Statistical Analysis Plan

Protocol HM-TRIA-101

A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HM15211 in Healthy Obese Subjects

Phase I

Original Protocol:
Version 1.0: 08-Dec-2017
Version 2.0: 04-Feb-2018
Version 3.0: 09-Feb-2018
Version 4.0: 06-Apr-2018

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This Statistical Analysis Plan has been reviewed and approved by:

Date: 17-Oct-2018

OakPil Han
BIOMETRICS Team Leader
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List of Abbreviations

Abbreviation	Definition of Term
_obs	observed
_pred	predicted
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-tlast	Area under the concentration time curve from zero to time of last time observed
BLQ	Below the limit of quantitation
BP	Blood pressure
CI	Confidence interval
CL	Apparent clearance
CL/F	Apparent clearance divided by bioavailability
Cmax	Maximum concentration
CRP	C-reactive protein
CRU	Clinical research unit
CSR	Clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
F	Bioavailability
FFA	Free fatty acid
FPG	Fasting plasma glucose
GCG	Glucagon
GIP	Gastric inhibitory peptide
GLP-1	Glucagon like peptide-1
HDL	High-density lipids
HR	Heart rate
HRV	Heart rate variability
IP	Investigational product
kel	Apparent elimination constant
LDL	Low-density lipids
LLOQ	Lower limit of quantitation
LS	Least squares
max	maximum
MedDRA	Medical dictionary for regulatory activities
min	minimum
n	sample size
nAbs	Neutralizing antibodies
NCA	Non-compartmental analysis

Abbreviation	Definition of Term
NN	Normal to normal R-R intervals
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PT	Preferred term
QTcF	Fridericia's corrected QT interval
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDNN	Standard deviation of the normal to normal R-R intervals
SE	Standard error
SOC	System organ class
t1/2	Half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum concentration
TMF	Trial master files
TSH	Thyroid stimulating hormone
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 DDE	World Health Organization drug dictionary enhanced

1. Introduction

This document describes the statistical methods and data presentation in the analysis and summary of the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of HM15211 with Placebo as comparator in healthy obese subjects. This statistical analysis plan (SAP) was developed based on the Hanmi Pharmaceutical Protocol HM-TRIA-101 (version 4.0 dated 06Apr2018).

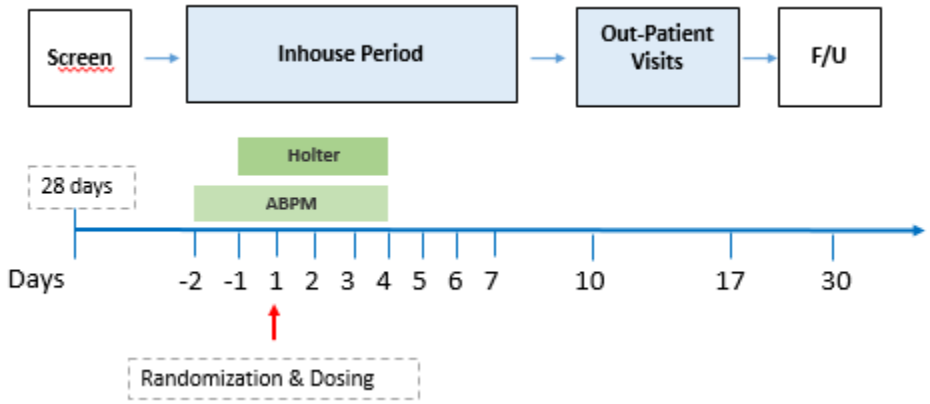
This SAP will be finalized prior to data analyses and before database lock. Any major differences between the statistical methods provided in the clinical study protocol and this SAP will be explained herein. Any major changes and deviations from this SAP to the final data analysis must be substantiated by sound statistical rationale and fully documented in the final clinical study report (CSR).

2. Study Overview

2.1. Study Design

This is a first-in-human, randomized, double-blind, SAD study to evaluate the safety, tolerability, and PK of HM15211 as primary objectives in healthy obese subjects.

