Statistical Analysis Plan

Protocol HM-GCG-102

# A Phase 1, study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with comorbidities

Phase 1

Original Protocol:

Version 1.0: 23 JULY 2019

Version 2.0: 28 AUGUST 2019

Version 3.0: 17 DECEMBER 2019

Version 4.0: 20 FEBRUARY 2020

Version 5.0: 20 MAY 2020

Version 6.0: 29 OCTOBER 2020

Current CRF Version: Version 5.0 (11 JUNE 2020) for Part 2 Study
Version 6.0 (6 JULY 2020) for Part 1 Study

Prepared by: _____

Version: Amendment 1

Date: 8 FEBRUARY 2021

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This Statistical Analysis Plan has been reviewed and approved by:

_____ Date:_____

Version: Amendment 1

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**Summary of Amendment 1**

| Revision/Rationale | Original Text | Amended Text |
|---|---|---|
| **Change of time point for dose escalation from Cohort 5 to Cohort 6 and additional Data Review Meeting (DRM)** | **Section 2.1 Study Design, the last paragraph:**<br><br>Dose escalation will proceed in the same manner for all subsequent cohorts. | **Original text has been replaced with the following paragraphs:**<br><br>Per DRM of Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit), in order to assess the safety data.<br>Dose escalation from Cohort 6 to the subsequent Cohort 7 will follow the same dose escalation scheme and DRM(s) of the previous cohort.<br>Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5. If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study. |

| Revision/Rationale | Original Text | Amended Text |
|---|---|---|
| | **Section 2.2 Randomization and Blinding Procedure, Table 1 footnote:**<br><br>Cohort 7 will be optional. | **Original sentence has been revised:**<br><br>The conduct of Cohorts 6 and 7 will be optional. |
| | **Section 2.3 Sample Size and Power**<br><br>None | **A new sentence has been added:**<br><br>Note that the conduct of Cohorts 6 and 7 will be optional. |
| | **Section 2.4 Dose Escalation Stopping Criteria, the last paragraph**<br><br>None | **A new paragraph has been added:**<br><br>Per DRM of Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit) to assess the safety data. |
| **As the investigators entered repeated vital signs measurements differently, a decision was made to allow unscheduled visits data to be included in analysis.** | **Section 6.1.3 Handling of Multiple Observations or Out of Window Observations**<br><br>None | **A new paragraph has been added:**<br><br>For vital signs data, if measurements are duplicated within the visit window, the data from the unscheduled visit will be used and the average of the scheduled and unscheduled visits will be taken for summary table. A footnote will be added to table to highlight the exception. |

**List of Abbreviations**

| | |
|---|---|
| ADAbs | Anti-drug antibodies |
| AE | Adverse event |
| ANOVA | Analysis of Variance |
| anti-PEG | Anti-polyethylene glycol |
| ATC | Anatomic therapeutic chemistry |
| AUC | Area under the curve |
| BLQ | Below limit of quantitation |
| BMI | Body mass index |
| CIs | Confidence Intervals |
| CL/F | Apparent clearance |
| $C_{max}$ | Max concentration |
| CRF | Case Report Form |
| CSR | Clinical study report |
| $C_{trough}$ | Trough concentration |
| CV | Coefficient of variation |
| DLT | Dose limiting toxicity |
| DMC | Data monitoring committee |
| DRM | Data Review Meeting |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FFAs | Free fatty acids |
| FGF 21 | Fibroblast growth factor 21 |
| FPG | Fasting plasma glucose |
| GIP | Gastric inhibitory polypeptide |
| GLP-1 | Glucagon-like peptide - 1 |
| HbA1c | Hemoglobin A1c |
| HDL | High density lipid |
| HOMA-B | Homeostatic Model Assessment for β Cell Function |
| HOMA-IR | Homeostatic Model Assessment for Insulin Resistance |
| hs-CRP | High sensitivity c-reactive protein |
| IP | Investigational product |
| IRB | Investigational Review Board |
| IV | Intravenous |
| $K_{el}$ | Terminal elimination rate constant |
| LDL | Low density lipid |
| LS | Least Squares |
| MAD | Multiple ascending dose |
| max | Maximum |
| MedDRA | Medical dictionary for regulatory affairs |

| | |
|---|---|
| min | Minimum |
| MRI | Magnetic resonance imaging |
| MRI-PDFF | Magnetic resonance imaging – proton density fat fraction |
| n | Sample size |
| nAbs | Neutralizing antibodies |
| PD | Pharmacodynamics, pharmacodynamic |
| PK | Pharmacokinetics, pharmacokinetic |
| PT | Preferred Term |
| QTcF | Frederica's QT corrected interval |
| $R_{dnm}$ | Ratio of dose normalized geometric means |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SD | Standard deviation |
| SE | Standard Error |
| SMBG | Self-monitoring of blood glucose |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to max concentration |
| TSH | Thyroid stimulating hormone |
| T2DM | Type 2 diabetes mellitus |
| VLDL | Very low density lipid |
| VS | Vital signs |
| Vz/F | Apparent volume of distribution |
| WHO DDE | World health organization drug dictionary |
| WHR | Waist hip ratio |

