renal function such that the entire group is not younger and of lower body weight than the impaired subjects.

Part 2 will be conducted if the point estimate of geometric mean ratio (GMR) of $AUC_{0-\infty}$ for the severe renal impairment group (Cohort 2) compared to the control group (Cohort 1) [redacted] Based on whether the decision criterion to proceed to Part 2 is met, up to 8 subjects with moderate renal impairment (Cohort 3) and 8 subjects with mild renal impairment (Cohort 4), matched for demographic character to control group will be enrolled.

For both Parts 1 and 2, subjects who withdraw from the study for non-safety related reasons and who are considered to be non-evaluable with respect to the primary objective may be replaced at the discretion of the sponsor but the maximum number of meaningfully evaluable patients will be not more than planned 8.

Each subject will receive a single dose of either HM15912 administered subcutaneous (SC) in the abdomen on the Day 1, and the assessments will be conducted based on Appendix 13.1 in this SAP. Blood samples will be collected from subjects to determine PK of HM15912 up to 29 days post-dose according to the scheduled pharmacokinetic sampling schedule as below:

Table 2 Pharmacokinetic Sampling Schedule

Study Day		PK Sampling Time Point
Day 1	Inpatient Period	Predose
Day 2 [a]		24 h (± 15 min)
Day 3 [b]		48 h (± 60 min)
Day 4 [b]		72 h (± 60 min)
Day 5 [b]		96 h (± 60 min)
Day 6 [b]		120 h (± 60 min)
Day 7 [b]		144 h (± 60 min)
Day 8		168 h (± 60 min)
Day 10	Outpatient Period	216 h (± 24 h)
Day 15		336 h (± 24 h)
Day 22		504 h (± 24 h)
Day 29		672 h (± 24 h)

a. After completion of study procedures on Day 2, if subjects request to discharge, subjects may be discharged from the Clinical research unit (CRU) on their desired date, at the discretion of investigator If subjects discharge

from CRU, all the remaining procedures will be conducted by outpatient visit.
b. If subjects discharge earlier than Day 8 based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visits.

3.2 Treatment Plan

The study drug, HM15912 0.5mg/kg, will be administered once by the authorized site staff via SC injection into abdominal wall.

3.3 Analysis Schedule

After all subjects in Cohort 1 and Cohort 2 have completed all scheduled procedures, preliminary analysis will be conducted to decide whether to proceed to Part 2, or not. Part 2 will be conducted if the point estimate of GMR of $AUC_{0-\infty}$ for the severe renal impairment group (Cohort 2) compared to the control group (Cohort 1) [redacted]

If the decision criterion to proceed to Part 2 is met, final analysis will be conducted after all subjects who are enrolled in the Part 2 complete or discontinue the study. However, if the decision criterion to proceed to Part 2 is not met, final analysis will be conducted follow up with preliminary analysis.

4 DETERMINATION OF SAMPLE SIZE

The planned sample size of 8 subjects for each cohort is selected to characterize the effect of renal impairment on the PK of HM15912 based on FDA and European Medicines Agency (EMA) guideline rather than calculated with consideration of statistical requirements. With 8 subjects for each cohort (renal impairment cohort and normal renal function cohort), half width of two-sided 90% confidence interval of natural log scaled $AUC_{0-\infty}$ difference between two cohorts is 0.2260 with consideration of between-subject standard deviation, 0.257, from the previous phase I study result of HM15912. This provides the 90% confidence interval (0.798, 1.254) for a geometric mean ratio of 1.0.

As stated in the study design part, approximately 16 subjects will be enrolled in Part 1 (8 subjects with severe renal impairment and approximately 8 subjects with normal renal function). If Part 2 is conducted, 8 subjects with moderate renal impairment and 8 subjects with mild renal impairment will be enrolled.

5 ANALYSIS SET

An analysis populations classification will be discussed to decide which subjects and/or data will be excluded from certain analyses. The decisions will be made before the database lock and will be documented and approved.

In this study, the following populations are defined.

Table 3 Analysis Set Definition

Population	Description
Screened Population	All subjects who signed the Informed consent form to proceed with screening. This population will be used only for the disposition summary and by-subject listings.
Safety Population	All subjects who received any amount of HM15912. All analyses other than that specified will be performed based on safety population.
PK Population	All subjects who have at least one evaluable HM15912 serum concentration after receiving any amount of HM15912 without important protocol deviations (IPDs) or events (i.e. significantly affect the PK of study drug). PK parameter analyses will be conducted with PK population.

6 ESTIMAND

6.1 Estimand for the Primary Objective

The primary estimand is defined through the following estimand attributes:

6.1.1 Treatment and Target Population

The target population of the estimand for the primary objective is all subjects who have at least one evaluable HM15912 serum concentration after receiving any amount of HM15912 without IPDs or events that significantly affect the PK of HM15912. This population is represented in this trial by PK Population.