Figure 1: Study Design Schematic



The study will be conducted in five sequential cohorts (cohort 1 to 5) comprising a total of up to approximately 40 subjects. Each cohort will enroll subjects to ensure that at least 8 subjects per cohort will complete the study. Drop-outs may be replaced in order to have 8 completed subjects in each cohort. Subjects will be allocated into sequential dosing cohorts based on their order of entry into the study and be randomized to investigational product (IP) or placebo in a 3:1 ratio, with 6 subjects on IP and 2 subjects on placebo. Cohorts may partially overlap after at least 6 subjects have completed at least D10 and a dose escalation decision has been made.

Dosing will follow a sentinel approach with the dosing between the first 2 subjects (1 on active, 1 on placebo) and the remainder of the cohort at least 24 hours apart. A minimum of 10-days

between the start date of consecutive dose levels will be maintained. Based on available safety, tolerability, and PK data of each cohort, and following a safety review and dose escalation meeting between the investigator and the sponsor, dose escalation to the next cohort may proceed. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels.

Each subject will undergo a screening visit, followed by one in-house/ treatment period per subject. Two additional outpatient visits will occur, prior to a final follow-up visit that will conclude subject study participation.

The duration of subject participation in this study, including screening, treatment and follow-up will approximately be 9 weeks for subjects.

Figure 2: Dose Escalation Schematic

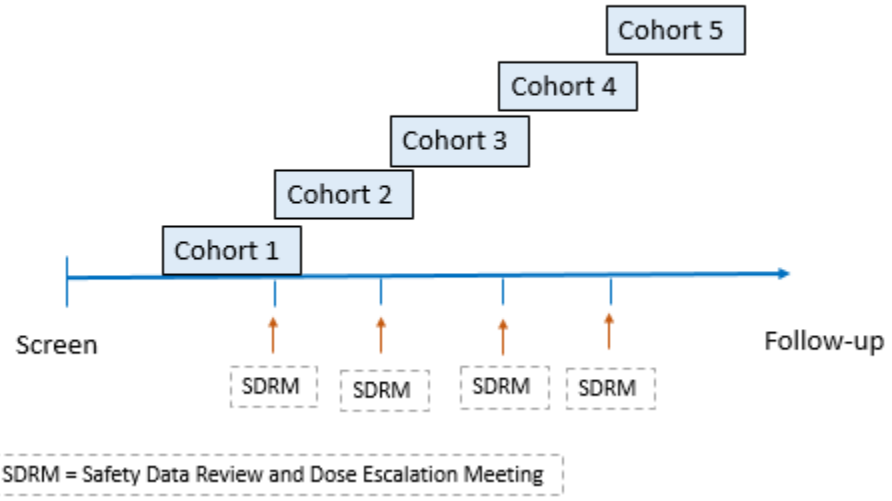


Table 1: Sample Allocation and Dose Escalation

Cohorts	Number of Subjects	Treatment Period
Cohorts 1	N=6	HM15211- 0.01 mg/kg
	N=2	Placebo
Cohorts 2	N=6	HM15211≤ 0.02 mg/kg
	N=2	Placebo
Cohorts 3	N=6	HM15211≤ 0.04 mg/kg
	N=2	Placebo
Cohorts 4	N=6	HM15211≤ 0.08 mg/kg
	N=2	Placebo
Cohorts 5	N=6	HM15211≤ 0.12 mg/kg
	N=2	Placebo

2.2. Randomization and Blinding

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 IP or placebo in a ratio of 3:1 (6 subjects to IP, 2 subjects to placebo) prior to dosing.

Subjects will be randomized to treatment based on a randomization list that will be developed by a statistician. Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacy staff at the clinical research unit (CRU).

Subjects will be assigned to the lowest randomization number available. Subjects who withdraw prior to dosing on Day 1 may be replaced. If the replacement subject drops from the study, a second replacement subject may be enrolled. Subjects will be replaced at the end of the study following discussion between the Investigator and Sponsor.

The code for a subject may be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment decision of the subject or if demanded by the subject. Whenever a code is broken, the person breaking the code must record the time, date, and reason as well as his/her initials in the source documents. During un-blinding procedure in case of medical emergency, it should be ensured that no study personnel is unblinded to other subjects.

