Statistical Analysis Plan

Study Title	A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HM15912 in Healthy Subjects
Protocol No	HM-GLP2-101
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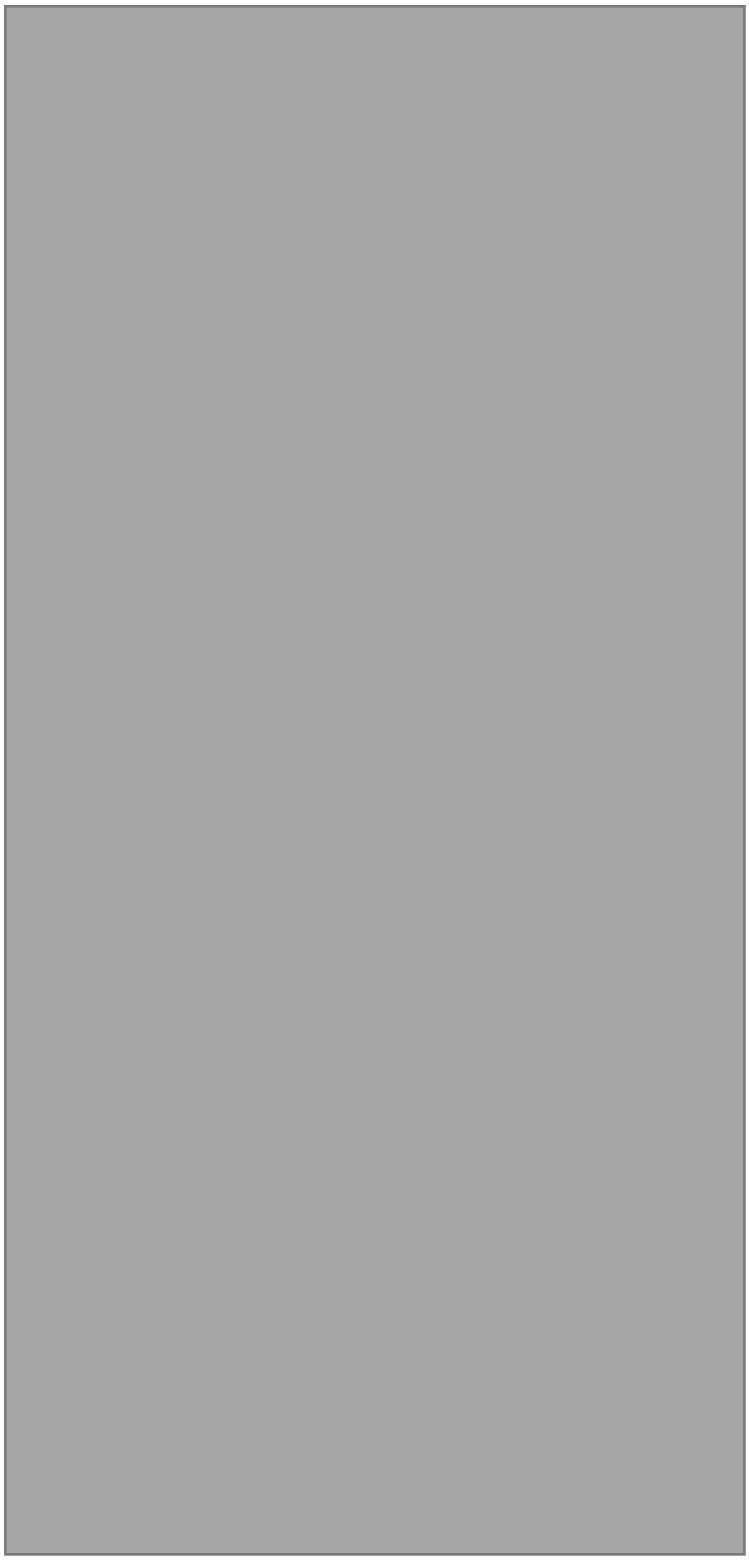
Signature Page

Prepared by

BioMetrics Associate
_Statistician



Reviewed by

Investigator

Clinical Operation Associate

Clinical Operation Manager

Clinical Science Associate

Clinical Science Manager

BioMetrics Associate
_Pharmacometrician

Biostaitstician
Parexel International

Approved by

Director of Biometrics

Revision history

Approval Date	Amended Version	Prepared by Name	Comment
24-Mar-2020	V1.0	[redacted]	Initial document
29-Apr-2020	V1.1	[redacted]	Per the amended protocol V4.2, updated Schedule of Assessments in 10. APPENDIX and listing of Alcohol Breath Test.
18-Aug-2020	V2.0	[redacted]	1. Study period in section 2.1 is corrected according to the protocol V4.2. 2. Analysis set definition is descripted in more detailed (section 4). 3. Range of listing of protocol deviations is changed to include all protocol deviation (section 5.7). 4. Summary criteria of multiple observations is changed from 'by visit' to 'by time-point' (section 6.1.2). 5. Change from baseline of Lab results (section 6.2.2) and PD results (section 6.4) are added for tabulation. 6. BMI is added for the tables and listings (section 6.2.3). 7. For the evaluations for the triplicated measured ECG values, the worst values would be used (section 6.2.4). 8. PK line plot by cohort is added (section 6.3.1). 9. Add detail explanation for the dose proportionality test (section 6.3.3). 10. Adding analysis related to COVID-19 (section 6.1 and 6.1.3) 11. Detailed description for immunogenicity analysis is added (section 6.2.7)

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ABBREVIATIONS

Abbreviation	Definition of Term
_obs	observed
_pred	predicted
ADA	Anti-drug antibody
ADAbs	Anti-drug antibodies
Adj_RSq	Adjusted r squared
AE	Adverse event
anti-PEG	Anti-polyethylene glycol antibodies
ATC	Anatomic Therapeutic Chemistry
AUC	Area under the concentration time curve
AUC0-inf	Area under the concentration time curve from zero to infinity
AUC0-t	Area under the concentration time curve from zero to time of last time observed, $AUC_{0\text{-}t} = AUC_{0\text{-}last}$
AUC%extrapolation	Percentage of AUCinf that is due to extrapolation beyond tlast
BLQ	Below the limit of quantitation
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CL	Apparent clearance
CL/F	Apparent clearance divided by bioavailability
Cmax	Maximum concentration
CS	Clinical significant
CV	Coefficient of variation
ECG	Electrocardiogram
F	Bioavailability
FFA	Free fatty acid
FPG	Fasting plasma glucose
GIP	Gastric inhibitory peptide
GLP-1	Glucagon like peptide-1
HDL	High-density lipids
HR	Heart rate
ICH	International Council for Harmonisation
IGF-1	Insulin-like growth factor-1
IP	Investigational product
IRB	Institutional Review Board

Abbreviation	Definition of Term
KGF	Keratinocyte growth factor
LDL	Low-density lipids
LLOQ	Lower limit of quantitation
LS	Least squares
max	maximum
MedDRA	Medical dictionary for regulatory activities
MFDS	Ministry of Food and Drug Safety
MID	Minimum intolerable dose
min	minimum
MTD	Maximum tolerated dose
n	sample size
nAbs	Neutralizing antibodies
NCA	Non-compartmental analysis
NCS	Non-clinical significant
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PT	Preferred term
QTcF	QT interval corrected for heart rate using Fridericia's correction
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System organ class
t1/2	Half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum concentration
VLDL	Very low-density lipids
Vz	Apparent volume of distribution at terminal phase
Vz/F	Apparent volume of distribution at terminal phase divided by bioavailability
WHO	World Health Organization
λ_z	Apparent elimination constant

1. INTRODUCTION

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

Protocol: A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HM15912 in Healthy Subjects (Korean Version 4.2, English version 4.2)

Electronic Case Report Form (eCRF), version 4.0

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

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

2. STUDY OVERVIEW

2.1 Study Design

This is a first-in-human, double-blind, randomized, placebo controlled, single ascending dose (SAD) study to investigate the safety, tolerability, PK and PD of the SC administration of HM15912 in healthy subjects.