6.1.2 Intercurrent Event and Handling Strategies

Table 4 Handling of Intercurrent Events for the Primary Estimand

Intercurrent event	Data collection and analysis
Use of prohibited medication	Depending on the assessment of the type of prohibited medication in the determination of PK Population, data collected after the intercurrent event will be used in analysis in line with a treatment policy strategy or a while on-treatment policy.
Early withdrawal from the study	Depending on the assessment of the timing of early withdrawal from the study in the determination of PK Population, the intercurrent event will be handled via a while on-treatment policy.

6.1.3 Variable and Population-level Summary

To evaluate the effect of severe renal impairment on the pharmacokinetics of HM15912

following single SC dose, PK parameters will be summarized by endpoint as presented in Table 5.

Table 5 Population level summary for Primary endpoints

Primary endpoint	Population-level summary
Maximum serum concentration (C_{max})	Geometric mean ratio (GMR) and corresponding 90% confidence interval (90% CI) between each renal impairment cohort and normal renal function cohort (i.e. Cohort 2, Cohort 3, Cohort 4 versus Cohort 1, respectively) will be presented with descriptive statistics [number of subjects, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric mean CV% median, minimum, and maximum values].
Area under the concentration-time curve from extrapolated to infinity ($AUC_{0-\infty}$)	

To explore the robustness of inferences from the main estimator, a sensitivity analysis will be conducted targeting the same estimand. If the adjusted regression coefficient (R^2) is less than 0.8 or the extrapolated area under the curve ($AUC_{\%Extrap}$) exceeds 20%, those will be excluded from the sensitivity analysis.

6.2 Estimand for the Secondary Objective

The secondary estimand is defined through the following estimand attributes:

6.2.1 Treatment and Target Population

The target population of the estimand for the secondary objective is all subjects who received any amount of HM15912. This population is represented in this trial by Safety Population.

6.2.2 Intercurrent Event and Handling Strategies

Table 6 Handling of Intercurrent Events for the Secondary Estimand

Intercurrent event	Data collection and analysis
Use of prohibited medication	Intercurrent events will be handled via a while on-treatment policy with a residual treatment effect period strategy. All intercurrent events will be ignored because of residual treatment effect. Safety summaries will be based on the available safety data collected until the last study visit.

6.2.3 Variable and Population-level Summary

To evaluate the safety and tolerability of a single SC dose of HM15912 in subjects between mild, moderate and severe renal impairment and normal renal function subjects, secondary

endpoints will be summarized as presented in Table 7.

Table 7 Population level summary for Secondary endpoints

Secondary endpoint	Population-level summary
Incidence of AEs, TEAEs, and SAEs	Number and percentages of subjects with TEAEs and SAE by cohort and in total. AEs which are occurred after signing of ICF and before first study drug administration will be included in by-subject listing with TEAE flag, and will not be summarized.
Change from baseline in vital signs and 12-lead ECG parameters	Descriptive statistics of change from baseline in vital signs and 12-lead ECG parameters by cohort and in total.

7 GENERAL STATISTICAL CONSIDERATION

All statistical analyses will follow the rules which is planned in this section unless other specified.

7.1 Summary and Representation of Data

In general, data will be summarized with descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum) for continuous variables, and number of subjects and percentages for categorical variables. All summaries and analyses will be presented by cohort and in total where applicable. By visit or timepoint analysis results will be summarized appropriately using nominal visit or timepoint as defined in the Schedule of Assessments.

For summary statistics, the arithmetic mean and median will be displayed to one more decimal place than the raw data and SD will be displayed to two more decimal places than the raw data. The minimum and maximum will be displayed to the same number of decimal places as the raw data. Percentages will be presented to one decimal place, and will not be presented for zero counts. The denominator in percentage calculations will be the number of subjects in each treatment group within the relevant analysis set. In general, the maximum number of decimal places reported shall be four for any summary statistic.

For pharmacokinetic analysis, data will be summarized with N (number of subjects), n (number of subjects with non-missing values), and n(BLQ) (number of subjects with BLQ samples), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric mean CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values, except for t_{max} and $t_{1/2}$.

Point estimate of geometric mean ratio and corresponding confidence interval (CI) will be presented to two decimal places.

All recorded and derived data which are related with analysis of this SAP will be presented in

the by-subject listing for Screened population. Each subject's cohort information and defined analysis population will be presented for all listings.

7.2 Baseline

The baseline value is defined as the last non-missing measurements collected prior to the first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values. Change from baseline and percent change from baseline will be calculated as below only when the both baseline and post-baseline values are available in each subjects.

- Change from Baseline = Post-baseline – Baseline
- Percent Change from Baseline (%) = (Post-baseline – Baseline) / Baseline * 100

7.3 Repeat and Unscheduled Data

Values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit and time point. All collected data will be included in the data listings.

7.4 Handling of Missing Data

Except as stated below, there will be no imputation of missing values, and all data will be included in the by-subject listings as it is.

7.4.1 Missing or Partial Dates

In general, missing or partial date will not be imputed except for classification of Treatment Emergent Adverse Event (TEAE) or Concomitant Medication (CM). If the start and/or stop date are partial, the dates will be compared as far as possible with the date of first study drug administration. However, if the missing or partial date interrupts classification, adverse events or medication will be treated as TEAE or CM.