If the CRU need to break the code, the sponsor should, if possible, be contacted prior to breaking the blinding. In all cases, the Trial Monitor must be notified within 24 hours after an emergency un-blinding without revealing the treatment.

All codes (whether broken or not) must be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure and will be collected by the Monitor. A copy may be maintained in the Trial Master File (TMF).

The randomization code will include 4-digit subject numbers, 1001-1008 for the first cohort, 2001-2008 for the second cohort and follow the same numbering rationale for cohorts 3 through 5. In case a subject need to be replaced, the replacement subject will receive the same treatment as the dropout subject. The replacement randomization numbers will have the second digit replaced (X1XX), for example subject 2101 will replace subject 2001 with the same treatment. If the replacement subject drops from the study, a second replacement subject may be enrolled with replacement number (X2XX). No replacement randomization list will be generated.

2.3. Sample Size and Power

Approximately 40 subjects, divided in 5 cohorts with 8 subjects per cohort. Due to exploratory nature of this study, a sample size of 8 subjects per cohort is empirically determined and consistent with typical sample sizes used for similar studies to assess PK and safety data.

2.4. Study Procedures and Visit Structure

Each subject will undergo a screening visit, up to 28 days prior to dosing. Each subject will undergo one in-house period of 9-day duration, two outpatient visits, and a follow-up visit.

Screening:

A Screening Visit will be performed up to 28 days prior to dosing to identify eligible subjects for the study.

In-house Period:

Subjects will check in to the clinic in the morning on Day -2 for a 9-day In-house Period. They will receive standardized meals throughout their inpatient stay. Subjects will be connected to an ABPM system, and overnight measurements will be taken to familiarize the subjects with the device. ABPM measurements will continue throughout Day 4. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation.

In the morning of Day -1, subjects will get connected to a Holter ECG for 24-hour measurements and will continue these until the morning of Day 4. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation.

Subjects will be randomized to a single SC injection of HM15211 or placebo.

On Day 1, the active study medication or placebo, will be administered in the morning at approximately 08:00 hours (t=0), SC into the abdominal wall by qualified study staff. Measurements of vital signs, PK and laboratory parameter will be performed for safety evaluation.

ABPM and Holter ECG monitoring will be continued until the morning of Day 4 for the post-dose evaluation. 24-hour monitoring evaluations will be performed together with available PK data, in order to determine the best time period for 24-h monitoring period around PK_{peak}.

Subjects will continue to stay in-house for safety evaluations and PK. They will be released from the CRU in the morning of Day 7 and will return for two outpatient visits on Day 10 and 17.

Outpatient Visits:

Subjects will return to the CRU on Days 10 (± 1) and 17 (± 1) for two outpatient visits. Blood samples for PK analysis will be collected, additional safety assessments as stated in Table 2 will occur.

Follow-up Visit:

A follow-up visit will take place on Day 30 (± 2).

Time points for study procedures and sample collections for PK measurements will be specified in detail in Table 3.

Safety assessments will occur throughout the duration of the study.

3. Study Objectives

3.1. Primary Objectives and Endpoints

To assess safety and tolerability of HM15211 after single subcutaneous doses, regarding:

- Incidence of adverse events
- Incidence of clinical laboratory abnormalities (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin)
- Immunogenicity (Anti-drug antibodies [ADAbs], neutralizing anti-drug antibodies [nAbs], anti-polyethylene glycol antibodies [anti-PEG])
- Change from baseline in vital signs (blood pressure, respiratory rate, temperature, and heart rate) measurements
- Incidence and severity of clinical findings on physical examination
- Injection site reaction
- Change from baseline in 12-lead ECG parameters; the primary ECG endpoint will be QTcF
- Blood pressure (BP) assessed by 24-hour ambulatory blood pressure monitoring (ABPM); (Mean day- and night time systolic/diastolic BP)
- Heart rate activity assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG); (Heart rate [HR] and heart rate variability [HRV], e.g. mean heart rate, difference between day and night HR, mean normal to normal [NN] intervals, standard deviation of all NN intervals [SDNN])

To assess the pharmacokinetic (PK) profile of HM15211 after single SC doses in regards, but not limited to:

