Statistical Analysis Plan

Protocol HM-TRIA-102

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of HM15211 in Obese Subjects with NAFLD

Phase I

Original Protocol:
Version 1.0: 27-Sep-2018
Version 2.0: 25-Oct-2018
Version 3:0: 13-Feb-2019
Version 4.0: 09-Apr-2019
Version 5.0: 02-Jul-2019

Prepared by: _____

Version: Final

Date: March 23, 2020

Statistical Analysis Plan

Protocol HM-TRIA-102

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of HM15211 in Obese Subjects with NAFLD

Phase I

Original Protocol:
Version 1.0: 27-Sep-2018
Version 2.0: 25-Oct-2018
Version 3:0: 13-Feb-2019
Version 4.0: 09-Apr-2019
Version 5.0: 02-Jul-2019

This Statistical Analysis Plan has been reviewed and approved by:

_____ Date:_____

Table of Contents

1. Introduction 9
2. Study Overview 9
2.1. Study Design 9
2.2. Randomization and Blinding 11
2.3. Sample Size and Power 11
2.4. Study Procedures and Visit Structure 11
3. Study Objectives 11
3.1. Primary Objectives and Endpoints 11
3.1.1. Safety and Tolerability of HM15211 11
3.1.2. Pharmacokinetics of HM15211 12
3.1.3. Pharmacodynamics of HM15211 12
3.2. Exploratory Objectives and Endpoints 12
4. Analysis Sets 13
4.1. Safety Set 13
4.2. Pharmacokinetic Analysis Set 13
4.3. Pharmacodynamic Analysis Set 14
5. Study Subjects 14
5.1. Subject Disposition 14
5.2. Demographic and Baseline Characteristics 14
5.3. Medical History 14
5.4. Subject Eligibility and Withdrawal Criteria 14
5.5. Exposure 14
5.6. Concomitant Medication 15
5.7. Protocol Deviations 15
6. Statistical Methods of Analysis 15
6.1. General Considerations 15
6.1.1. Statistical Notation and Presentation 15
6.1.2. Handling of Multiple Observations, Missing Observations or Out of Window Observations 16
6.1.3. Handling of Missing or Partial Dates 16
6.1.4. Handling of Outliers and Unquantifiable Measurements 17

6.1.5. Study Baseline 18
6.2. Pharmacokinetic Analyses 18
6.2.1. PK Concentration 18
6.2.2. PK Parameters 18
6.2.3. Dose Proportionality 19
6.3. Pharmacodynamic Analyses 20
6.3.1. MRI-PDFF 20
6.4. Exploratory Analyses 20
6.4.1. Incretins Secretion 20
6.4.2. Body Weight, Body Mass Index, and Waist Circumference 20
6.4.3. Serum Lipid Profile and Particles 20
6.4.4. Amino Acids 21
6.4.5. Inflammatory Marker 21
6.4.6. Bone Metabolism 21
6.4.7. Glucose Metabolism 21
6.4.8. Ketone Bodies 21
6.4.9. Liver Steatosis and Liver Stiffness 21
6.4.10. Visceral Fat Volume 22
6.5. Safety Analyses 22
6.5.1. Adverse Events 22
6.5.2. Clinical Laboratory Assessments 22
6.5.3. Immunogenicity 22
6.5.4. Physical Examination 23
6.5.5. Vital Signs 23
6.5.6. 24-Hour Ambulatory Blood Pressure Monitoring 23
6.5.7. 24-Hour Holter ECG 23
6.5.8. 12-Lead Electrocardiograms 23
6.5.9. Injection Site Reactions 23
7. Interim Analysis 24
8. Statistical Software 24
9. Changes to the Planned Analyses from Protocol 24

10. References 24
11. Appendix 25

List of In-Text Tables and Figures

Table 1: Treatment Allocation and Dose Escalation (NAFLD) 10
Table 2: Schedule of Events, Cohorts 1-1 and 1-2 25
Table 3: Schedule of Events, Cohorts 1-3 (not including Day 82) 28
Table 4: Schedule of Events, Cohorts 1-3 (including Day 82) 31
Table 5: Schedule of Events, Cohorts 1-4 34
Table 6: Schedule of Events, Cohorts 1-5 and up 37
Table 7: PK Sampling Schedule for cohorts 1-1 and 1-2 40
Table 8: PK Sampling Schedule starting from cohort 1-3 41

Figure 1: Dose Escalation Schematic 10

List of Abbreviations

Abbreviation	Definition of Term
_obs	observed
_pred	predicted
ADAbs	Anti-drug antibodies
Adj_RSq	Adjusted r squared
AE	Adverse event
ANCOVA	Analysis of Covariance
anti-PEG	Anti-polyethylene glycol antibodies
ATC	Anatomic Therapeutic Chemistry
AUC	Area under the concentration-time curve
AUC0-168h SS	Area under the concentration-time curve for HM15211 during steady state
BLQ	Below the limit of quantitation
BMI	Body mass index
BP	Blood pressure
CAP	Controlled attenuation parameter
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum concentration
CSR	Clinical study report
Ctrough	Trough serum concentration
CTX-1	Carboxy-terminal crosslinked telopeptide of type 1 collagen
CV	Cardiovascular
CV%	Coefficient of variation
ECG	Electrocardiogram
FFA	Free fatty acid
FGF21	Fibroblast growth factor 21
FPG	Fasting plasma glucose
GCG	Glucagon
GI	Gastrointestinal
GIP	Gastric inhibitory peptide
GLP-1	Glucagon like peptide-1
HA	Hyaluronic acid
HDL	High-density lipid
HDL-C	High-density lipid cholesterol content
HDL-P	High-density lipid particles
HR	Heart rate
IP	Investigational product
IWRS	Interactive Web Response System
kel	Apparent elimination constant
LDL	Low-density lipid
LDL-C	Low-density lipid cholesterol content