7.4.2 Missing Assessment of Adverse Event

If the assessment of the severity or relationship to study drug is missing for the AEs, the event will be classified as 'Severe (or Grade 3)' or 'Related', respectively, for summary purposes.

7.5 Study Day

The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1. The date preceding first study drug administration is designated as study day -1 (there will be no Day 0).

- If the date of event is before the study drug administration, then:

Study Day = (Date of event - Date of first study drug administration)

- If the date of event is on or after the study drug administration, then:
  Study Day = (Date of event - Date of first study drug administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for the end date of ongoing events at the end of the study.

7.6 End of Study

A subject is considered to have completed the study if subject has completed all periods of the study including the last scheduled procedure shown in the Schedule of Assessments. The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure for the last subject in the trial globally.

7.7 Software

PK parameters will be derived with standard non-compartmental analysis (NCA) methods using PKanalix® version 2023 (application of the MonolixSuite™ for NCA) or any available software for the PK analysis, and the other analysis will be performed using SAS® version 9.4 or higher.

All analyzed tables, listings, and figures will be generated using SAS® Version 9.4 or higher.

8 CHANGE FROM PROTOCOL

There is no change from protocol.

9 STATISTICAL METHODS

9.1 Study Subjects

9.1.1 Disposition of Subjects and Analysis Population

For screened population, subject disposition at the end of screening and at the end of study will be summarized including the reason of termination from each study milestone. The number of screened subjects will be used as denominator for the summary of end of screening status, and the number of screening completed subjects will be used as denominator for the summary of end of study status.

The summary of subjects who included / excluded in each analysis population (i.e., Safety population and PK population) and the reason for exclusion will be provided.

9.1.2 Protocol Deviation

A full list of protocol deviations (PD) for the study will be reviewed prior to database lock, and the important protocol deviations will be identified.

Based on Safety population, the summary of protocol deviation will be provided by protocol deviation category and sub-category, with a focus on important protocol deviation. By-subject listing of all protocol deviations will be provided.

9.2 Efficacy Evaluation

9.2.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the safety population and the PK population. Demographic and baseline characteristics include, but are not limited to: age, sex, race, ethnicity, weight, height, body mass index (BMI), and eGFR at baseline. BMI and eGFR at baseline will be calculated according to the formula below.

- Baseline BMI (kg/m^2) = Baseline weight (kg) / [Baseline height (cm) / 100]^2
- Baseline eGFR ($mL/min/1.73m^2$) = The mean of the eGFR obtained from two screening visits

9.2.2 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or higher. Based on Safety population, the summary of medical history will be provided by System Organ Class (SOC) and Preferred Term (PT), with a focus on ongoing status. By-subject listing of all medical histories will be provided.

9.2.3 Prior and Concomitant Medication

Prior medication is defined as any medications that start and end before the first study drug administration. Concomitant medication is defined as any medications that were administered after the first study drug administration (including medications that start prior to dosing and continued after).

The WHO Drug Global (B3) Version September, 2022 or higher will be used to categorize the verbatim descriptions of medications into the Anatomic Therapeutic Chemical (ATC) classification system.

Prior and Concomitant medications will be summarized by ATC level 2 (therapeutic class) and preferred term for the Safety population. Subjects who used the same medication on multiple occasions will only be counted once in each specific category.

By-subject listing will be provided with flags to distinguish the prior and concomitant medications.

9.2.4 Extend of Exposure

Detailed information for the study drug administration will be listed by subject for the Safety population.

9.2.5 Pharmacokinetic Concentration

HM15912 serum concentrations at each nominal sampling time will be summarized by cohort and in total for the Safety population as well as PK population, and all individual data will be listed as it is reported for the Safety population.

The serum concentration-time profiles will be depicted on a linear and semi-logarithmic scale as follows:

- Individual HM15912 serum concentrations-time plots
- Overlaid individual HM15912 serum concentrations-time plots
- Mean (± SD) HM15912 serum concentrations-time plots

In general, concentration values that are below the limit of quantification (BLQ) will be set to zero for the purposes of PK concentration analysis, but the embedded BLQ value between 2 quantifiable concentrations or BLQ value following the last quantifiable concentration in a profile will be set to missing. If there are missing values (e.g., Not available (N/A)) in the concentration data, these will be set to missing.

9.2.6 Pharmacokinetic Parameters

PK parameter will be presented for the PK population, and all available individual data will be listed for the Safety population.

PK parameters will be calculated using the standard NCA method with the log-up linear-down method of AUC. Actual sampling times will be used for deriving PK parameters.

The following PK parameters of HM15912 will be summarized.