- Maximum concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Total area under the concentration time curve (AUC), including AUC(0-inf)
- Apparent terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution at terminal phase (Vz/F)
- Terminal elimination rate constant (k_{el})

3.2. Exploratory Objectives and Endpoints

To assess pharmacodynamics (PD) properties of HM15211 after single SC doses in comparison to placebo on:

- Lipid metabolism:
  - Total cholesterol
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Very low-density lipoprotein (VLDL)

  - Triglycerides
  - Free fatty acid (FFA)
- Body weight
- Glucose metabolism:
  - Fasting plasma glucose (FPG)
  - Insulin
  - C-peptide
- Incretin secretion:
  - Glucagon (GCG)
  - Leptin
  - Glucagon-like peptide-1 (GLP-1)
  - Gastric inhibitory peptide (GIP)
  - Amino acids
- Inflammatory marker:
  - C-reactive protein (CRP)

4. Analysis Sets

4.1. Safety Set

The Safety analysis set will include all subjects who received study medication (HM15211 or Placebo). The Safety analysis set will be used for demographic, baseline characteristics and safety summaries.

4.2. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who received HM15211 with all evaluable PK data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism, or excretion of HM15211). PK analysis set will be used for analysis of PK endpoints.

4.3. Pharmacodynamic Analysis Set

The PD analysis set will include all subjects who received HM15211 or placebo with all evaluable PD data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the PD of HM15211). PD analysis set will be used for analysis of PD endpoints.

5. Study Subjects

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

5.1. Subject Disposition

Subject disposition will be summarized for the Safety Set. Summary tables will be presented.

5.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for all subjects in the Safety Set. Demographic and baseline characteristics include, but are not limited to: age, sex, ethnicity, race, body weight, height, body mass index, fasting plasma glucose, smoking status at Screening, HbA1c, total cholesterol, HDL, LDL, and triglycerides.

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 21.0) and summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety Set. Medical history will be listed.

5.4. Subject Eligibility and Withdrawal Criteria

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

5.5. Exposure

Study medication exposure data will not be summarized. Study drug administration information will be listed.

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.
- Pre-treatment medication is defined as any non-study medication that stops before the date of dosing of study medication.

The WHO DRUG Dictionary Enhanced (WHO DDE, March 2018) 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.

The number and percentage of subjects receiving concomitant medications (including both prior and new concomitant medications) will be summarized 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

Protocol deviations may include the deviations from entry criteria, the study procedures, study medication intake/administration, or study restrictions, etc. Major protocol deviations will be identified prior to database lock and will be summarized for the Safety Set. Subjects with major protocol deviations that may impact the primary PK and PD endpoints will be excluded from the PK and PD Evaluable Sets.

6. Statistical Methods of Analysis

6.1. General Considerations

PK, PD, and Safety analyses will be performed with the PK Evaluable Set, PD Evaluable Set, and Safety Set, respectively. All data collected during the study for Safety Set will be included in data listings.

6.1.1. Statistical Notation and Presentation

The continuous variables will be summarized by number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For categorical variables, the count 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, if needed, 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

For PK and PD data, if a blood sample was collected outside the protocol specified blood sampling time window, such data will still be included in data analysis, and the actual clock time will be used for PK and PD parameters calculations such as area under the curve (AUC).

All values, scheduled or unscheduled, will be presented in data listings.

On scheduled visits with missing assessments, unscheduled assessments within the visit window, if available, may be used for analysis. Assessments collected during scheduled visits that are outside the visit window can be used for analysis.

6.1.3. Handling of Missing or Partial Dates

In cases of incomplete dates for adverse events (AEs) or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. The imputation rule is to conservatively capture AEs with missing start dates as treatment-emergent AEs (TEAEs) with the following algorithms:

- If "day" is the only missing field, impute the "day" as the later one between the first day of the month and the dosing date if their "month" are the same.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the later one between January 1 of the year or the dosing date if the "year" is the same as the dose date.
- If "day", "month", and "year" are all missing, to be conservative, the event will be assumed to occur on the same day as the dosing was administered.