Abbreviation	Definition of Term
LDL-P	Low-density lipid particles
LLOQ	Lower limit of quantitation
LS	Least squares
LSM	Liver stiffness measurements
max	maximum
MedDRA	Medical dictionary for regulatory activities
min	minimum
MRI-PDFF	Magnetic resonance imaging-estimated proton density fat fraction
n	sample size
nAbs	Neutralizing antibodies
NAFLD	Non-alcoholic fatty liver disease
NCA	Non-compartmental analysis
NN	Normal to normal R-R intervals
OC	Osteocalcin
P_1NP	Procollagen type $_1$ N-terminal propeptide
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PT	Preferred term
QTcF	Fridericia's corrected QT interval
R_{dnm}	Ratio of the dose normalized geometric means
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDANN	Standard deviation of the 5-minute average NN interval
SDNN index	Mean of standard deviations of all NN intervals for all 5 min segments of the entire recording.
SE	Standard error
SOC	System organ class
t1/2	Half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum concentration
TSH	Thyroid stimulating hormone
VCTE	Vibration controlled transient elastography
VLDL	Very low-density lipid
VLDL-C	Very low-density lipid cholesterol content
VLDL-P	Very low-density lipid particles
Vz/F	Apparent volume of distribution at terminal
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, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of HM15211 with Placebo as comparator in obese subjects with non-alcoholic fatty liver disease (NAFLD). This statistical analysis plan (SAP) was developed based on Hanmi Pharmaceutical Protocol HM-TRIA-102 (version 5.0 dated 02Jul2019).

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 randomized, placebo-controlled, multiple-ascending dose study to investigate the safety, tolerability, PK, and PD of subcutaneous (SC) administration of HM15211.

This study will be single-blind and conducted in up to 6 cohorts comprising a total of up to 72 obese subjects with NAFLD. Each cohort will enroll subjects to ensure that at least 12 subjects per cohort will complete the study. Subjects will be randomized to investigational product (IP) or placebo in a 3:1 ratio via an Interactive Web Response System (IWRS). Per cohort (n=12 subjects), 9 subjects will be randomized to HM15211 and 3 subjects to placebo. Cohorts may partially overlap after at least 9 subjects have completed 2-4 weeks of treatment (2 weeks of treatment is reached at Visit week 3) and a dose escalation decision has been made. Study drug will be administered weekly over a period of 12 weeks.

Based on the safety and available PK and PD 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. Cohorts will start in sequential order but may overlap partially during execution. Replacement of dropouts and withdrawals may take place.

Each subject will undergo a screening visit, 2 in-house/ treatment periods and multiple outpatient visits. A final follow-up visit that will conclude subject study participation.

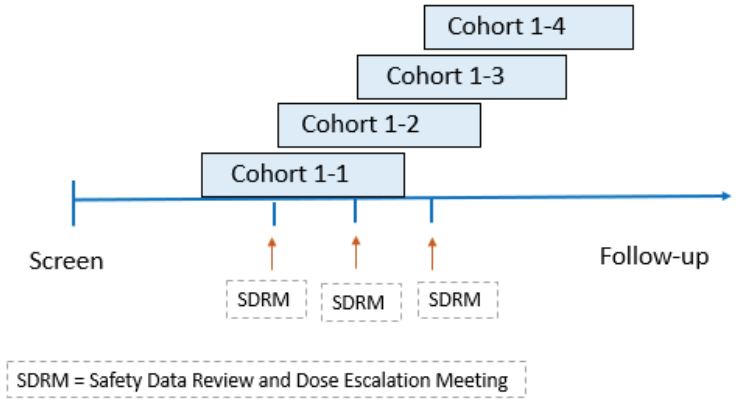
The duration of participation in this study including Screening, Treatment and Follow-up will be approximately 23 weeks for each subject including 12 weeks of treatment period.

Table 1: Treatment Allocation and Dose Escalation (NAFLD)

Cohorts	Number of Subjects	Treatment
Cohort 1-1	N=9	HM15211 0.01 mg/kg
	N=3	Matching Placebo
Cohort 1-2	N=9	HM15211 0.02 mg/kg
	N=3	Matching Placebo
Cohort 1-3	N=9	HM15211 0.04 mg/kg
	N=3	Matching Placebo
Cohort 1-4	N=9	HM15211 0.06 mg/kg
	N=3	Matching Placebo
Cohort 1-5	N=9	HM15211 0.08 mg/kg
	N=3	Matching Placebo
Cohort 1-6	N=9	HM15211 0.12 mg/kg
	N=3	Matching Placebo

Additional cohorts may be added if necessary, to provide sufficient data. Proposed doses for cohort 1-2 and 1-3 and 1-4 may be adjusted but will not exceed the doses stated in the table.