Table 8 PK parameters

Parameter	Description
Primary endpoint	
$AUC_{0-\infty}$ *	Area under the serum concentration-time profile (AUC) from time zero extrapolated to infinite time
C_{max}	Maximum serum concentration
Exploratory endpoint	
t_{max}	Time to maximum serum concentration
$t_{1/2}$ *	Elimination half-life
Vd/F *	Volume of distribution
CL/F *	Clearance (CL/F = Dose / $AUC_{0-\infty}$)
λ_z *	First order rate constant associated with the terminal (log-linear) portion of the curve
AUC_{last}	AUC from time zero to the last observable concentration
$AUC_{\%Extrap}$ *	Percentage of $AUC_{0-\infty}$ due to extrapolation from t_{last} to infinity

* As data permit

To determine the apparent first-order terminal elimination constant (λ_z), linear regression will be conducted by the logarithmically scaled concentration against time. The constant λ_z and its related parameters will be flagged and excluded in the statistical analysis if data points are

less than 3 after C_{max}.

In order to comparing the exposures among cohorts, box and whisker plots of C_{max}, $AUC_{0-\infty}$ and AUC_{last} will be generated.

After Part 1, PK parameter of HM15912 from severe renal impairment group (Cohort 2) will be estimated and compared to control group (Cohort 1). A one-way analysis of variance (ANOVA) will be used to compare log transformed PK parameter. The estimates of mean difference (Cohort 2 – Cohort 1) and corresponding 90% confidence intervals (CI), as well as each exponentiation of estimates will be presented to provide the estimates of geometric mean ratio. After statistical or clinical evaluation of results from Part 1, whether to proceed to Part 2 will be further discussed.

If Part 2 is conducted, the same analysis with Part 1 will be implemented to compare of each moderate (Cohort 3) or mild (Cohort 4) renal impairment subjects and normal renal function subjects in Cohort 1. In case the demographics (weight and age) of the moderate or mild renal impairment group compared to the normal renal function group are not within the criteria specified in the protocol, it will be considered to add that demographic information as a covariate of ANOVA. If needed, further evaluation to characterize the relationship between renal function and PK parameter will be explored.

9.3 Safety Analysis

Safety data will be summarized for the Safety population, and all safety data will be listed.

9.3.1 Adverse Events

All AEs will be coded using the MedDRA Version 25.1 or higher, and each AEs will be assessed by the investigator for relationship to the study drug (i.e., ‘Not-related’, ‘Related’) and severity using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. In this study, neoplasms (malignant and benign), suspicion of liver injury, and cholecystitis are treated as adverse events of special interests (AESIs).

AE analyses will focus on treatment-emergent AEs (TEAEs) which are defined as any AE that begins, or worsens in severity on or after the date of first study drug administration until the last follow up visit.

Summaries of TEAEs will include the following:

- Overall summary of TEAEs
- Incidence of TEAEs
- Incidence of TEAEs with Maximum Severity
- Incidence of Treatment-related AEs (TRAEs)
- Incidence of TRAEs by Maximum Severity
- Incidence of Treatment-emergent serious adverse event (TESAEs)
- Incidence of Treatment-related TESAEs
- Incidence of AEs of Special Interest (AESIs)

In general, incidence will be summarized using the number and percentage of subjects experiencing an event by SOC and PT, and in case of AESIs, the AESI category and PT are used for summarization.

If the subjects who experience more than one AE with the same preferred term, then the subject will be counted only once in that preferred term, and will be included in the most severe and most related category for the summarization by severity and by relationship to study drug.

Any injection site reactions will be reported as AEs, and included in the summary of TEAEs. Details of injection site assessments for each pain on palpation, itching, erythema, edema, induration, and other injection site reaction at each study day and timepoint will be listed separately.

For the following AEs, additional listings will be provided to deserve special attention.

- All SAEs
- All TEAEs leading to drug interruption / withdrawn
- All TEAEs leading to death

9.3.2 Clinical Laboratory Assessments

Clinical laboratory test results performed by the central laboratory will be summarized for the parameters below:

Table 9 Clinical Laboratory Parameters

Hematology	Coagulation	Clinical Chemistry	Urinalysis
• RBC count • WBC count (with differential) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes • Platelet count • Hemoglobin • Hematocrit • RBC indices: • MCV • MCH • %Reticulocytes	• PT (INR) • aPTT	• Fasting plasma glucose • BUN • Creatinine • Potassium • Sodium • AST • ALT • GGT • Alkaline phosphatase • Total and direct bilirubin	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal) • Pregnancy test

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

By nominal visit and timepoint, observed value and the change from baseline value of quantitative laboratory parameters will be summarized using descriptive statistics, and the frequency tabulation for the qualitative laboratory parameters will also be provided.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be replaced with the value without the sign (e.g., <2.2 will be imputed as 2.2) for the summarization purpose.

Each laboratory test results will be evaluated by the investigator as 'Normal', 'Abnormal, Not Clinically Significant', or 'Abnormal, Clinically Significant'. Shift tables will be generated showing the number and percentage of subjects with shifts from baseline to each post-baseline visit.

All by-visit summary of laboratory test data will be provided based on the test results at scheduled visit, but all the data will be listed by subject regardless of measurements at scheduled or unscheduled.