Concomitant medications with partial or missing start dates are assumed to have started prior to the dosing of the study medication. Non-study medications with missing or partial dates will be imputed similarly.

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.

6.1.4. Handling of Outliers and Unquantifiable Measurements

Prior to database lock, PK data will be reviewed by the principal investigator, pharmacokinetic scientists, consulting scientists, data management representatives, statisticians, and the sponsor to assess whether individual concentration values are inconsistent with other values from the same subject or if there are errors with the samples. The pharmacokineticist will provide input that will determine whether the sample result is plausible given the PK profile of the subject. Such values may be re-analyzed or may be removed from the analysis prior to calculation of PK parameters at the discretion of the pharmacokineticist. Determination of data points subject to re-analysis or removal from determination of PK parameters (i.e., implausible data) will be documented prior to database lock. 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. 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:

- For graphical presentations of the individual subject data: BLQ and values deemed implausible will not be displayed but will be flagged for reference and retained in the data as assayed.
- If any values are deemed implausible, final decisions and rationale will be documented in the pre-database lock meeting minutes.

For the calculation of summary statistics of concentrations or derivation of PK and PD parameters: values that are BLQ and values deemed implausible will be set to missing.

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. Pharmacokinetic Analyses

6.2.1. PK Concentration

Concentration of HM15211 will be summarized descriptively by treatment group. Line plots of HM15211 individual subject concentration overlaid with the mean concentration for each cohort will be plotted separately. In addition, a line plot of the HM15211 mean concentration by treatment group will be plotted.

6.2.2. PK Parameters

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

- Maximum concentration (C_{max}) is defined as the maximum HM15211 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 HM15211 up to the last point with concentrations above the lower limit of quantification (LLOQ), $AUC_{0\text{-last}}$, will be calculated by linear trapezoidal method.
- Area under the concentration-time curve with extrapolation to infinity for HM15211, AUC0-inf, will be calculated by AUC0-last + Clast/ k_{el}, where Clast is the last observed concentration (_obs), or the last predicted concentration (_pred).
- k_{el}, first-order terminal elimination rate constant, calculated by linear regression of time vs. log concentration curve in the terminal phase. For k_{el} to be acceptable, it shall be determined over a time interval equal to at least 1.5 x $t_{½}$ k_{el}, with at least 3 different time

points in the terminal phase for the regression analysis, and the coefficient of determination Adj_RSq shall be ≥0.8. If at least one of these three conditions is not fulfilled, the parameters depending on k_{el} (e.g., AUC0-inf, the terminal half-life t1/2 k_{el}, 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 pharmacokineticists in charge of PK analysis.

- Apparent terminal half-life $t_{1/2}$, will be determined from equation ln2/ k_{el}.
- CL (_obs, _pred), apparent total body clearance will be calculated by Dose/AUC0-inf. Note, the Dose in calculating CL for HM12460A will be the total administered dose, which is the sum of IV bolus dose and IV infusion dose.
- Vz (_obs, _pred), apparent volume of distribution at terminal phase and will be calculated by CL/ k_{el}.
- F, bioavailability
- Apparent clearance divided by bioavailability (CL/F)
- Apparent volume of distribution at terminal phase divided by bioavailability (Vz/F)

Box plots of Cmax, AUC0-last and AUC0-inf for each cohort may be generated.

6.2.3. Dose Proportionality

The power model will be used to analyze the dose proportionality in AUC and C_{max} of HM15211. The estimate of the ratio of the dose normalized geometric means, R_{dnm}, 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.

$\mathcal{E}_i$ 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 (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.

6.3. Pharmacodynamic Analyses

6.3.1. Lipid Metabolism

Observed values and the change from baseline for parameters related to lipid metabolism, such as total cholesterol, LDL, HDL, VLDL, triglycerides, and FFA, will be summarized descriptively by treatment group and visit.

6.3.2. Body Weight

The observed values, change from baseline, and percent change from baseline in body weight will be summarized by treatment group and visit.

6.3.3. Glucose Metabolism

Observed values and the change from baseline for parameters related to glucose metabolism, such as insulin and C-peptide, will be summarized descriptively by treatment group, visit and time point.