## 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 HM15136 in obese or overweight subjects with comorbidities. The original statistical analysis plan (SAP) was developed based on Hanmi Pharmaceutical Protocol HM-GCG-102 (version 5.0 dated 20 MAY 2020) and case report form version 5.0 dated 11 JUNE 2020 for Part 2 Study and 6.0 dated 6 JULY 2020 for Part 1 Study.

The original SAP was finalized prior to data analyses and before database lock of Part 1 Study. The current SAP amendment is created to incorporate contents from protocol version 6.0 (dated 29 OCTOBER 2020, post Part 1 database lock) regarding the change of time point for dose escalation from Cohort 5 to Cohort 6 and additional Data Review Meeting (DRM). The conduct of Cohorts 6 and 7 is determined to be optional for Part 2 Study.

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 double-blind, randomized, placebo controlled, multiple ascending dose (MAD) study to investigate the safety, tolerability, PD, and PK of the subcutaneous (SC) administration of HM15136 in obese subjects or overweight subjects with co-morbidities. This study will be conducted in Part 1 and 2. In Part 1, enrolling 12 subjects per cohort (HM15136 group 9 subjects, placebo group 3 subjects) will participate, and 3 cohorts will proceed sequentially, but may overlap during the conduct. In Part 2, enrolling 30 subjects in Cohort 4 (HM15136 group 15 subjects, placebo group 15 subjects) will participate, and up to 3 additional cohorts may proceed with 12 subjects per Cohorts 5-7 (HM15136 group 9 subjects, placebo group 3 subjects). 12 subjects per cohort assigned to Part 1 and Part 2 will be randomized to HM15136 and placebo in a ratio of 3:1, and 30 subjects per Cohort 4 assigned to Part 2 will be randomized to HM15136 and placebo in a ratio of 1:1. The final analysis for each part will be performed separately once each part is complete. Due to COVID-19 outbreak, an interim analysis based on partially validated data for Part 1 will be performed for administrative purpose prior to database lock of Part 1.

After Cohort 1 randomization is completed, the Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations to decide whether subjects can be randomized into Cohort 2. Details will be defined in the DMC charter.

Dose escalation from Cohort 2 to next dose level for the subsequent Cohort 3 will be based on the safety, tolerability, available PD, and available PK data obtained from Cohort 1 and through the 9th subject's visit on Day 29 in Cohort 2. An independent DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations.

The next dose level for the subsequent cohort (Cohort 4 in Part 2) will be based on the safety, tolerability, available PD, and available PK data obtained from Cohort 1, 2 and through the 9th subject's visit on Day 29 in Cohort 3. An independent DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations. If dose escalation is stopped, dose de-escalation may occur in subsequent cohorts, to further refine clinically relevant dose levels.

The dose of Cohorts 3 and 4 can be adjusted, but may not be over the planned dose of 0.08 mg/kg. The escalated dose should not be more than 2 times over the dose of the previous cohort.

In Part 2, after the review of the safety data, obtained by the 9th subject's visit on Day 29 of Cohort 3 (in Part 1), Cohort 4 can proceed with a dose of ≤ 0.08 mg/kg dose, which is the planned maximum dose.

A DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations for the study progress of Part 2. After the review of the safety data in Part 1, Part 2 may or may not proceed. Cohort 4 may be conducted with a lower number of subjects. Cohort 5 may start immediately and may overlap with the conduct of subjects in Cohort 4.

In Part 2, dose escalation from Cohort 5 to the subsequent Cohort 6 will be made after a DRM, held by Sponsor, Investigator and Medical Monitor, and the safety data obtained from the 9th subject's visit on Day 43 (=after 6 weeks of dosing) will be reviewed. Per DRM of Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit), in order to assess the safety data.

Dose escalation from Cohort 6 to the subsequent Cohort 7 will follow the same dose escalation scheme and DRM(s) of the previous cohort.

Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5. If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study.

### 2.2. Randomization and Blinding Procedures

The subjects enrolled in this study would be assigned randomly to each treatment group. Subjects in Part 1 will be assigned to HM15136 and placebo in a 3:1 ratio, in the case of Part 2, up to 66 subjects will be assigned to HM15136 and placebo. Thirty subjects in Cohort 4 will be

assigned to HM15136 and placebo in a ratio of 1:1, and 12 subjects in Cohorts 5 to 7 will be assigned to HM15136 and placebo in a 3:1 ratio according to rules below in Table 1.