Figure 1: Dose Escalation Schematic



2.2. Randomization and Blinding

Subjects who meet all inclusion and exclusion criteria or check-in criteria will be assigned a subject randomization number via an IWRS. The system will randomize in a 3:1 ratio to HM15211 or placebo. Randomization will continue until a total of up to 72 subjects have completed the study (or until 12 subjects per cohort have completed the study). If a subject fails to start dosing, or if a subject can't be randomized, the reason will be entered into the screening disposition page. The IWRS must be notified within 2 days that the subject was not randomized. In the event of an emergency, e.g. when it becomes necessary for the investigator to know which study drug the subject is taking, the subject code can be broken by the investigator, preferably after consultation with the medical monitor. Emergency code breaks can be performed using the IWRS, see section 8.7 in the protocol. As the study is single-blind, subjects and the clinical staff caring for the subjects are blinded to treatment. Staff involved in the data management, statistical analyses and staff from Pharmaceutical Services who are responsible for preparing the IP, will be unblinded. Unblinded staff will not be involved in the subjects' care.

After all subjects in one cohort have completed the Follow-up Visit, necessary steps to start with the data analysis may be taken. Data may be unblinded and data analysis for the completed cohort may start.

2.3. Sample Size and Power

Due to the exploratory nature of this study, a sample size of 12 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

In the appendix, Tables 2-6 describe the procedures and visit structure for this study for all Cohorts; Tables 7 and 8 describe the PK sampling schedules; the schedule of events and PK sampling schedules for each cohort can also be found in the clinical trial protocol.

3. Study Objectives

3.1. Primary Objectives and Endpoints

3.1.1. Safety and Tolerability of HM15211

To assess safety and tolerability of HM15211 after administration of multiple subcutaneous doses in obese subjects with NAFLD by:

- Incidence of adverse events (AEs) (cardiovascular [CV] events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal [GI] events, and gall stone formation [cholelithiasis] will be managed following separate AE guidance document).
- Incidence of clinical lab abnormalities (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin)

- Immunogenicity (Anti-drug antibodies [ADAbs], neutralizing antibodies [nAbs], anti-polyethylene glycol antibodies [anti-PEG])
- Incidence and severity of clinical findings on physical examination
- Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature]);
  BP assessed by 24-hour ambulatory blood pressure monitoring (ABPM);
  HR assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG; central reader)
- Change from baseline in 12-lead ECG parameters; the primary ECG endpoint will be QTcF
- Injection site reactions.

3.1.2. Pharmacokinetics of HM15211

To assess the pharmacokinetic (PK) profile of HM15211 after administration of multiple SC doses in obese subjects with NAFLD by, but not limited to:

- Maximum concentration (C_{max})
- Time to reach Cmax (t_{max})
- Trough serum concentration (C_{trough})
- Area under the concentration-time curve (AUC), eg, AUC_{0-t} at steady state
- Terminal elimination rate constant (k_{el})
- Terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vz/F)

3.1.3. Pharmacodynamics of HM15211

To assess a reduction of liver fat after administration of multiple doses in obese subjects with NAFLD by:

- Absolute and % changes of fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF)

3.2. Exploratory Objectives and Endpoints

To assess additional pharmacodynamic properties of HM15211 after multiple SC doses in comparison to placebo by:

- Incretins/ metabolic hormones
  - Glucagon-like peptide-1 (GLP-1)
  - Gastric inhibitory peptide (GIP)
  - Glucagon
  - Fibroblast growth factor 21 (FGF21)
  - Leptin

- Body weight and body mass index (BMI)
- Waist circumference
- Serum lipid profile and particles
    - Total cholesterol
    - Low-density lipoprotein (LDL): LDL-C, LDL-P (particles)
    - High-density lipoprotein (HDL): HDL-C, HDL-P (particles)
    - Very low-density lipoprotein (VLDL): VLDL-C, VLDL-P (particles)
    - Triglycerides
    - Free Fatty Acids (FFAs)
- Amino acid profile
- Inflammatory marker
    - Adiponectin
- Bone metabolism parameters
    - Fasting carboxy-terminal crosslinked telopeptide of type $_1$ collagen (CTX-$_1$)
    - Osteocalcin (OC)
    - Procollagen type $_1$ N-terminal propeptide (P$_1$NP)
- Glucose metabolism parameters:
    - Fasting plasma glucose (FPG)
    - Fasting insulin, fasting C-peptide
    - HbA1c
- Ketone bodies
    - Beta-hydroxybutyrate
- Changes in liver steatosis and liver stiffness assessed by FibroScan® (VCTE), determined as absolute and percent change from baseline in controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) (For Cohort 4 and 5)
- Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI imaging. (Will no longer be performed)

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 evaluable PK data appropriate for the evaluation of interest (without important 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 evaluable PD data appropriate for the evaluation of interest (without important 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 and treatment overall, 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, smoking status at Screening, alcohol use at Screening, VCTE, Liver Fat via MRI-PDFF, CAP and LSM by FibroScan®, HbA1c, c-peptide, insulin, fasting plasma glucose, total cholesterol, cholesterol and particles of HDL, LDL, and VLDL, triglycerides, Free Fatty Acids, creatinine, bilirubin, ALT, AST, GGT, and incretins/metabolic hormones.

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 23.0) 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

Total study dose administrated (mg/kg) and number of administration by visit and overall will be summarized by treatment and treatment overall, with pooled placebo. 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 Global version B3, March 2020) 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. Important protocol deviations will be identified prior to database lock and will be summarized for the Safety Set. Subjects with important protocol deviations that may impact the primary PK and PD endpoints will be excluded from the PK and PD Evaluable Sets. All deviations will be listed.

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 (if applicable), 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, if applicable, 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, Missing Observations or Out of Window Observations

If there are multiple measurements within the same scheduled visit which are scheduled to be collected once at each visit and are recorded as triplicate 12-lead ECG's except the ECG at Screening, the average of the multiple measurements will be computed at each visit for all subjects and this averaged value will be used in all the analyses and summaries.