Observed values and the change from baseline for the parameters related to glucose metabolism, such as fasting plasma glucose will be summarized descriptively by treatment group and visit.

6.3.4. Incretin Secretion

Observed values and the change from baseline for parameters related to incretin secretion, such as GCG, GLP-1, and GIP will be summarized descriptively by treatment group, visit, and time point.

Observed values and the change from baseline for the parameters related to incretin secretion, such as leptin will be summarized descriptively by treatment group and visit.

6.3.5. Amino Acids

Observed values and the change from baseline for amino acids will be summarized descriptively by treatment group and visit.

6.3.6. C-Reactive Protein

Observed values and the change from baseline for the inflammatory marker, CRP, will be summarized descriptively by treatment group and visit..

6.4. Safety Analyses

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

6.4.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA, version 21.0. AEs will be summarized for the Safety Set.

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.

TEAEs will be summarized by SOC and PT, and by SOC, PT, and maximum severity for each cohort and overall. 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.

6.4.2. Clinical Laboratory Assessments

All hematology, clinical chemistry, and urinalysis results (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin) will be summarized. Laboratory assessments that are outside of normal ranges and/or with potential clinical importance will be summarized and flagged in the listings. Shift tables of hematology, clinical chemistry, and urinalysis results will be generated to summarize the normal and abnormal (abnormal high and abnormal low) status changes from baseline.

6.4.3. Vital Signs

Observed vital sign values (blood pressure, respiratory rate, temperature, and heart rate) at each day and change from baseline at each post-baseline day will be summarized.

6.4.4. Physical Examination

The clinical findings on PE and their severity will be listed.

6.4.5. Injection Site Reactions

The number and percentage of subjects with any injection site reactions will be summarized by treatment group for the entire in-house period and by visit and time point within in-house period. The number and percentage of subjects with specific site reactions such as pain on palpation, itching, erythema, edema, and induration will be summarized by visit, time point, and Draize scale. In addition, diameter of affected areas will be summarized descriptively by visit and time point.

6.4.6. 12-Lead Electrocardiograms

Observed and change from baseline values of QTcF and other ECG parameters will be summarized. Status of 12-lead ECG parameters, normal, abnormal not clinically significant, and abnormal clinically significant, and their shifts from baseline will be summarized.

6.4.7. 24-Hour Ambulatory Blood Pressure Monitoring

Mean day time (10:00 to 20:00) and night time (00:00-6:00) systolic and diastolic BP will be summarized for each day from Day -2 to Day 4 (Fagard 2008).

6.4.8. 24-Hour Holter ECG

Observed values from 24-Hour Holter ECG will be summarized by time point for each day from Day -1 to Day 4. Parameters calculated over the entire day such as mean HR, mean difference between day and night HR, mean NN intervals, and SDNN will be summarized by day.

6.4.9. Immunogenicity

Anti-drug antibodies (ADAbs, anti-HM15211 antibodies) will be summarized categorically, displaying the Positive and Negative tests by treatment group with Positive tests further summarized by absolute titer values or titer fold categories.

Neutralizing antibodies (nAbs) and anti-polyethylene glycol antibodies (anti-PEG) will be summarized categorically, displaying the Positive and Negative tests by treatment group. Percent specific binding and the change from baseline will be summarized descriptively by treatment group and day.

7. Interim Analysis

No formal interim analysis is planned.

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 WinNonlin v5.2 or higher and/or SAS® version 9.4.

9. References

Fagard RH, Celis H, Lutgarde T, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension*. 2008; **51**: 55-61.

10. Appendix

Table 2: Schedule of Events

ASSESSMENT	SCREEN	IN-HOUSE PERIOD									OUTPATIENT VISITS		F/U
Visit/ Time Point (Day)	**- 28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10 (± 1)**	**17 (± 1)**	**30 (± 2)**
IP Administration				**X**									
Informed consent	X												
Demography	X												
Medical history	X												
Sequestered in clinic/unit		X	X	X	X	X	X	X	X	X			
Physical examination (PE)	X												X
Abbreviated PE		X								X	X	X	
Hematology, serum chemistry, urinalysis	X		X	X		X				X		X	X
Amylase, Lipase	X		X		X	X	X	X	X		X	X	X
Calcitonin	X												X
Coagulation	X		X			X							
TSH	X												X
HbA1c	X												
Hep B, Hep C, HIV	X												
ADAbs, nAbs & anti-PEG			X									X	X
Pregnancy test (urine)		X									X	X	X
Pregancy test (serum)	X												
FSH if postmenopausal	X												
Urine drug screen & alcohol breath test	X	X									X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Height, BMI	X												
Vital signs	X	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X	X
Standardized meals		X	X	X	X	X	X	X	X	X			
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AE'S	X	X	X	X	X	X	X	X	X	X	X	X	X