The study will be conducted in approximately 5 sequential dosing cohorts, enrolling 8 subjects per cohort. Subjects will be randomized to HM15912 or placebo in a ratio of 6:2 (6 active, 2 placebo).

To follow a sentinel dosing approach in this first-in-human (FiH) study, each cohort will be divided in 2 blocks in order to implement the sentinel dosing approach. Within each cohort, the first block will consist of 2 sentinel subjects; 1 subject will receive HM15912, and 1 subject will receive matched placebo. The second block will consist of 6 subjects randomized to receive HM15912 (n = 5) or matched placebo (n = 1). Individual subjects in the second block will be dosed at least 24 hours after the first block.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of either HM15912 or matched placebo-administered SC in the abdomen on the morning (8:00 AM – 10:00 AM) of Day 1. Subjects will continue fasting through approximately 4 hours post dose. Water intake is also limited for approximately 1 hour before dosing and approximately 2 hours after dosing.

The planned maximum dose of HM15912 is 1.5 mg/kg; however, higher doses may be administered if safety is confirmed in previous cohorts. If dose is escalated to 1.5 mg/kg or above, approval of the Ministry of Food and Drug Safety (MFDS) will be obtained. After at least 6 subjects (HM15912, n ≥ 4) in each cohort have completed assessments through at least Day 17, blinded safety data will be reviewed and a dose decision/dose escalation decision for the subsequent cohort will be made by the Principal Investigator and the Sponsor. If there are PK/PD data obtained from the preceding or current cohorts, the PK/PD data will be reviewed as well when necessary. Escalation will only proceed if safety and tolerability data related to the dose of the prior cohort are verified. Determination of whether to proceed to the next cohort will be made by the Principal Investigator and the Sponsor, and changes in the dose and the number of cohorts will be approved by the MFDS and the IRB.

PK data will only be reviewed if available. After review of the PK data from preceding or current cohorts, changes in time points for PK collection, clinical laboratory assessments, and PD collection may be required and will be approved by the MFDS and the IRB.

If dose escalation is stopped based on available blinded safety data, the current dose level will be considered as the minimum intolerable dose (MID). The dose just below the MID will be regarded as the maximum tolerated dose (MTD). If the dose escalation is stopped due to reaching exposure limit without dose-limiting safety findings, the MTD cannot be determined. Dose de-escalation may occur in the last cohort or additional cohorts to further refine clinically relevant dose levels.

The study will be comprised of:

- A Screening visit up to 28 days before dosing
- An inpatient assessment period of approximately 8 days, with admission to the institution on Day -1, dosing on Day 1 and discharge on Day 7 once the planned schedule is completed
- For Cohort 1~3
  - Two Outpatient visits on Day 10 (± 1 day) and Day 17 (± 1 day)
  - A final Follow-up visit on Day 30 (± 3 days)
- For Cohort 4~5
  - Four Outpatient visits on Day 8 (± 4 hours), Day 10 (± 1 day), Day 17 (± 1 day) and Day 30 (± 3 days)
  - A final Follow-up visit on Day 44 (± 3 days)

The total duration of the clinical study per subject will be up to approximately 58 days for Cohort1-3 and 72 days for Cohort4-5, including the Screening period.

Table 1: Sample Allocation and Dose Escalation

Cohorts	Number of Subjects	Treatment Period
Cohorts 1	N=6	HM15912 0.05 mg/kg
	N=2	Placebo
Cohorts 2	N=6	HM15912 0.1 mg/kg
	N=2	Placebo
Cohorts 3	N=6	HM15912 0.5 mg/kg
	N=2	Placebo
Cohorts 4	N=6	HM15912 1.0 mg/kg
	N=2	Placebo
Cohorts 5	N=6	HM15912 1.5 mg/kg
	N=2	Placebo

2.2 Randomization and Blinding Procedures

To maintain the double-blind of the study, except for the unblinded persons involved in the preparation of the IPs (these persons are not involved in any other study activities), everyone involved in the trial will be blinded until after completion of the study and the final data review. Subjects will be randomized to HM15912 or placebo in a ratio of 3:1 (6 subjects to HM15912, 2 subjects to placebo) prior to dosing.

Prior to dosing on Day 1, subjects will be assigned a randomization number in accordance with the randomization code. The randomization code of each randomization number will be maintained in a room with restricted access to the non-blinded clinical research pharmacist only, and will be

accessed by other personnel only in case of unblinding. The randomization number will include 3-digit subject numbers as shown in Table 2.

Table 2: Randomization Numbers and Treatment Assignment

Cohort	Randomization Numbers	Treatment Assignment	
1	101-108	0.05 mg/kg HM15912 (N = 6)	Placebo (N = 2)
2	201-208	0.1 mg/kg HM15912 (N = 6)	Placebo (N = 2)
3	301-308	0.5 mg/kg HM15912 (N = 6)	Placebo (N = 2)
4	401-408	1.0 mg/kg HM15912 (N = 6)	Placebo (N = 2)
5	501-508	1.5 mg/kg HM15912 (N = 6)	Placebo (N = 2)

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdraw prematurely from the study and are replaced under the direction of the Sponsor, then a replacement randomization number will be assigned when a replaced subject has successfully completed screening. A replacement randomization code will be generated such that replacement subjects are assigned to the same treatment as the discontinued subjects. The replacement randomization code will differ only in randomization numbers. It is composed of 4 digits by adding “1” in front of the randomization number for a withdrawn subject. For example, if Subject 202 withdraws and is replaced, then the randomization number for the replacement subject will be 1202.

The study blind should not be broken except in a medical emergency (where knowledge of the IP administered would affect the treatment of the emergency), or if dose limiting toxicities occur or if it is necessary for dose escalation decisions. The decision to break the blind will be made by the Principal Investigator on a case-by-case basis. The Investigator or the Principal Investigator will contact Hanmi Pharmaceutical Co., Ltd. and deliver related documents when breaking the blind. The results of breaking the blind for each subject will not be revealed. The Investigator or the Principal Investigator will record blind-breaking dates and reasons in the CRF.

If blinding is not maintained in the Investigator, the institution’s staff or subjects, the subject must be withdrawn. If blinding is accidently broken during the study or blinding is broken before completion of the study due to SAEs, the Investigator must record this and rapidly report to Hanmi Pharmaceutical Co., Ltd. However, if blinding is broken for ethical reasons or blind breaking is seen to have little effect on the subject’s safety, the subject may continue to participate in the clinical study in the judgement of the Investigator after discussing with Hanmi Pharmaceutical Co., Ltd.