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. A footnote will be added to tables where unscheduled visits are used to impute missing scheduled visits.

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.

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 aims to capture AEs with missing start dates as treatment-emergent AEs (TEAEs) in a conservative manner 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 post-dose on the same day as the first dose administration day.

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. Appropriate representatives will also review PK and PD parameter results 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 derived using non-compartmental analysis and summarized by treatment group for the PK Analysis Set.

- Maximum concentration (C_{max}) is defined as the maximum HM15211 concentration measured after SC dose. Will be calculated for Week 1 (1st dose) and Week 12 (12th dose):
  - C_{max} (Week 1)
  - C_{max} (Week 12)
- Time to reach C_{max} (T_{max}) is defined as the time from initial injection to time of C_{max}. Will be calculated for Week 1 (1st dose) and Week 12 (12th dose):
  - T_{max} (Week 1)
  - T_{max} (Week 12)
- C_{trough}, the trough serum concentration is defined as the minimum HM15211 concentration just prior to next dose administration. Will be calculated for Week 1 (pre 1st dose) and Week 12 (pre 12th dose):
  - C_{trough} pre-dose on Day 1 (Week 1)
  - C_{trough} pre-dose on Day 78 (Week 12)
- Area under the concentration-time curve for HM15211, $AUC_{0\text{-}168h}$ after 1st and 12th dosing (steady state), will be calculated by linear trapezoidal method.
  - $AUC_{0\text{-}168h}$ (Week 1) and $AUC_{0\text{-}inf}$ (Week 1)
  - $AUC_{0\text{-}168h}$ (Week 12)
- 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 three 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., 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 pharmacokineticist in charge of PK analysis. Will be calculated for Week 1 (1st dose) and Week 12 (12th dose):

  - k_{el} (Week 1)
  - k_{el} (Week 12)

- Apparent terminal half-life $t_{1/2}$ will be determined from equation ln2/ k_{el}. Will be calculated for Week 1 (1st dose) and Week 12 (12th dose).
  - $t_{1/2}$ (Week 1)
  - $t_{1/2}$ (Week 12)
- Apparent clearance divided by bioavailability (CL/F). Will be calculated for Week 1 (1st dose) and Week 12 (12th dose).
  - CL/F (Week 1)
  - CL/F (Week 12)
- Apparent volume of distribution at terminal phase divided by bioavailability (Vz/F). Will be calculated for Week 1 (1st dose) and Week 12 (12th dose).
  - Vz/F (Week 1)
  - Vz/F (Week 12)
- Accumulation ratio (AR). Will be calculated for Week 1 (1st dose) and Week 12 (12th dose).

Box plots of C_{max} and $AUC_{0\text{-}168h\ SS}$ for each cohort may be generated.

6.2.3. Dose Proportionality

The power model will be used to analyze the dose proportionality in C_{max} and $AUC_{0\text{-}168h\ SS}$ of HM15211. The estimate of the ratio of the dose normalized geometric means (mg/kg), 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 (C_{max} or $AUC_{0\text{-}168h}$) 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. MRI-PDFF

The observed values, change from baseline, and the percent change from baseline of liver fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) will be summarized descriptively by treatment group, visit, and time point.

A mixed model repeated measures analysis will be performed with the change from baseline in liver fat as the dependent variable, treatment group, analysis time point and the interaction between treatment group and analysis time point as factors, and the baseline of the dependent variable as a covariate. Repeated measures on each subject, at each visit week, will assume an unstructured covariance structure. If the model fails to converge, other covariance structures will be considered and selected based on model fit as determined by Akaike information criterion. The LS mean, SE of LS mean and 95% confidence interval will be presented by treatment group for each post baseline analysis time point. The LS mean difference from pooled placebo, SE of the LS mean difference from pooled placebo, and the 95% confidence interval will be presented by active treatment group for each post baseline analysis time point.

6.4. Exploratory Analyses

6.4.1. Incretins Secretion

Observed values and the change from baseline for parameters related to incretins secretion, such as GLP-1, GIP, GCG, FGF21, and leptin will be summarized descriptively by treatment group, visit, and time point. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.2. Body Weight, Body Mass Index, and Waist Circumference

The observed values, the change from baseline, and the percent change from baseline in body weight and waist circumference will be summarized by treatment group and visit. Observed values and change from baseline for BMI will be summarized similarly. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.3. Serum Lipid Profile and Particles

Observed values and the change from baseline for parameters related to lipid metabolism, such as total cholesterol, LDL-C, LDL-P, HDL-C, HDL-P, VLDL-C, VLDL-P, triglycerides, and

FFAs, will be summarized descriptively by treatment group and visit. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.4. Amino Acids

Observed values and the change from baseline for amino acids will be summarized descriptively by treatment group and visit. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.5. Inflammatory Marker

Observed values and the change from baseline for adiponectin will be summarized descriptively by treatment group and visit. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.6. Bone Metabolism

Observed values and the change from baseline for CTX-1, OC, and P_1NP will be summarized descriptively by treatment group and visit. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.7. Glucose Metabolism

Observed values and the change from baseline for parameters related to glucose metabolism, such as FPG, fasting insulin, fasting C-peptide, and HbA1c will be summarized descriptively by treatment group, visit and time point. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.8. Ketone Bodies

Observed values and the change from baseline for beta-hydroxybutyrate will be summarized descriptively by treatment group and visit. MMRM analysis that will be specified similarly to the analysis of MRI-PDFF will be used.