ASSESSMENT	SCREEN	IN-HOUSE PERIOD									OUTPATIENT VISITS		F/U
Visit/ Time Point (Day)	**- 28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10 (± 1)**	**17 (± 1)**	**30 (± 2)**
IP Administration				**X**									
Injection site assessment				X[3]	X	X	X	X	X	X			
12-lead ECG	X	X[2,7]					X[2,7]	X[7]		X[7]	X[7]	X[7]	X[7]
Holter monitoring[4]			X	X	X	X	X						
ABP monitoring[4]		X	X	X	X	X	X						
PK assessment[5]				X	X	X	X	X		X	X	X	X
Insulin, C-peptide, glucagon[6]				X	X	X	X	X		X	X	X	X
GLP-1, GIP, amino acid panel[6]				X	X	X	X	X		X	X	X	X
FPG	X		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Lipid panel, incl. FFA	X			X[6]		X[6]				X[6]		X[6]	
Leptin[6]				X		X				X		X	
CRP[6]				X		X				X		X	

[1]Measurements of blood pressure will be performed twice (morning and evening) on Day -1. On Day 1, measurements will be performed pre-dose and at 4, 8 and 12 hours post-dose, on Day 2 at 24 and 36 hours post-dose, on Day 3 at 48 hours, on Day 4 at 72 hours, on Day 5 at 96 hours, on Day 6 at 120 hours, on Day 7 at 144 hours post-dose with a sampling window of ± 15 min for each time point.

Measurements of pulse rate and respiration rate will be performed at time points together with blood pressure measurements. Pulse rate will be assessed in combination with both, supine and standing blood pressure measurements. Respiration rate will be assessed at time points of supine blood pressure measurements.

[2]ECG measurements are to be collected on Day -2 before subjects are connected to the ABPM and on Day 4 after subjects have been disconnected from the ambulatory devices.

[3]Measurements of local injection site reaction on Day 1 at pre-dose, at 4 and 12-hour post-dose.

[4]Time points may be adjusted after evaluation of PK data.

[5]Sampling time points according to Table 3 PK Sampling Schedule.

[6]Sampling time points according to Table 4 PD Sampling Schedule.

Table 3: PK Sampling Schedule

Inpatient Period	Day 1	Pre-Dose 4 h 8 h 12 h
	Day 2 Day 3 Day 4 Day 5 Day 7	24 h 36 h 48 h 72 h 96 h 144 h
Outpatient Visit	Day 10 (±1) Day 17 (±1)	216 h 384 h
Follow-up Visit	Day 30 (±2)	696 h

Table 4: PD Sampling Schedule

			Leptin, Lipid panel (incl. FFA), CRP	**FPG**	**Insulin, C-peptide, GCG, GLP-1, GIP**	**Amino acids**
Inpatient Period	Day -1		--	X	--	--
	Day 1	Pre-dose 4 h 8 h 12 h	X -- -- --	X -- -- --	X X X X	X X X X
	Day 2	24 h 36 h	-- --	X --	X X	X X
	Day 3 Day 4 Day 5 Day 6 Day 7	48 h 72 h 96 h 120 h 144 h	X -- -- -- X	X X X X X	X X X -- X	X X X -- X
Outpatient Visit	Day 10 (± 1) Day 17 (± 1)	216 h 384 h	-- X	X X	X X	X X
Follow-up Visit	Day 30 (± 2)	696 h	--	X	X	X

- Date and time for dosing and PD sampling should be record, D1 blood collection time “pre-dose” should be noted as “pre-dose”