After database lock, the overall randomization code will be broken.

2.3 Sample Size and Power

Due to exploratory nature of this study, sample size 8 subjects (6:2) is empirically determined and consistent with typical sample sizes used for similar studies to assess PK and safety data. No formal sample size calculation will be performed.

3. STUDY OBJECTIVES

3.1 Primary Objectives and Endpoints

To assess the safety and tolerability of HM15912 after single SC doses, regarding:

- General safety variables: Adverse event (AE) assessments; clinical laboratory tests (hematology, clinical chemistry, coagulation and urinalysis); vital signs (blood pressure [BP], pulse, tympanic temperature and respiratory rate [RR]); 12-lead electrocardiogram (ECG); physical examinations
- Specific safety variables: Injection site assessments; immunogenicity assessments (ADA, Nab and anti-PEG) (performed only if analysis is necessary)

3.2 Secondary Objectives and Endpoints

To assess the PK profile of HM15912 after single SC doses, regarding:

- C_{max}: Maximum serum HM15912 concentration determined from the concentration-time profile
- T_{max}: Time of maximum serum HM15912 concentration determined from the concentration-time profile
- AUC_{0-t}: Area under the concentration-time curve from predose (time 0) to the last quantifiable concentration
- AUC_{inf}: Area under the concentration-time curve from predose (time 0) extrapolated to infinite time ($AUC_{0-t} + C_{last}/\lambda_z$) calculated using the linear-log trapezoidal rule
- $AUC_{\%extrap}$: Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
- λ_z: The terminal elimination rate constant determined by selection of at least 3 data points on the terminal phase of the concentration-time curve
- $t_{½}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$
- CL/F: Total body clearance calculated as: $Dose/AUC_{inf}$
- Vz/F: Apparent volume of distribution calculated as: $Dose/(AUC_{inf} * \lambda_z)$

3.3 Exploratory Objectives and Endpoints

To assess the PD properties of HM15912 after single SC doses, regarding:

- Blood plasma citrulline
- Albumin, prealbumin
- Fasting lipid panel (total cholesterol, triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], very low-density lipoprotein [VLDL], free fatty acid [FFA])
- Blood glucose-related panel (fasting plasma glucose, gastric inhibitory polypeptide [GIP], glucagon-like peptide-1 [GLP-1], C-peptide, glucagon, insulin)

- Insulin-like growth factor-1 (IGF-1) and keratinocyte growth factor (KGF)

4. ANALYSIS SET

An analysis sets classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses. Decisions made regarding the exclusion of patients and/or patient data from analyses will be made after the database lock and before the unblinding and will be documented and approved.

Prior to unblinding, analysis populations will be defined through blinded data review. In this clinical study, the PK population is subject to PK assessments whereas the PD population is subject to PD assessments. The safety population is subject to all other analyses unless described otherwise. Each analysis population is included in the analyses, based on the actually administered IP and dosage.

4.1 Safety Set

All randomized subjects who received at least 1 dose of the IP, HM15912 or placebo (actual treatment).

4.2 Pharmacokinetic Analysis Set

All subjects who are treated HM15912 (actual treatment) with at least one quantifiable HM15912 concentration.

4.3 Pharmacodynamics Analysis Set

All randomized subjects who received at least 1 dose of the IP, HM15912 or placebo. (actual treatment)

5. STUDY SUBJECT

Study subject data will be summarized by dose level, with pooled placebo using the Safety Set.

5.1 Subject Disposition

Subjects disposition will be summarized into the numbers and percentages of subjects dosed after randomization, subjects included in each analysis population, subjects completing the study, subjects who were withdrawn (including reasons for withdrawal) and subjects who have seriously violated the protocol.

5.2 Demographic and Baseline Characteristics

Demographic data, such as age, sex, height, weight, and BMI, and descriptive statistics of baseline characteristics or the number and percentage of subjects by category will be provided.

5.3 Medical History

Medical history is any significant medical condition or disease that is present at study start (signing of informed consent). The medical history recorded through clinically significant laboratory, electrocardiogram (ECG), or physical examination (PE) abnormalities noted at screening examination will be listed.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or over) and summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety Set. Medical history data will be listed by subject, description of the disease/procedure, MedDRA SOC, PT, start date and stop date (or ongoing if applicable).

5.4 Subject Eligibility and Withdrawal Criteria

Subject eligibility and subjects who meet withdrawal criteria will be presented in listings.

5.5 Exposure

A listing of IP administration will be created by subject and will include the date and time of administration and dosage, etc.

5.6 Concomitant Medication

Concomitant medication is medication given in addition to the study medication (including over-the-counter medications, herbal medications, and vitamin supplements) administered between screening and follow-up. Medication will be categorized into the three following types:

- Prior concomitant medication is defined as any medications that start before the date of

dosing of study medication and continue beyond that date.

- New concomitant medication is defined as any medications that start after the date of dosing of study medication, including those started in the follow-up period.
- Prior medication is defined as any non-study medication that stops before the date of dosing of study medication.

The WHO DRUG Dictionary Global (March 2019 or over) will be used to categorize the verbatim descriptions of medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

Drug administration dates and times will be listed for each subject and the number and percentage of subjects receiving concomitant medications (including both prior and new concomitant medications) will be summarized and by ATC classification (ATC level 2 and level 4) for the Safety Set. Pre-treatment medication administered during the study will only be listed.

5.7 Protocol Deviations

All the protocol deviations will be listed by subject. Category of important/non-important will be included in the listing. Protocol deviations will be handled in accordance with ICH guidelines and local regulation for management. Important protocol deviations will be identified prior to database lock and will be summarized for the Safety Set.

6. Statistical Methods

6.1 General Considerations

PK, PD, and Safety analyses will be performed with the PK Analysis Set, PD Analysis Set, and Safety Set, respectively. Placebo subjects will be pooled in summaries and listings.

Exploratory analysis may be conducted assess any patterns due to COVID-19.

All data collected during the study will be listed using the Safety Set.

6.1.1 Statistical Notation and Presentation

The continuous variables will be summarized by number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Where appropriate, change from baseline will also be summarized. For categorical variables, the number and percentage of subjects in each category will be provided. For log-normal distributed data, geometric mean, standard error (SE) of the geometric mean, and coefficient of variation (CV) will also be provided. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV is calculated as CV% = 100%$* sqrt(\exp(\sigma^2) - 1)$, where σ is the SD of the data on the natural log scale. Minimum and maximum values will be rounded to the precision of the original value. Means, least squares (LS) means, and medians will be rounded to 1 decimal place greater than the precision of the original value. SDs, SEs, and confidence intervals (CIs) will be rounded to 2 decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values will be presented with 4 decimal places and values less than 0.0001 will be presented as <.0001.

All inferential statistical testing will be two-sided and conducted at the 0.05 significance level, unless specified otherwise. No multiplicity adjustment is planned for this study.

6.1.2 Handling of Multiple Observations or Out of Window Observations

[redacted]

6.1.3 Handling of Missing and Partial Dates

In cases of incomplete dates for adverse events (AEs) or concomitant medications, the missing component(s) will be assumed as the most conservative value(s) possible. The imputation rule are designed to conservatively capture AEs as treatment-emergent AEs (TEAEs) and medications as concomitant. For example, the following algorithm for missing start date of AEs will be followed:

[redacted]

Adverse events and medications with missing or partial end dates will be imputed to conservatively capture treatment-emergent or concomitant status.