6.4.9. Liver Steatosis and Liver Stiffness

Observed values and the absolute and percent change from baseline for CAP and LSM will be summarized descriptively by treatment group and visit. For Cohorts 4 and up, an analysis of covariance (ANCOVA) model with treatment as factor and baseline CAP (or LSM) value as a covariate will be performed to evaluate the change from baseline in CAP and LSM in each treatment group versus the pooled placebo group. The LS mean difference from pooled placebo, SE of the LS mean difference from pooled placebo, and the 95% confidence interval will be derived by treatment group for the single post-baseline visit. If data are not normally distributed based on the Shapiro-Wilks normality test, the Wilcoxon-Mann-Whitney test will be performed to analyze the change from baseline in CAP and LSM for each active treatment group versus the pooled placebo group. The Hodges-Lehmann estimator of the median and its 95% confidence interval will be provided.

6.4.10. Visceral Fat Volume

Visceral Fat Volume will no longer be collected or analyzed.

6.5. Safety Analyses

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

6.5.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA, version 23.0. 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 by treatment group, with pooled placebo. TEAEs that are related to study medication per investigator's decision, TEAEs leading to study discontinuation, TEAEs that are serious (treatment-emergent SAEs) and adverse events of special interest (such as necrolytic migratory erythema, cholelithiasis and pancreatitis) will be summarized similarly.

AEs with missing severity will not be imputed. AEs with missing relationship will be imputed as related.

6.5.2. 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.

6.5.3. Immunogenicity

Anti-drug antibodies (ADAbs, anti-HM15211 antibodies) will be summarized categorically, displaying the tier 1 (putative positive and negative) and tier 2 (positive and negative) tests by treatment group with positive tests further summarized by tier 3 absolute titer values and domain specificity. Tier 3 neutralizing antibody (nAbs) results will be summarized with ADAbs data in the same table.

In a separate table, anti-polyethylene glycol antibodies (anti-PEG) will be summarized categorically, displaying the screening result and specificity. The Anti-PEG specificity test will only be performed for samples where the titer increased more than 4 times compared to Day 1.

6.5.4. Physical Examination

The clinical findings on PE will have their incidence and severity listed.

6.5.5. Vital Signs

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

6.5.6. 24-Hour Ambulatory Blood Pressure Monitoring

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

6.5.7. 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, pNN50, RMS SD, SDANN and SDNN index will be summarized by day.

Heart Rate Variability will be assessed by the following parameters:

- Percentage Greater than 50 msec (PRR_GT50), aka pNN50, the percentage of successive differences in RR values greater than 50 milliseconds (can be increases or decreases) during the time period.
- RMS SD, the square root of the mean of the squares of successive differences between the RR values during the time period.
- Magid SD, also known as SDNN index, the average of five-minute period standard deviations of the RR intervals during the time period.
- Kleiger SD, also known as SDANN, standard deviation of all five-minute average RR intervals during the time period.

6.5.8. 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.

6.5.9. 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, induration and other 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.

7. Interim Analysis

No 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. Changes to the Planned Analyses from Protocol

Visceral Fat Volume will no longer be collected or analyzed. Cohort 1-6 was not conducted.

10. 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.

11. Appendix

Table 2: Schedule of Events, Cohorts 1-1 and 1-2

	Screen	Admin		Treatment Period																				Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2					Outpatient Visit		
Week				1				2	3	4	5	6	7	8	9	10	11		12					13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	85	99	113
Visit Window																									±2	±2
Confinement		X	X	X	X	X	X	X											X	X	X	X	X			
Dosing				X				X		X	X	X	X	X	X	X	X	X		X						
Randomization			X																							
Screening Procedures																										
Informed Consent	X																									
Inclusion/Exclusion Criteria	X	X[1]																								
Demography	X																									
Medical History/Prior Medication	X																									
Smoking and Alcohol History	X																									
Height	X																									
Estimated Glomerular Filtration Rate (eGFR)	X																									
Thyroid Function Test (TSH)	X			X								X				X								X		X
HBA1C, FPG	X																									
Serum Insulin	X																									
Alpha-2 Macroglobulin	X																									
Viral Serology	X																									
VCTE (FibroScan)	X																									
Check-in Criteria to In-house Period		X																	X							
Pregnancy Test[2]	X	X							X	X	X	X	X	X	X	X	X	X	X					X	X	X
Urine Drug Screen & Alcohol Breath Test	X	X							X	X	X	X	X	X	X	X	X	X	X					X	X	X
Safety and Exploratory Assessments																										
Physical Examination (PE)	X																									X
Abbreviated PE		X								X		X				X			X					X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X[4]	X[4]				X				X		X	X			X			X[4]				X			
Holter Monitoring			X	X	X	X														X	X	X	X			
ABPM		X	X	X	X	X													X	X	X	X	X			