By-subject listing for all laboratory test data including the parameters which are not specified in the Table 9 (i.e., HbA1c, eGFR, serum hCG pregnancy test, serum FSH test, serology, urine drugs of abuse and alcohol breath test) will be provided as recorded in the raw data.

9.3.3 Vital Signs

Observed value and the changes from baseline value for vital signs measurements [tympanic body temperature, respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)] will be summarized using descriptive statistics by scheduled visit. For summary of body temperature, Celsius degree will be used with the conversion formula as below:

- Celsius degree (℃) = [Fahrenheit degree (°F) – 32] x 5 / 9

For SBP, DBP, and HR which are measured greater than or equal to 2 consecutive times of each visit, mean value of consecutive measurements will be used for summarization. If there is missing data among the consecutive measurements, only the non-missing value will be used to calculate the mean value.

Overall interpretation ('Normal', 'Abnormal, Not Clinically Significant', or 'Abnormal, Clinically Significant') for the vital signs will be summarized using shift table to compare the investigator's evaluation between baseline and each post-baseline visit and timepoint.

By-subjects listing for all vital signs data which is recorded and derived will be listed.

9.3.4 Physical Examination

Physical examination findings ('Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant'), height, weight, and BMI will be listed by subject.

9.3.5 12-lead Electrocardiograms

A triplicate 12-lead ECGs will be performed at screening period and Day 1. At all other times, however, single 12-lead ECGs will be performed. For the ECGs measurement taken in triplicate, mean of the triplicates measurements will be used as baseline and post-baseline

value of each visit and timepoint. If there is missing data among the triplicated measurements, only the non-missing value will be used to calculate the mean value.

Automatically calculated HR, PR, QRS, QT, and corrected QT using the Fridericia correction formula (QTcF) will be used to summarize the observed value and change from baseline value by visit and timepoint.

Additional categorical analysis for the QT and QTcF will also be performed based on categories as below:

- Observed value: ≤450 ms, >450 and ≤480 ms, >480 and ≤500 ms, >500ms
- Change from baseline value: ≤30 ms, >30 ms and ≤60 ms, >60 ms

Overall interpretation ('Normal', 'Abnormal, Not Clinically Significant', or 'Abnormal, Clinically Significant') of 12-lead ECG will be summarized using shift table to compare the investigator's evaluation between baseline and each post-baseline visit and timepoint.

9.3.6 Immunogenicity

Anti-drug antibodies (ADAs) will be summarized categorically, hierarchically displaying the positive and negative results from screening assay and confirmatory assay by scheduled visit and cohort. Confirmed positive ADAs will be further summarized by titer fold categories. Domain specificity will be listed along with the screening, confirmatory assay and titer results.

Neutralizing antibodies (NAbs) will be summarized categorically for the subjects who have ADA positive results from confirmatory assay, hierarchically displaying the positive and negative results from screening assay and confirmatory assay by scheduled visit and cohort. Cross-reactivity for confirmed positive NAbs will be summarized by scheduled visit and cohort.

Anti-polyethylene glycol (Anti-PEG) antibodies will be summarized categorically, displaying the positive and negative results from screening assay, confirmatory titer and specificity by scheduled visit and cohort.

10 INTERIM ANALYSIS

No formal interim analyses are planned for this study, but preliminary analysis will be conducted to decide whether proceed to Part 2 as stated in the section 3.3 of this SAP.

11 SAS PROCEDURES

One-way ANOVA to compare PK parameter between cohort:

```
PROC MIXED DATA=data;
        CLASS cohort;
        MODEL lnpk = cohort / DDFM=KR;
        REPEATED / TYPE=UN SUBJECT=subjid GROUP=cohort;
        ESTIMATE 'Severe vs Normal' cohort -1 1 / CL ALPHA=0.1;
```

```
RUN;
```

12 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH Harmonised Guideline, Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials (E9 (R1)), 20 November 2019.

4. Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing. FDA Guidance, September 2020.

5. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function. EMA Committee for Medicinal Products for Human use, 17 December 2015.