Date imputation will only be used for computational purposes; e.g., treatment-emergent status or identifying concomitant medications. Actual data values, as they appear in the clinical database, will be shown in the data listings.

Missing visits due to COVID-19 will be listed with the reason for missing.

6.1.4 Handling of Outliers and Unquantifiable Measurements

Prior to unblinding, PK data will be reviewed by the PK scientist and statistician to assess whether individual concentration values are inconsistent with other values from the same subject or if there are errors with the samples. Determination of data points subject to re-analysis or removal from determination of PK parameters (i.e., implausible data) will be documented prior to unblinding

PK and PD parameter results will also be reviewed by appropriate representatives and a determination of plausibility will be made. Individual subject results deemed implausible may be removed prior to summarization of PK and PD parameter results by treatment group. Removal of individual subject PK/PD parameter results will be documented.

The following rules will be applied when blood samples are assayed as below the limit of quantitation (BLQ) or if individual concentration results are deemed implausible prior to database lock:

[redacted]

6.1.5 Study Baseline

Baseline will be defined as the last non-missing observation obtained prior to the administration of the study drug.

6.2 Safety Analyses

Safety data will be summarized by treatment, with pooled placebo. All safety data will be listed.

6.2.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA, version 22.0 or over. All AEs will be listed.

AEs with onset on or after the date of informed consent but before the date of dosing of study medication will be considered pre-treatment AEs. Pre-treatment AE will be listed only.

AEs with onset date/time on or after receiving the dosing of study medication, or pre-existing AEs that increase severity on or after receiving the dosing of study medication will be considered as TEAE.

The number and percentage of subjects who experience one or more AEs will be tabulated by SOC and PT and by SOC, PT and maximum severity for each cohort and overall. The sorting is by descending frequency of SOC and PT. TEAEs that are related to study medication per investigator's decision, TEAEs leading to study discontinuation, and TEAEs that are serious (treatment-emergent SAEs), will be summarized similarly.

6.2.2 Clinical Laboratory Assessments

Individual data listings of laboratory results will be presented for each subject. The observed values and change from baseline of all hematology, clinical chemistry, coagulation and urinalysis results (observed values) will be summarized according to section 6.1.1. Laboratory assessments that are outside of normal ranges and with potential clinical importance will be summarized and flagged in the listings with the PI's or investigator's assessment such as NCS or CS. Shift tables of hematology, clinical chemistry, coagulation and urinalysis results will be generated to summarize the normal, NCS and CS status changes from baseline.

6.2.3 Vital Signs

Observed and change from baseline - vital sign values (body weight, BMI, blood pressure [BP], pulse, respiratory rate, and tympanic temperature) at each day and time-point will be listed and summarized.

6.2.4 12-lead Electrocardiograms

Average and individual triplicate ECG intervals will be listed with mean change from baseline by subject, day, and time point. Observed and change from baseline values of ECG parameters will be

summarized. The worst case of triplicated status of 12-lead ECG parameters, Normal, Abnormal NCS, and Abnormal CS, and their shifts from baseline will be summarized.

6.2.5 Physical Examination

The clinical findings (Abnormal NCS and Abnormal CS) on PE and severity will be listed.

6.2.6 Injection Site Reactions

Multiple syringes may be injected subcutaneously in the right upper abdomen (if not applicable, left upper abdomen) as the dose increases. All injection site irritation events will be documented as AEs and included in the AEs analysis in the Section 6.2.1. The number and percentage of subjects with specific site reactions such as erythema and edema will be summarized by treatment group, day, time point, and Draize scale. In addition, diameter of affected areas will be summarized descriptively by treatment group, day and time point.

6.2.7 Immunogenicity

Immunogenicity assessments will be performed when deemed necessary by the Principal Investigator or the Sponsor in any of the following cases:

- When ADA formation is suspected based on PK/PD analysis results
- When biomarker changes related to drug efficacy are not observed at expected pharmacologically effective doses
- When AEs suspected as immune responses occur after administration
- When necessary for other clinical/scientific reasons

Anti-drug antibodies (ADAbs, anti-HM15912 antibodies) will be summarized categorically, hierarchically displaying the Positive and Negative results from screening assay and confirmatory assay by treatment group and visit. Confirmed positive ADAbs 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, hierarchically displaying the Positive and Negative results from screening and confirmatory assay by treatment group and visit. Cross reactivity for confirmed positive Nabs will be summarized by treatment group and visit.

Anti-polyethylene glycol antibodies (anti-PEG) will be summarized categorically, displaying the Positive and Negative results from screening assay and specificity by treatment group and visit. The titer results are listed only.

6.3 Pharmacokinetic Analyses

6.3.1 PK Concentration

Concentration of HM15912 will be summarized descriptively by treatment group and time point. A line plot for mean concentration +/- standard deviation over time will be generated for the PK set with dose level overlaid. Line plots on linear and log scales of HM15912 individual subject concentration overlaid with the mean concentration for each cohort will be plotted separately.

6.3.2 PK Parameter

The following PK parameters will be summarized by treatment group for the PK Analysis Set.

- Maximum concentration (C_{max}) is defined as the maximum HM15912 concentration measured after single SC dose
- Time to reach C_{max} (T_{max}) is defined as the time from initial injection to time of C_{max}
- Area under the concentration-time curve for HM15912 up to the last point with concentrations above the lower limit of quantification (LLOQ), $AUC_{0\text{-}last}$, will be calculated by linear-up log-down method.
- Area under the concentration-time curve with extrapolation to infinity for HM15912, $AUC_{0\text{-}inf}$, will be calculated by $AUC_{0\text{-}last} + C_{last}/ \lambda_z$, where C_{last} is the last observed concentration (_obs), or the last predicted concentration (_pred).
- $AUC_{\%extrap}$: Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
- λ_z, first-order terminal elimination rate constant, calculated by linear regression of time vs. log concentration curve in the terminal phase. For λ_z to be acceptable, it shall be determined over a time interval equal to at least 1.5 x $t_{½}$ λ_z, with at least 3 different time points in the terminal phase for the regression analysis, and the coefficient of determination Adj_RSq shall be $\geq$0.8. If at least one of these three conditions is not fulfilled, the parameters depending on λ_z (e.g., $AUC_{0\text{-}inf}$, the terminal half-life $t_{1/2}$, λ_z, CL and Vz) shall be flagged as not reliable if calculated and listed. They will generally be excluded from descriptive statistics and statistical testing procedures, unless otherwise judged by the pharmacometrician in charge of PK analysis.
- Apparent terminal half-life $t_{1/2}$, will be determined from equation $\ln 2/ \lambda_z$.
- CL (_obs, _pred), apparent total body clearance will be calculated by $Dose/AUC_{0\text{-}inf}$. Note, the Dose in calculating CL for HM15912 will be the total administered dose, which is the subcutaneous dose.
- Vz (_obs, _pred), apparent volume of distribution at terminal phase and will be calculated by CL/ λ_z.
- Apparent clearance divided by bioavailability (CL/F)
- Apparent volume of distribution at terminal phase divided by bioavailability (Vz/F)

Box plots of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ for each cohort may be generated. The planned last sampling

time of each cohort will be informed as an annotation at $AUC_{0\text{-last}}$ of summary stat and box plot as planned last sampling times for Cohort 1-3 and Cohort 4-5 are different as Day 30 and Day 44, respectively.