	Screen	Admin		Treatment Period																				Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2					Outpatient Visit		
Week				1				2	3	4	5	6	7	8	9	10	11		12					13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	85	99	113
Visit Window																									±2	±2
Hematology, Chemistry, Coagulation, Urinalysis	X			X				X		X		X	X			X				X				X	X	
CRP[10]					X																					
Lipid Panel	X																									
Amylase, Lipase	X			X						X		X				X								X		
Calcitonin	X			X								X												X		
Body Weight[12]	X			X				X		X	X	X	X	X	X	X	X	X	X	X				X	X	X
BMI Calculation	X			X				X		X		X				X				X				X	X	X
Waist Circumference	X																									X
Pharmacodynamic Assessments																										
Lipid Profile and Particles				X												X								X		
MRI-PDFF[5]	X															X								X		
Amino Acid Panel				X				X		X		X				X				X				X		
Incretins[6]				X				X		X		X				X				X				X		
Bone Metabolism Parameters				X								X				X								X		
Glucose Metabolism Parameters[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Biomarkers[11]				X												X								X		
Ketone Bodies				X												X								X		
Pharmacokinetic and Immunogenicity Assessments																										
PK Sampling[8]				X	X	X		X	X	X	X	X	X		X	X				X		X	X	X	X	X
Immunogenicity				X							X				X					X				X	X	
Other Safety Assessments																										
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Tolerability				X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[1]Confirmation of eligibility

[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points

[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from ambulatory device.

[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).

[6]All incretins will be collected at the same time points together with the PK sample collection.

[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 3: Schedule of Events, Cohorts 1-3 (not including Day 82)

	Screen	Admin		Treatment Period																				Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2					Outpatient Visit		
Week				1				2	3	4	5	6	7	8	9	10	11		12					13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	85	99	113
Visit Window																									±2	±2
Confinement		X	X	X	X	X	X	X											X	X	X	X	X			
Dosing				X				X		X	X	X	X	X	X	X	X	X		X						
Randomization			X																							
Screening Procedures																										
Informed Consent	X																									
Inclusion/Exclusion Criteria	X	X[1]																								
Demography	X																									
Medical History/Prior Medication	X																									
Smoking and Alcohol History	X																									
Height	X																									
Waist Circumference	X																							X		X
Estimated Glomerular Filtration Rate (eGFR)	X																									
Thyroid Function Test (TSH)	X			X								X				X								X		X
HBA1C	X																							X		
FPG	X																									
Serum Insulin	X																									
Alpha-2 Macroglobulin	X																									
Viral Serology	X																									
VCTE (FibroScan)	X																									
Check-in Criteria to In-house Period		X																	X							
Pregnancy Test[2]	X	X							X	X	X	X	X	X	X	X	X	X	X					X	X	X
Urine Drug Screen & Alcohol Breath Test	X	X							X	X	X	X	X	X	X	X	X	X	X					X	X	X
Safety and Exploratory Assessments																										
Physical Examination (PE)	X																									X
Abbreviated PE		X								X		X				X			X					X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X[4]	X[4]				X				X		X	X			X			X[4]				X			
Holter Monitoring			X	X	X	X														X	X	X	X			
ABPM		X	X	X	X	X													X	X	X	X	X			

	Screen	Admin		Treatment Period																				Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2					Outpatient Visit		
Week				1				2		3	4	5	6	7	8	9	10	11	12					13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	85	99	113
Visit Window																									±2	±2
Hematology, Chemistry, Coagulation, Urinalysis	X			X				X		X		X	X			X				X				X	X	
CRP[10]					X																					
Lipid Panel	X																									
Amylase, Lipase	X			X						X		X				X								X		
Calcitonin	X			X								X												X		
Body Weight[12]	X		X	X[12]				X		X	X	X	X	X	X	X	X	X	X	X				X	X	X
BMI Calculation	X			X				X		X		X				X				X				X	X	X
Pharmacodynamic Assessments																										
Lipid Profile and Particles				X												X								X		
MRI-PDFF[5]	X															X								X		
Amino Acid Panel				X				X		X		X				X				X				X		
Incretins[6]				X				X		X		X				X				X				X		
Bone Metabolism Parameters				X								X				X								X		
Glucose Metabolism Parameters[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inflammatory Biomarkers[11]				X												X								X		
Ketone Bodies				X												X								X		
Pharmacokinetic and Immunogenicity Assessments																										
PK Sampling[8]				X	X	X		X	X	X	X	X	X		X	X				X	X	X	X	X	X	X
Immunogenicity				X							X				X					X				X	X	
Other Safety Assessments																										
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Tolerability				X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[1]Confirmation of eligibility

[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points

[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 4 and 81 after subject have been disconnected from ambulatory device.

[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).

[6]All incretins will be collected at the same time points together with the PK sample collection.

[7]Subjects need to be in fasting condition for collection.

[8]PK sampling will follow the PK sampling schedule. Cohort 3 will start to collect additional PK sample with start of Day 78.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 4: Schedule of Events, Cohorts 1-3 (including Day 82)