13 APPENDICES

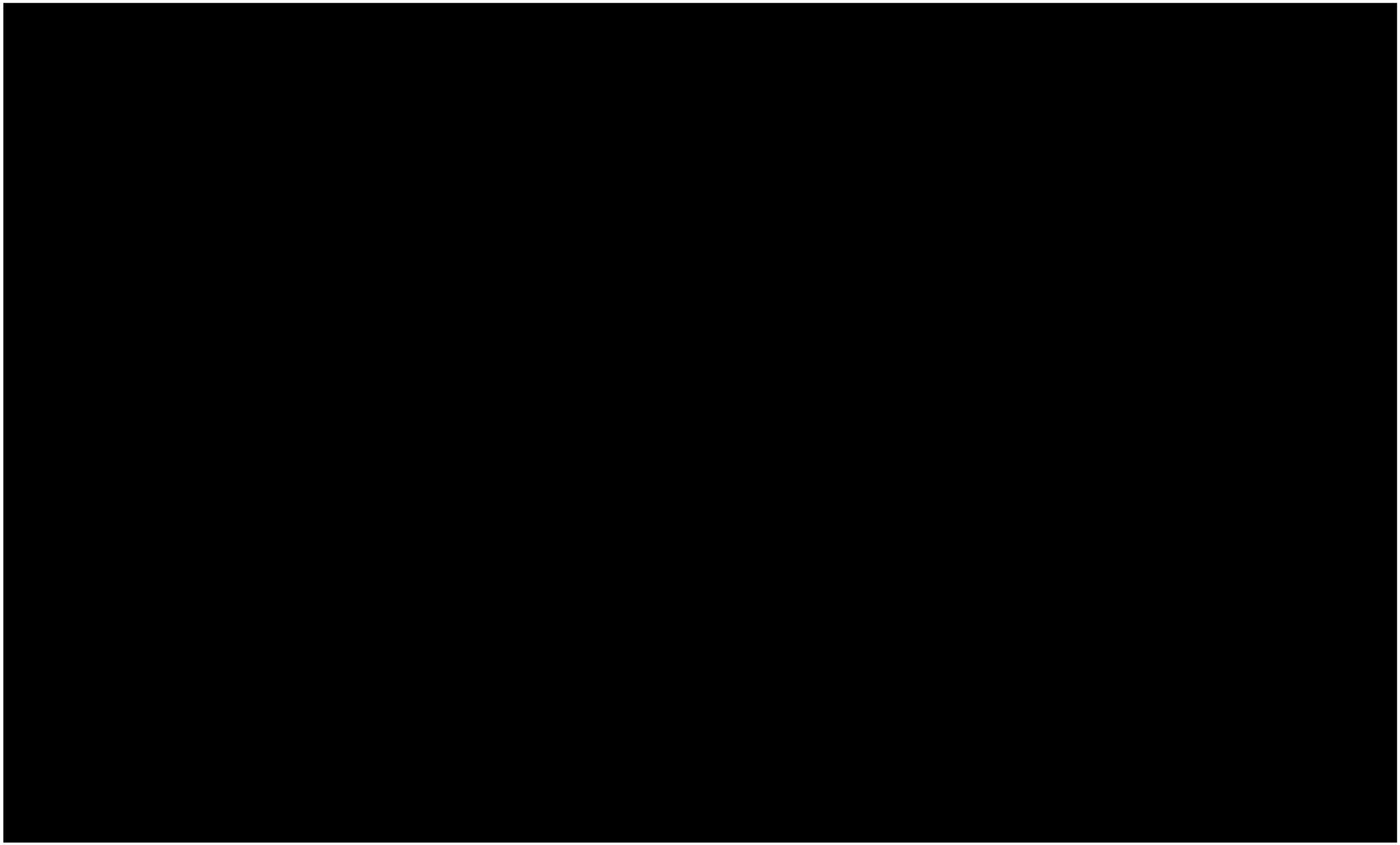
13.1 Schedule of Assessments

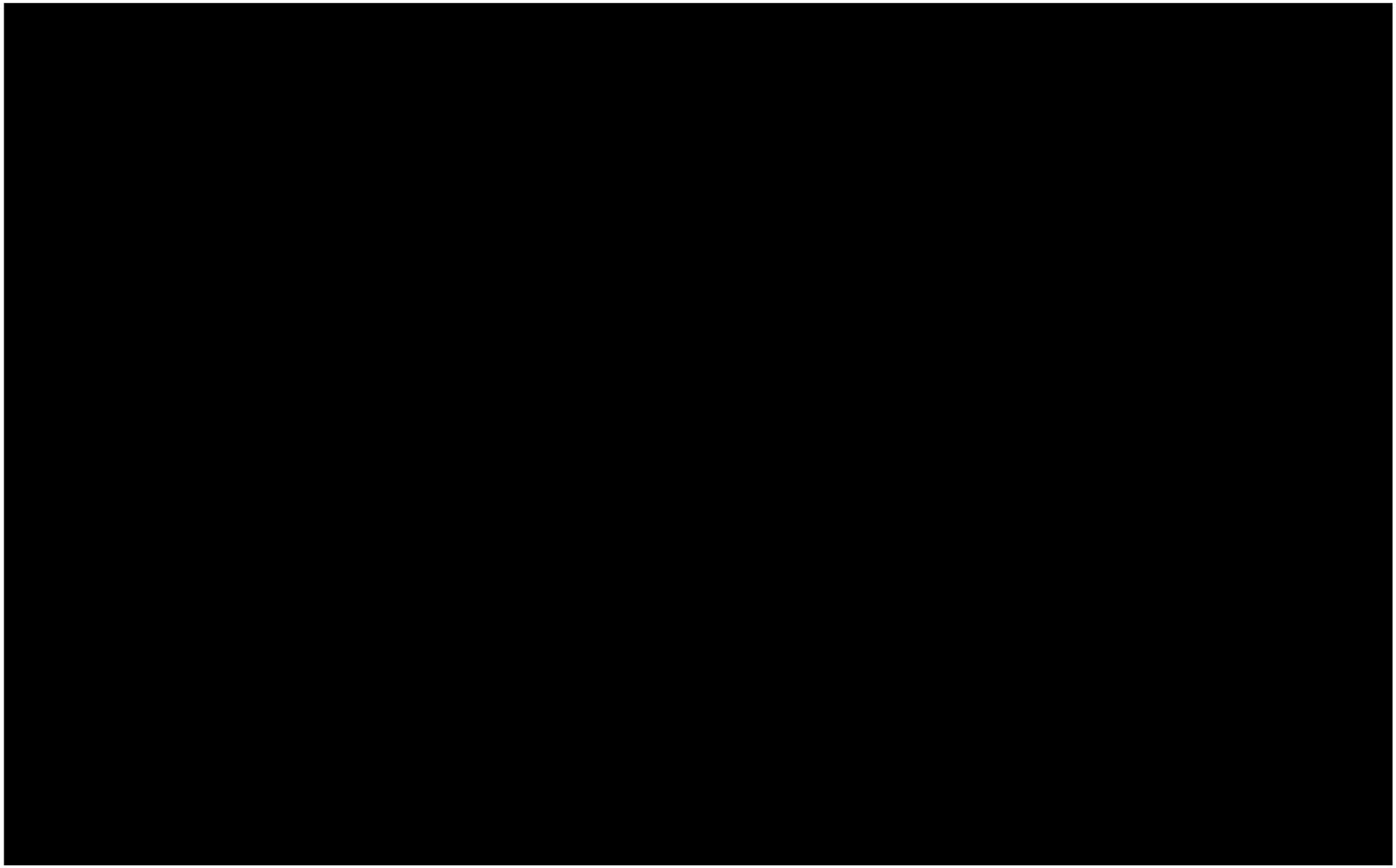
Visit	Screening Visit[a]		Inpatient Period									Outpatient Period			
Day	S1	S2	-1	1	2	3[e]	4[e]	5[e]	6[e]	7[e]	8	10 (±1day)	15 (±1day)	22 (±1day)	29[m] (±1day)
Informed consent	X														
Inclusion/exclusion criteria	X		X												
Medical history	X		X												
eGFR assessment[a]	X	X													
Demographic data (age, sex, etc.)	X														
Height[b]	X														
BMI, Body weight[b]	X			X											X
Pregnancy test (female subjects with childbearing potential only)[c]	X		X												X
Serum FSH (postmenopausal females only)	X														
HbA1c	X														
Urine drugs of abuse and alcohol breath test	X		X								X[f]	X	X	X	X

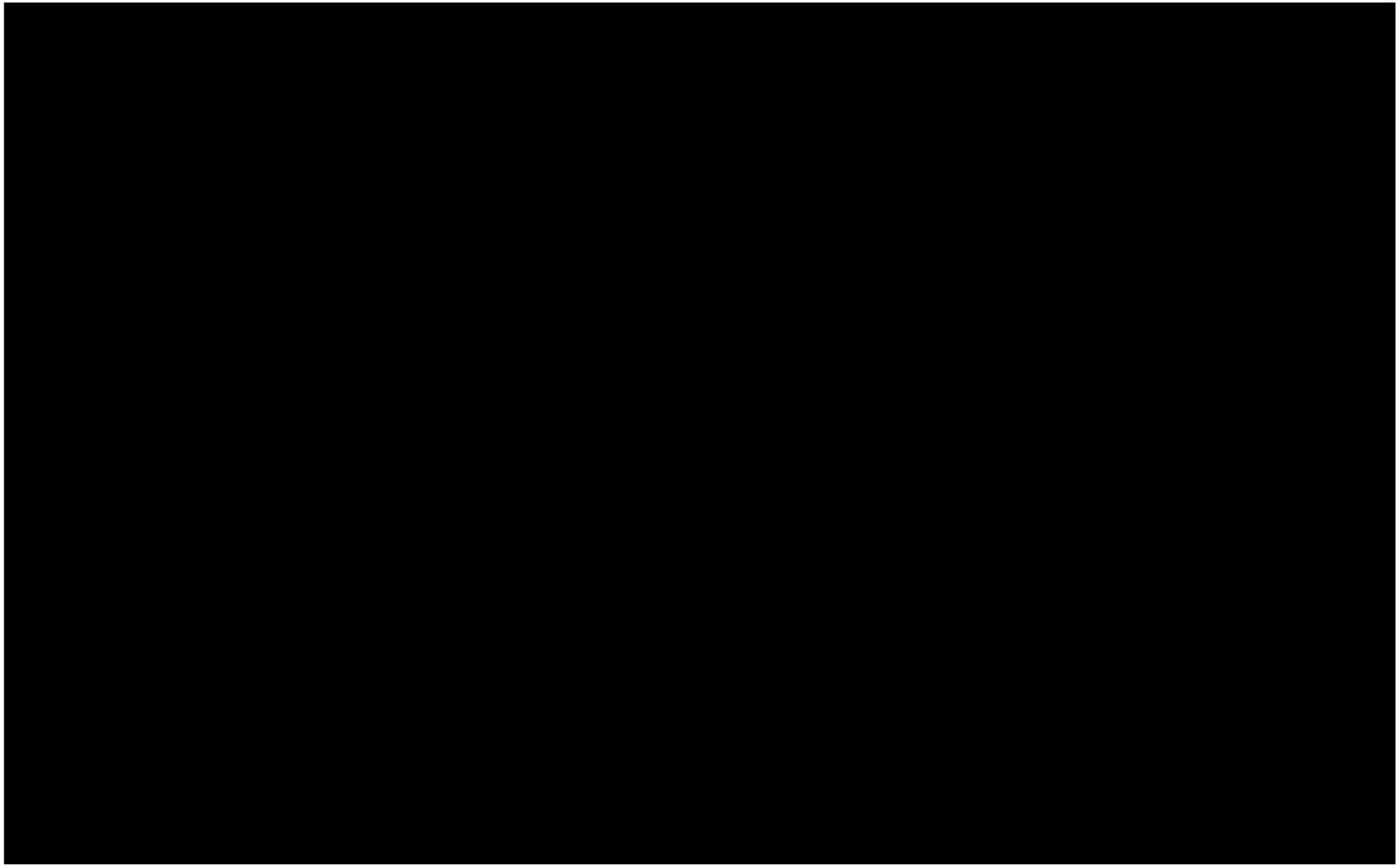
Visit	Screening Visit[a]		Inpatient Period									Outpatient Period			
Day	S1	S2	-1	1	2	3[e]	4[e]	5[e]	6[e]	7[e]	8	10 (±1day)	15 (±1day)	22 (±1day)	29[m] (±1day)
Check-in			X												
Check-out[d]											X				
IP administration				X											
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, tympanic body temperature, RR)[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (hematology, coagulation, chemistry[h], urinalysis)	X	X[i]	X	X	X						X		X	X	X
12-lead ECG[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG antibody)			X										X		X
Injection site assessments[k]				X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations[l]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling				X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody; anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; HR=heart rate; IP = investigational product; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous;