6.3.3 Dose Proportionality

The power model will be used to analyze the dose proportionality in $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} of HM15912. The estimate of β and the corresponding 90% CI will be derived.

The power model is defined as follows:

$$log(PK_i) = \alpha + (\beta) * log(dose_i) + \mathcal{E}_i$$

where PK_i is the PK parameter (AUC or C_{max}) observation for the subject *i*.

α is the population intercept.

β is the population slope.

$\mathrm{dose_i}$ is the dosage(mg) for the subject i.

$\mathcal{E}_i$ is the random error; $\mathcal{E}_i \sim N(0, \sigma_\varepsilon^2)$ and independent.

The assumption for the Power Model is that the underlying relationship between log(PK parameter) and log(dose) is linear. The dose proportionality corresponds to the ratio of dose normalized geometric means ($\mathrm{R_{dnm}}$), which is defined as ratio of the predicted geometric mean of the highest dose relative to the predicted geometric mean of the lowest dose, The dose proportionality would be declared when the 90% CI for the R_{dnm} falls entirely within the limit of 0.8 to 1.25.[3] Scatter plot of log(PK parameter) and log(dose) will be plotted with an estimated line.

6.4 Pharmacodynamic Analyses

6.4.1 Fasting Lipid Panel

The observed values and the change from baseline of fasting lipid panels, such as total cholesterol, triglycerides, LDL, HDL, VLDL, and FFA, will be summarized by treatment group, day and time point according to section 6.1.1.

6.4.2 Blood Glucose-related Panel

The observed values and the change from baseline of blood glucose panels, such as fasting plasma glucose, GIP, GLP-1, C-peptide, glucagon, and insulin will be summarized by treatment group, day and time point according to section 6.1.1.

6.4.3 Albumin and Pre-albumin

The observed values and the change from baseline of albumin and pre-albumin will be summarized by treatment group, day and time point according to section 6.1.1.

6.4.4 Blood Plasma Citrulline

The observed values and the change from baseline of blood plasma citrulline will be summarized by treatment group, day and time point according to section 6.1.1.

6.4.5 Growth Factor

The observed values and the change from baseline of insulin-like growth factor-1 and keratinocyte growth factor will be summarized by treatment group, day and time point according to section 6.1.1.

7. Interim Analysis

In the dose escalation meeting, blinded safety data collected at least 17 days post dose from at least 6 subjects (HM15912, n≥4) in each cohort shall be reviewed prior to initiating the dosing of the next cohort. All pertinent blinded safety data, available PK and PD data, will be reviewed to make one of the following determinations:

- To continue with the study without modification.
- To continue with the study and add additional safety evaluations.
- To continue the study with adjustments made to the dose.
- Hold further enrollment pending evaluation / resolution of adverse events.

The dose escalation meeting will be held after at least the 6th subject completes the investigation of safety lab results at Day 17 in each Cohort. It is possible and acceptable that some queries may remain open and SDV will not be 100% for the applicable data. The level of SDV % will vary depending on factors such as monitoring schedule and availability of completed data entry and will not affect the dose escalation decision.

7.1 Dose Administration

- List of dose administration

7.2 Subject status

- Listing of Demographic data (including randomization numbers and cohort)
- List of completed subjects and early discontinued subjects with reasons

7.3 Adverse Events(AEs) and Serious AEs

- Listing of all AEs experienced, including reported terms, start/end date and time, severity, seriousness, relationship to study drug and outcome
- Highlight severity of “Moderate” or “Severe”
- Highlight relationship to study drug “Related”
- Identification of any AEs marked “Serious”
- Listing of dose administration

7.4 Clinical Laboratory Results

- Listing of all clinical laboratory tests, including hematology, clinical chemistry, coagulation and urinalysis according to SAP section 6.1.1
- Graphs of all laboratory results, including High/Low indicators
- Listings of abnormal laboratory values (with CS or NCS)

7.5 12-lead ECG

- List of all ECG results
- Graphs of all ECG results
- Listing of abnormal ECG findings (with CS or NCS)

7.6 Vital Signs

- List of all body weight, systolic/diastolic blood pressure, pulse rate, tympanic body temperature and respiratory rate assessments
- Graphs of vital sign assessments

7.7 Abnormal Physical Examination Results

- Listing of all PEs performed, not assessed as Normal, ordered by clinical relevance and body system

7.8 Injection Site Reaction

- Listing of all positive site reactions with diameter

7.9 Concomitant Medication

- Listing of prior concomitant medications that start before the date of dosing of study medication and continue beyond that date
- Listing of new concomitant medications that start after the first study dose date, including those started in the follow-up period

7.10 Medical History

- Listing of medical history by subject, description of the disease/procedure, MedDRA SOC, PT, start date and stop date (or ongoing if applicable)

7.11 Pharmacodynamic (PD) Assessments (if available)

- Graphs of all laboratory results, including High/Low indicators
- Listings of abnormal laboratory values (with CS or NCS)

7.12 Pharmacokinetic (PK) Assessments (if available)

- Graph of PK concentration
- Listing of PK concentration data
- Table of PK parameter with summary value

8. Statistical Software

All statistical analyses will be performed using SAS® version 9.4. All PK and PD parameters will be derived with standard NCA methods using SAS® version 9.4 or higher.

9. 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. Hummel J, Mckendrick S, Brindley C, French R. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. Pharm Stat. 2009;8(1):38–49.

10. APPENDIX

Table 3 Schedule of Assessments

Table 3-1. Schedule of Assessments (Cohort 1-3)

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Outpatient[a]	Visit 4 Outpatient[a]	Visit 5 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	10 (±1 day)	17 (±1 day)	30 (±3 days)
Informed consent	X												
Inclusion/exclusion criteria	X	X[c]											
Demographic data	X												
Height[d], BMI[e]	X	X								X	X	X	X
Body weight[d]	X	X								X	X	X	X
Medical history	X	X[f]											
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test (all females)[g]	X	X											X
Serum FSH (postmenopausal females only)	X												
Urine drugs of abuse and alcohol screening	X	X									X	X	X
Viral serology	X												
Check-in			X										
Check-out										X			
Outpatient	X	X									X	X	X
Randomization		X											
Standardized meals			X	X[h]	X	X	X	X	X				

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Outpatient[a]	Visit 4 Outpatient[a]	Visit 5 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	10 (±1 day)	17 (±1 day)	30 (±3 days)
IP administration[h]				X									
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, pulse, tympanic temperature, RR)[i]	X	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X
Clinical laboratory tests (hematology, chemistry, coagulation, urinalysis)[j]	X	X		X[k]		X[k]	X[k]			X		X	X
12-lead ECG[l]	X	X		X[l]	X	X	X			X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG)			X[m]								X		X
Injection site assessments[n]				X	X	X	X	X	X	X			
Physical examinations	X	X		X	X	X	X	X	X	X	X	X	X
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Citrulline[p]				X	X	X	X	X	X	X	X	X	X
GIP, GLP-1, C-peptide, glucagon, insulin[q]				X			X			X		X	X
IGF-1 and KGF[r]				X			X			X		X	X