	Screen	Admin		Treatment Period																					Elimination	FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit	
Week				1					2	3	4	5	6	7	8	9	10	11	12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82*	85	99	113
Visit Window																										±2	±2
Confinement		X	X	X	X	X	X	X											X	X	X	X	X	X			
Dosing				X				X		X	X	X	X	X	X	X	X	X		X							
Randomization			X																								
Screening Procedures																											
Informed Consent	X																								X		X
Inclusion/Exclusion Criteria	X	X[1]																									
Demography	X																										
Medical History/Prior Medication	X																										
Smoking and Alcohol History	X																										
Height	X																								X		X
Waist Circumference	X																								X		X
Estimated Glomerular Filtration Rate (eGFR)	X																								X		X
Thyroid Function Test (TSH)	X			X								X				X									X		X
HBA1C	X																								X		
FPG	X																										
Serum Insulin	X																										
Alpha-2 Macroglobulin	X																										
Viral Serology	X																										
VCTE (FibroScan)	X																										
Check-in Criteria to In-house Period		X																	X								
Pregnancy Test[2]	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Urine Drug Screen & Alcohol Breath Test	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Safety and Exploratory Assessments																											
Physical Examination (PE)	X																										X
Abbreviated PE		X								X		X				X			X						X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Admin		Treatment Period																					Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit		
Week				1					2	3	4	5	6	7	8	9	10	11	12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82*	85	99	113
Visit Window																										±2	±2
12-lead ECG	X[4]	X[4]				X				X		X	X			X			X[4]					X			
Holter Monitoring			X	X	X	X														X	X	X	X	X			
ABPM		X	X	X	X	X													X	X	X	X	X	X			
Hematology, Chemistry, Coagulation, Urinalysis	X			X				X		X		X	X			X				X					X	X	
CRP[10]					X																						
Lipid Panel	X																										
Amylase, Lipase	X			X						X		X				X									X		
Calcitonin	X			X								X													X		
Body Weight[12]	X		X	X[12]				X		X	X	X	X	X	X	X	X	X	X	X					X	X	X
BMI Calculation	X			X				X		X		X				X				X					X	X	X
Pharmacodynamic Assessments																											
Lipid Profile and Particles				X												X									X		
MRI-PDFF[5]	X															X									X		
Amino Acid Panel				X				X		X		X				X				X					X		
Incretins[6]				X				X		X		X				X				X					X		
Bone Metabolism Parameters				X								X				X									X		
Glucose Metabolism Parameters[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Inflammatory Biomarkers[11]				X												X									X		
Ketone Bodies				X												X									X		
Pharmacokinetic and Immunogenicity Assessments																											
PK Sampling[8]				X	X	X		X	X	X	X	X	X		X	X				X	X	X	X	X	X	X	X
Immunogenicity				X							X				X					X					X	X	
Other Safety Assessments																											
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Tolerability				X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[1]Confirmation of eligibility

[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points

[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule. Cohort 3 will start to collect additional PK sample with start of Day 78.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.
*Day 82 is optional for subjects already participating in cohort 1-3.

Table 5: Schedule of Events, Cohorts 1-4

	Screen	Admin		Treatment Period																					Elimination	FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit	
Week				1					2	3	4	5	6	7	8	9	10	11	12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82	85	99	113
Visit Window																										±2	±2
Confinement		X	X	X	X	X	X	X											X	X	X	X	X	X			
Dosing				X				X		X	X	X	X	X	X	X	X	X		X							
Randomization			X																								
Screening Procedures																											
Informed Consent	X																										
Inclusion/Exclusion Criteria	X	X[1]																									
Demography	X																										
Medical History/Prior Medication	X																										
Smoking and Alcohol History	X																										
Height	X																										
Waist Circumference	X																								X		X
Estimated Glomerular Filtration Rate (eGFR)	X																										
Thyroid Function Test (TSH)	X			X								X				X									X		X
HBA1C	X																								X		
FPG	X																										
Serum Insulin	X																										
Alpha-2 Macroglobulin	X																										
Viral Serology	X																										
VCTE (FibroScan)	X																								X		
Check-in Criteria to In-house Period		X																	X								
Pregnancy Test[2]	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Urine Drug Screen & Alcohol Breath Test	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Safety and Exploratory Assessments																											
Physical Examination (PE)	X																										X
Abbreviated PE		X								X		X				X			X						X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Admin		Treatment Period																					Elimination	FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit	
Week				1					2	3	4	5	6	7	8	9	10	11	12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82	85	99	113
Visit Window																										±2	±2
12-lead ECG	X[4]	X[4]				X				X		X	X			X			X[4]				X			
Holter Monitoring			X	X	X	X														X	X	X	X	X			
ABPM		X	X	X	X	X													X	X	X	X	X	X			
Hematology, Chemistry, Coagulation, Urinalysis	X			X				X		X		X	X			X				X					X	X	
CRP[10]					X																						
Lipid Panel	X																										
Amylase, Lipase	X			X						X		X				X									X		
Calcitonin	X			X								X													X		
Body Weight[12]	X		X	X[12]				X		X	X	X	X	X	X	X	X	X	X	X					X	X	X
BMI Calculation	X			X				X		X		X				X				X					X	X	X
Pharmacodynamic Assessments																											
Lipid Profile and Particles				X												X									X		
MRI-PDFF[5]	X															X									X		
Amino Acid Panel				X				X		X		X				X				X					X		
Incretins[6]				X				X		X		X				X				X					X		
Bone Metabolism Parameters				X								X				X									X		
Glucose Metabolism Parameters[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Inflammatory Biomarkers[11]				X												X									X		
Ketone Bodies				X												X									X		
Pharmacokinetic and Immunogenicity Assessments																											
PK Sampling[8]				X	X	X		X	X	X	X	X	X		X	X				X	X	X	X	X	X	X	X
Immunogenicity				X							X				X					X					X	X	
Other Safety Assessments																											
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Tolerability				X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[1]Confirmation of eligibility

[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points

[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 6: Schedule of Events, Cohorts 1-5 and up