a. Screening will consist of two CRU outpatient visits (Screening Visit 1 and 2) -between 3 to 14 days apart, with the 1st screening visit occurring within 28 days prior to IP administration (Day 1). At each screening visit, blood sample will be taken for the eGFR assessment. The 2nd screening visit is only to demonstrate stable renal function with eGFR ≤ 25% of the value obtained at Screening visit 1. Other screening procedures completed during the first visit do not need to be repeated except eGFR, adverse event assessment and physical examinations.
b. Height and weight measurements will be performed with shoes removed. Weight will be recorded rounded to 1 decimal place. If weight is measured rounded to 2 decimal places, the number is rounded off from the second digit after the decimal point. BMI will be calculated with the height measured at S1.
c. Serum pregnancy tests at the Screening visit; serum or urine pregnancy tests at the Day -1 and Day 29. A woman is considered to have childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile.
d. After completion of study procedures on Day 2, if subjects request to discharge, subjects may be discharged from the CRU on their desired date, upon investigator's discretion. If subjects discharge from CRU, all the remaining procedures scheduled for inpatient period will be conducted by outpatient visit.
e. If subjects discharge earlier than Day 8 based on the subject's request, Day 3, 4, 5, 6, and 7 procedures can be done in outpatient visits.
f. On Day 8, urine drug test and alcohol screening will be performed only if subjects discharge earlier than Day 8.
g. Supine BP and HR will be measured for 2 consecutive times, at least 2 minutes apart, after the subject has been recumbent and at rest ≥ 5 minutes, and mean values will be recorded. If abnormal, at the Screening visit, measurement will be repeated 1 more time and the average of the 3 BP values should be used to determine the subject's eligibility.
h. Samples for a chemistry test will be collected after at least 4 hours of fasting.
i. The 2nd screening visit is only to demonstrate stable renal function with eGFR ≤25% of the value obtained at Screening visit 1. Other clinical laboratory tests except serum creatinine assessment, do not need to be repeated.
j. The 12-lead ECGs will be performed after the subject has been resting supine for ≥ 5 minutes. A triplicate 12-lead ECGs will be performed at screening period and Day1. At all other times, however, single 12-lead ECGs will be performed. Limited to Day 1, ECGs will be performed at predose and at 4 hours postdose, and a ±30-minute assessment window is allowed for measurement 4 hours postdose. Triplicate ECGs will be recorded at least 30 seconds apart from each other, not exceeding a time period of 3 minutes for the completion of all 3 ECGs.
k. Injection site assessments will be performed at predose and at 4 and 12 hours postdose on Day 1.
l. Full physical examination at Screening Visit 1 (S1); brief physical examination at all other time points.
m. At the early discontinuation visit, every effort must be made to complete the assessments planned at Day 29.







[redacted]