ADA = anti-drug antibody; Anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; FFA = free fatty acid; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IP = investigational product; LDL = low-density lipoprotein; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous; VLDL = very low-density lipoprotein

a. An additional Outpatient visit may be included in later cohorts, if required, after PK data are evaluated. If so, assessments scheduled on Day 17 will be performed at the additional Outpatient visit.

b. If a subject is discontinued from the study or withdraws consent, the Principal Investigator must make every possible effort to perform the evaluations described for the Follow-up visit. Efforts will be made to perform the Follow-up visit within 30 days from the date the subject is discontinued from the study or withdraws consent.

c. The criteria applicable for admission prior to randomization, i.e., exclusion criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31, will be checked again.

d. Height will be measured only at the Screening visit. 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.

e. BMI will be calculated by the following formula: BMI = Weight (kg) ÷ ((Height (m) x Height (m)). The calculated BMI will be rounded to 1 decimal place. The height measured at the Screening visit will be used for BMI calculation, and if a value is calculated as 2 decimal places, the number is rounded off to the first place.

f. Medical history which will be checked on Day-1 is limited to the medical history related to exclusion criteria 1, 2, 3, 6, 8, 9, 10, 11, 13, 14, 15, and 17.

g. Serum pregnancy tests at the Screening visit and on Day-1; urine pregnancy tests at the Day 30/Follow-up visit.

h. HM15912 or placebo will be administered via SC injection into the abdomen on the morning of Day 1 after a minimum 10-hour fast. Subjects will continue fasting through approximately 4 hours postdose. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing. After the planned 4-hour post-dose blood sampling (clinical laboratory tests and analysis of citrulline) and testing (12-lead ECG) are performed, subjects will be served lunch by the institution.

i. Vital signs will be measured twice per day on Day 1 through Day 6 (AM and PM). Vital signs will be measured at predose and 6 hours postdose on Day 1. Vital signs will be measured whenever possible in the morning and afternoon between Day 2 and Day 6. All other assessments will be performed once per day whenever possible. BP and pulse will be measured for 2 consecutive times after a subject has been lying down or sitting to rest ≥ 5 minutes, and mean values will be recorded.

j. Samples for clinical laboratory tests will be collected after at least 12 hours of fasting. If the PK sampling time points are changed, the sampling times for clinical laboratory tests may be adjusted accordingly.

k. 4, 48 and 72 hours postdose

l. The 12-lead ECGs will be performed after a subject has been resting supine for ≥ 5 minutes. ECGs will be measured in triplicate in the morning during admission. Only for Day 1, however, ECGs will be measured in triplicate predose and 4 hours postdose, and a ±30-minute sampling window is allowed for measurement at 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. 12-lead ECGs during the Outpatient visit will be measured once per day whenever possible.

m. Blood sampling for immunogenicity assessments will be performed only for hospitalized patients after admission on Day-1, Day 10, and Day 30.

n. Injection site assessments will be performed predose, within 1 hour postdose and at 4 and 12 hours postdose on Day 1, and then between 9:00 AM and 12:00 PM daily from Day 2 through Day 7.

o. [redacted] See Table 2-1 for the PK sampling schedule.

p. If the PK sampling time points are changed, the citrulline sampling times may be adjusted accordingly. See Table 4-1 for the citrulline sampling schedule.

q. Blood will be collected for GIP, GLP-1, C-peptide, glucagon and insulin immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30/Follow-up visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

r. Blood will be collected for IGF-1 and KGF immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30/Follow-up visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

Table 4-2. Schedule of Assessments (Cohort 4, 5)

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Out patient[a]	Visit 4 Out patient[a]	Visit 5 Out patient[a]	Visit 6 Out patient[a]	Visit 7 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	8 (±4 hours)	10 (±1 day)	17 (±1 day)	30 (±3 days)	44 (±3 days)
Informed consent	X														
Inclusion/exclusion criteria	X	X[c]													
Demographic data	X														
Height[d], BMI[e]	X	X								X		X	X	X	X
Body weight[d]	X	X								X		X	X	X	X
Medical history	X	X[f]													
Prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (all females)[g]	X	X													X
Serum FSH (postmenopausal females only)	X														
Urine drugs of abuse and alcohol screening [s]	X	X									X	X	X	X	X
Viral serology	X														
Check-in			X												
Check-out										X					
Outpatient	X	X									X	X	X	X	X
Randomization		X													
Standardized meals			X	X[h]	X	X	X	X	X						
IP administration[h]				X											
Adverse event assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Visit 1 Screening	Visit 2 Inpatient Treatment Period									Visit 3 Out patient[a]	Visit 4 Out patient[a]	Visit 5 Out patient[a]	Visit 6 Out patient[a]	Visit 7 Follow-up[b]
Day	-28 ~ -2	-1 Outpatient	-1 Inpatient	1	2	3	4	5	6	7	8 (±4 hours)	10 (±1 day)	17 (±1 day)	30 (±3 days)	44 (±3 days)
Vital signs (BP, pulse, tympanic temperature, RR)[i]	X	X		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X	X	X
Clinical laboratory tests (hematology, chemistry, coagulation, urinalysis)[j]	X	X		X[k]			X[k]			X			X	X	X
12-lead ECG[l]	X	X		X[l]	X	X	X			X	X	X	X	X	X
Immune response assessments (ADA, NAb, anti-PEG)			X[m]										X		X
Injection site assessments[n]				X	X	X	X	X	X	X					
Physical examinations	X	X		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GIP, GLP-1, C-peptide, glucagon, insulin[q]				X			X			X			X	X	
IGF-1 and KGF[r]				X			X			X			X	X	

ADA = anti-drug antibody; Anti-PEG = anti-polyethylene glycol; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; FFA = free fatty acid; FPG = fasting plasma glucose; FSH = follicle-stimulating hormone; GIP = gastric inhibitory polypeptide; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; IP = investigational product; LDL = low-density lipoprotein; NAb = neutralizing antibody; PK = pharmacokinetics; RR = respiratory rate; SC = subcutaneous; VLDL = very low-density lipoprotein

a. An additional Outpatient visit may be included in later cohorts, if required, after PK data are evaluated. If so, assessments scheduled on Day 17 will be performed at the additional Outpatient visit.

b. If a subject is discontinued from the study or withdraws consent, the Principal Investigator must make every possible effort to perform the evaluations described for the Follow-up visit. Efforts will be made to perform the Follow-up visit within 30 days from the date the subject is discontinued from the study or withdraws consent.

c. The criteria applicable for admission prior to randomization, i.e., exclusion criteria 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, and 31, will be

checked again.

d. Height will be measured only at the Screening visit. 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.

e. BMI will be calculated by the following formula: BMI = Weight (kg) ÷ ((Height (m) x Height (m)). The calculated BMI will be rounded to 1 decimal place. The height measured at the Screening visit will be used for BMI calculation, and if a value is calculated as 2 decimal places, the number is rounded off to the first place.

f. Medical history which will be checked on Day-1 is limited to the medical history related to exclusion criteria 1, 2, 3, 6, 8, 9, 10, 11, 13, 14, 15, and 17.

g. Serum pregnancy tests at the Screening visit and on Day-1; urine pregnancy tests at the Day 44/Follow-up visit.