	Screen	Admin		Treatment Period																					Elimination	FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit	
Week				1				2	3	4	5	6	7	8	9	10	11		12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82	85	99	113
Visit Window																										±2	±2
Confinement		X	X	X	X	X	X	X											X	X	X	X	X	X			
Dosing				X				X		X	X	X	X	X	X	X	X	X		X							
Randomization			X																								
Screening Procedures																											
Informed Consent	X																								X		X
Inclusion/Exclusion Criteria	X	X[1]																									
Demography	X																										
Medical History/Prior Medication	X																										
Smoking and Alcohol History	X																										
Height	X																								X		X
Waist Circumference	X																								X		X
Estimated Glomerular Filtration Rate (eGFR)	X																								X		X
Thyroid Function Test (TSH)	X			X								X				X									X		X
HBA1C	X																								X		
FPG	X																										
Serum Insulin	X																										
Alpha-2 Macroglobulin	X																										
Viral Serology	X																										
VCTE (FibroScan)	X																								X		
Check-in Criteria to In-house Period		X																	X								
Pregnancy Test[2]	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Urine Drug Screen & Alcohol Breath Test	X	X							X	X	X	X	X	X	X	X	X	X	X						X	X	X
Safety and Exploratory Assessments																											
Physical Examination (PE)	X																										X
Abbreviated PE		X								X		X				X			X						X	X	
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Admin		Treatment Period																					Elimination		FU
		In House Period 1							Outpatient Visit										In house Period 2						Outpatient Visit		
Week				1					2	3	4	5	6	7	8	9	10	11	12						13	15	17
Day	-44 to -3	-2	-1	1	2-3	4	5-7	8	10	15	22	29	36	43	50	57	64	71	77	78	79	80	81	82	85	99	113
Visit Window																										±2	±2
12-lead ECG	X[4]	X[4]				X				X		X	X			X			X[4]				X			
Holter Monitoring			X	X	X	X														X	X	X	X	X			
ABPM		X	X	X	X	X													X	X	X	X	X	X			
Hematology, Chemistry, Coagulation, Urinalysis	X			X				X		X		X	X			X				X					X	X	
CRP[10]					X																						
Lipid Panel	X																										
Amylase, Lipase	X			X						X		X				X									X		
Calcitonin	X			X								X													X		
Body Weight[12]	X		X	X[12]				X		X	X	X	X	X	X	X	X	X	X	X					X	X	X
BMI Calculation	X			X				X		X		X				X				X					X	X	X
Pharmacodynamic Assessments																											
Lipid Profile and Particles				X												X									X		
MRI/MRI-PDFF[5]	X															X									X		
Amino Acid Panel				X				X		X		X				X				X					X		
Incretins[6]				X				X		X		X				X				X					X		
Bone Metabolism Parameters				X								X				X									X		
Glucose Metabolism Parameters[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Inflammatory Biomarkers[11]				X												X									X		
Ketone Bodies				X												X									X		
Pharmacokinetic and Immunogenicity Assessments																											
PK Sampling[8]				X	X	X		X	X	X	X	X	X		X	X				X	X	X	X	X	X	X	X
Immunogenicity				X							X				X					X					X	X	
Other Safety Assessments																											
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection Site Tolerability				X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[1]Confirmation of eligibility

[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points

[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from ambulatory device.
[5]Subjects will undergo an MRI/MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 7: PK Sampling Schedule for cohorts 1-1 and 1-2

PK sampling schedule			
Treatment Period	Week 1	Day 1	Pre-dose 1st dosing
			8 h after 1st dosing
		Day 2	24 h after 1st dosing
		Day 3	48 h after 1st dosing
		Day 4	72 h after 1st dosing
	Week 2	Day 8	Pre-dose 2nd dosing
		Day 10	48 h after 2nd dosing
	Week 3	Day 15	Pre-dose 3rd dosing
	Week 4	Day 22	Pre-dose 4th dosing
	Week 5	Day 29	Pre-dose 5th dosing
	Week 6	Day 36	Pre-dose 6th dosing
	Week 8	Day 50	Pre-dose 8th dosing
	Week 9	Day 57	Pre-dose 9th dosing
	Week 12	Day 78	Pre-dose 12th dosing
			8 h after 12th dosing
		Day 80	48 h after 12th dosing
		Day 81	72 h after 12th dosing
Elimination Period (±2)	Week 13	Day 85	168 h after 12th dosing
	Week 15	Day 99	504 h after 12th dosing
F/U (±2)	Week 17	Day 113	840 h after 12th dosing

Table 8: PK Sampling Schedule starting from cohort 1-3

PK sampling schedule			
Treatment Period	Week 1	Day 1	Pre-dose 1st dosing
			8 h after 1st dosing
		Day 2	24 h after 1st dosing
		Day 3	48 h after 1st dosing
		Day 4	72 h after 1st dosing
		Day 5*	96 h after 1st dosing
	Week 2	Day 8	Pre-dose 2nd dosing
		Day 10	48 h after 2nd dosing
	Week 3	Day 15	Pre-dose 3rd dosing
	Week 4	Day 22	Pre-dose 4th dosing
	Week 5	Day 29	Pre-dose 5th dosing
	Week 6	Day 36	Pre-dose 6th dosing
	Week 8	Day 50	Pre-dose 8th dosing
	Week 9	Day 57	Pre-dose 9th dosing
	Week 12	Day 78	Pre-dose 12th dosing
			8 h after 12th dosing
		Day 80	48 h after 12th dosing
		Day 81	72 h after 12th dosing
		Day 82**	96 h after 12th dosing
Elimination Period (±2)	Week 13	Day 85	168 h after 12th dosing
	Week 15	Day 99	504 h after 12th dosing
F/U (±2)	Week 17	Day 113	840 h after 12th dosing

*Sampling on Day 5 will start with Cohort 1-4 and will not be taken for cohort 1-3.

**Sampling on Day 82 will be optional for cohort 1-3 but will be taken in cohort 1-4.