h. HM15912 or placebo will be administered via SC injection into the abdomen on the morning of Day 1 after a minimum 10-hour fast. Subjects will continue fasting through approximately 4 hours postdose. Water consumption will also be limited for 1 hour before dosing and for approximately 2 hours after dosing. After the planned 4-hour post-dose blood sampling (clinical laboratory tests) and testing (12-lead ECG) are performed, subjects will be served lunch by the institution.

i. Vital signs will be measured twice per day on Day 1 through Day 6 (AM and PM). Vital signs will be measured at predose and 6 hours postdose on Day 1. Vital signs will be measured whenever possible in the morning and afternoon between Day 2 and Day 6. All other assessments will be performed once per day whenever possible. BP and pulse will be measured for 2 consecutive times after a subject has been lying down or sitting to rest ≥ 5 minutes, and mean values will be recorded.

j. Samples for clinical laboratory tests will be collected after at least 12 hours of fasting. If the PK sampling time points are changed, the sampling times for clinical laboratory tests may be adjusted accordingly.

k. 4 and 72 hours postdose

l. The 12-lead ECGs will be performed after a subject has been resting supine for ≥ 5 minutes. ECGs will be measured in triplicate in the morning during admission. Only for Day 1, however, ECGs will be measured in triplicate predose and 4 hours postdose, and a ±30-minute sampling window is allowed for measurement at 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. 12-lead ECGs during the Outpatient visit will be measured once per day whenever possible.

m. Blood sampling for immunogenicity assessments will be performed only for hospitalized patients after admission on Day-1, Day 17, and Day 44.

n. Injection site assessments will be performed predose, within 1 hour postdose and at 4 and 12 hours postdose on Day 1, and then between 9:00 AM and 12:00 PM daily from Day 2 through Day 7.

o. [redacted] See Table 2-2 for the PK sampling schedule.

p. If the PK sampling time points are changed, the citrulline sampling times may be adjusted accordingly. See Table 4-2 for the citrulline sampling schedule.

q. Blood will be collected for GIP, GLP-1, C-peptide, glucagon and insulin immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30 Outpatient visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

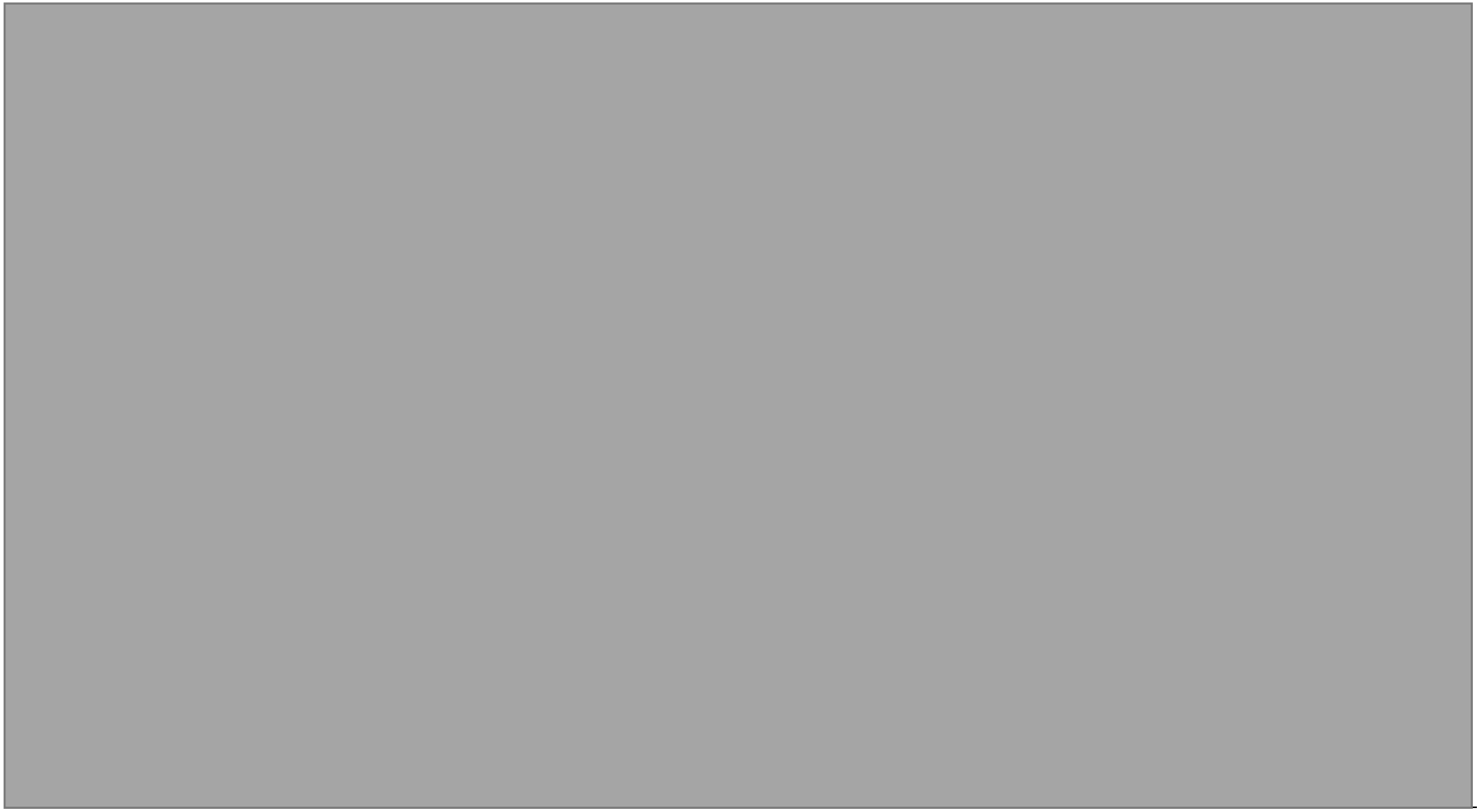
r. Blood will be collected for IGF-1 and KGF immediately before administration and once daily on Days 4 and 7, at the Day 17 Outpatient visit and at the Day 30 Outpatient visit. If the PK sampling time points are changed, sampling times may be adjusted accordingly.

s. Alcohol breath test procedure could be replaced with the examination by interview to avoid infection of COVID-19.

Table 4 Citrulline Sampling Schedule for Exploring PK Samples and PD

Table 4-1 Citrulline Sampling Schedule for Exploring PK Samples and PD (Cohort 1~3)

Table 4-2 Citrulline Sampling Schedule for Exploring PK Samples and PD (Cohort 4, 5)



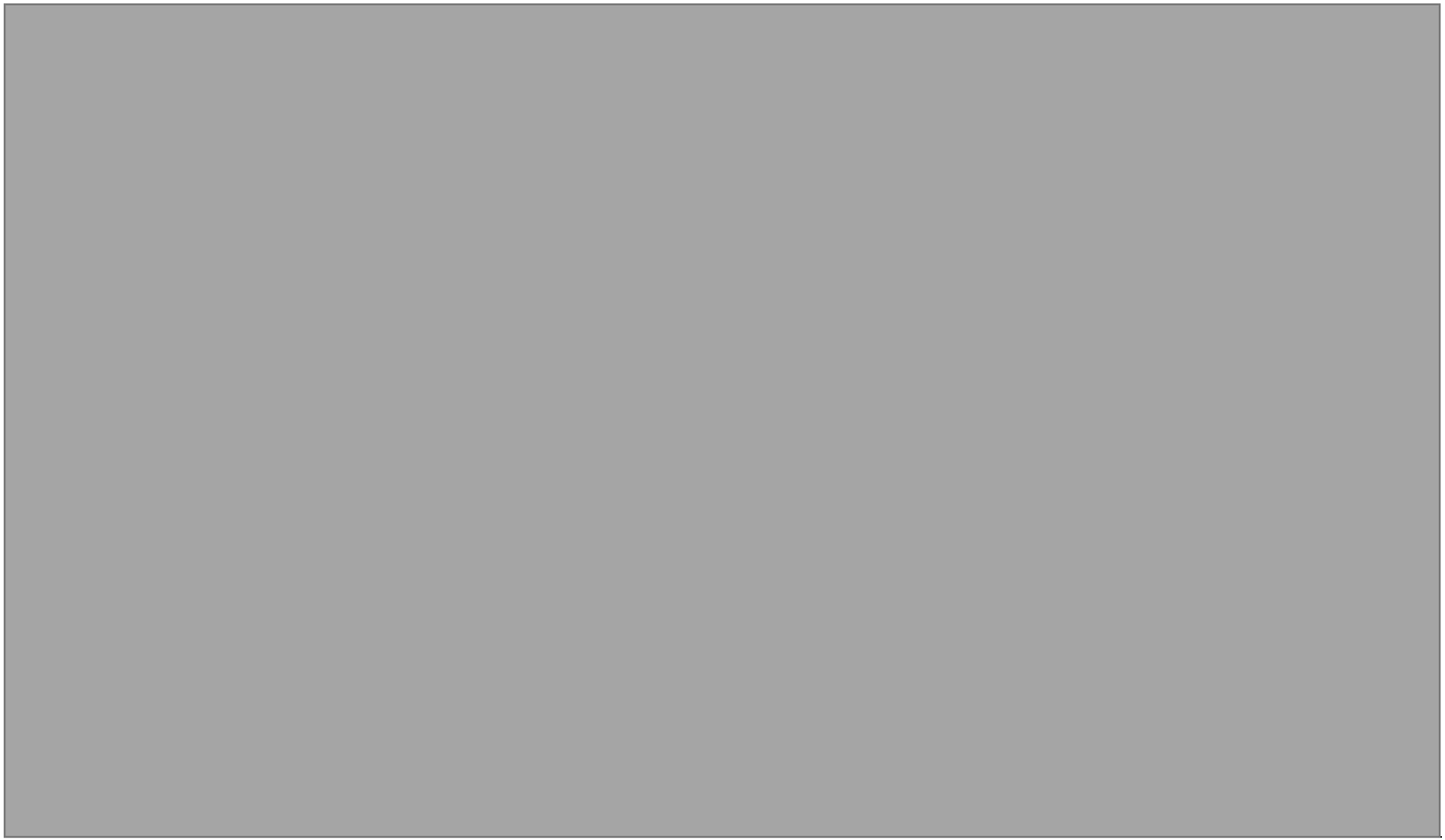


Table 5 PD Sampling Schedule

Table 5-1 PD Sampling Schedule (Cohort 1~3)

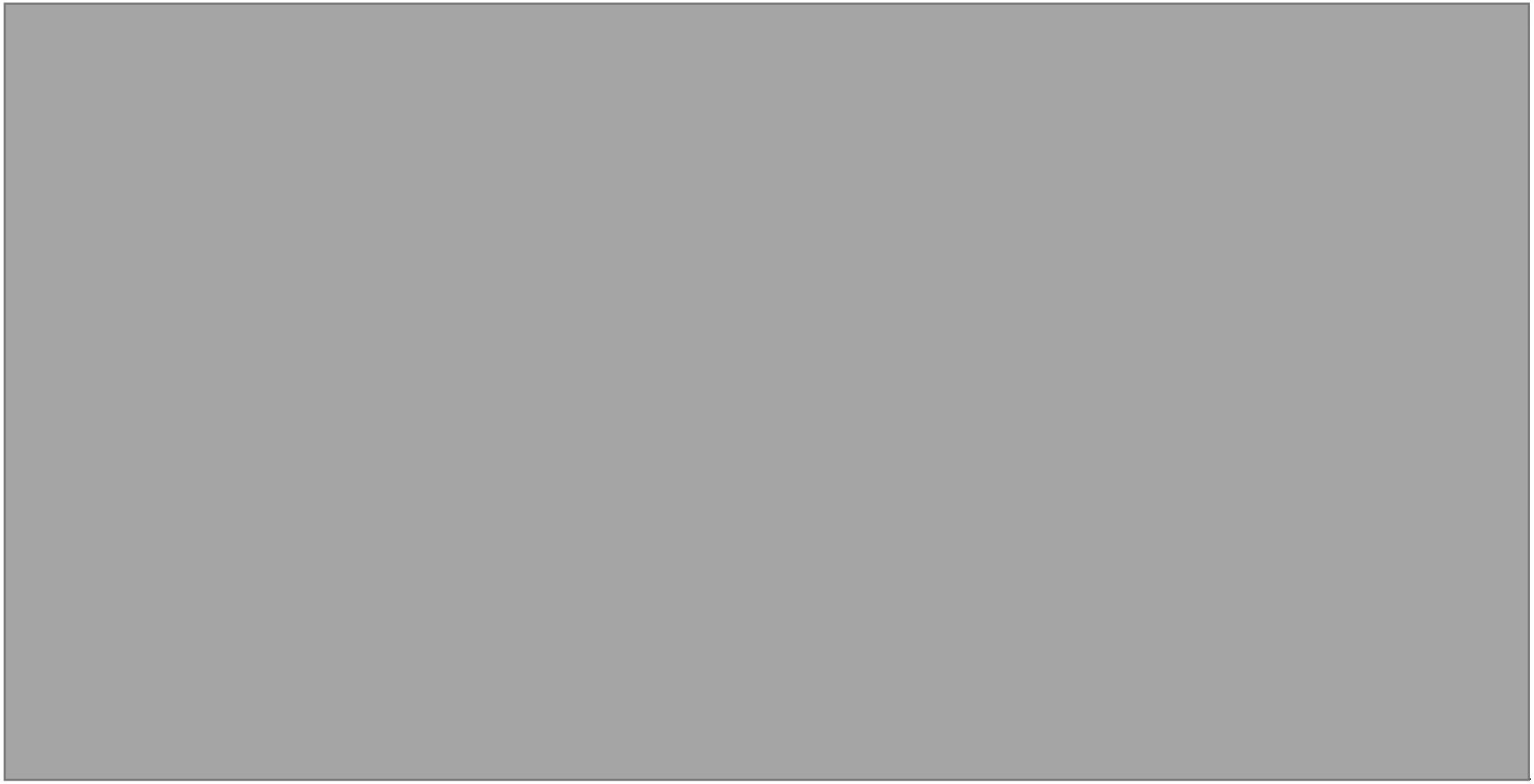


Table 5-2 PD Sampling Schedule (Cohort 4, 5)