**Table 1. Treatment Assignment**

| Part | Cohort | Treatment Assignment* | |
|---|---|---|---|
| Part 1 | 1 | HM15136 0.02 mg/kg (N=9) | Placebo (N=3) |
| | 2 | HM15136 0.04 mg/kg (N=9) | Placebo (N=3) |
| | 3 | HM15136 ≤0.08 mg/kg (N=9) | Placebo (N=3) |
| Part 2 | 4 (DM) | HM15136 0.06 mg/kg (N=15) | Placebo (N=15) |
| | 5 (DM) | HM15136 ≤0.02 mg/kg (N=9) | Placebo (N=3) |
| | 6 (DM) | HM15136 ≤0.04 mg/kg (N=9) | Placebo (N=3) |
| | 7 (DM) | HM15136 ≤0.06 mg/kg (N=9) | Placebo (N=3) |

* In Part 1, dosage of Cohort 3 can be adjusted, but not be over the dosage presented in the table. The escalated dose should not be over twice the dose of the previous cohort.

* In Part 2, if necessary, after the review of the safety data obtained by the 9th subject's visit on Day 29 of Cohort 3 in Part 1, the Cohorts 4 to 7 can proceed within the doses in Table 1. The dose and study progress of Part 2 should be guided by the recommendations of the DMC. After the review of the safety data in Part 1, Part 2 may or may not proceed. The conduct of Cohorts 6 and 7 will be optional.

Due to COVID-19 outbreak, an interim analysis based on partially validated data for Part 1 will be performed for administrative purpose prior to database lock of Part 1. For this planned interim analysis, unblinding will occur after partially validated data transfer for Part 1. Designated personnel not involved in the study conduct will perform the interim analysis. Only authorized members who are listed in the Interim Analysis Unblinding and Information Dissemination Plan will have access to review the summary tables or figures of the interim analysis results, in which the information is presented in a grouped fashion with the actual treatment, e.g., mean treatment effect.

Unblinding for final analysis of each part will also occur after the corresponding database locks for each Part 1 and Part 2. The final analysis for each part will be performed separately, once each part is completed. For the second planned interim analysis described in Section 7, unblinding will occur after database lock for Part 1, to analyze the data from all healthy subjects (i.e. data from completed Cohorts 1-3). The study will proceed as planned with Part 2 in a blinded fashion. Otherwise, unblinding may be conducted only for the subject who have medical emergencies that can be a problem for the subject's safety (in the case of knowing the information of IP administered to the subject may affect the treatment of the emergency situation), or DLT (Dose limiting toxicity) occurred, or for determining whether to increase or decrease dosage as specified in the protocol. Except for these reasons, unblinding should not occur. The investigator must contact the principal investigator and Hanmi Pharm. Co., Ltd. to discuss this issue before unblinding takes place. Emergency unblinding can be performed by the

principal investigator using the IWRS. It should be ensured that no study personnel are unblinded to other subjects. Study site personnel directly associated with the conduct of the study will not be unblinded. The investigator should record the date and reason why unblinding occurred in the CRF.

If the investigator, or the staff performing evaluations, or a subject that is not kept in blind, this subject should be withdrawn from this study. And if unblinding occurred prior to completion of this study accidently or caused by SAE, the investigator should record this issue and provide prompt notice to Hanmi Pharm. Co., Ltd. However, if it is judged that the ethical reason or the unblinding effect on the safety of the subject is small, the subject can continue to participate in the study in judgement of investigator with Hanmi Pharma. Co., Ltd.

### 2.3. Sample Size and Power

This study determined the number of subjects without consideration of statistical validity. The number of subjects for the Part 1 will be 12 (HM15136: placebo = 9:3) for each cohort, and for the Part 2 will be up to 66, 30 for Cohort 4 (HM15136: placebo = 15:15) and 12 for Cohorts 5-7 (HM15136: placebo = 9:3). This is consistent with the typical sample size used in the similar study to evaluate safety and PK. Therefore, no formal sample size calculation will be performed. Note that the conduct of Cohorts 6 and 7 will be optional. Safety and tolerability of the study drug will be assessed based on adverse events, laboratory parameters, physical examination, vital signs, and ECG parameters throughout the duration of the study. Safety analysis will involve examination of the descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety.

### 2.4. Dose Escalation Stopping Criteria

The procedure for determining the dose is as follows

- The main criteria for determining tolerability is emesis/vomiting (=gastrointestinal tolerability).
- Vomiting is associated with the pharmacologic administration of GLP-1 agonists and glucagon, and the severity of vomiting in this study is defined as:
    - Moderate: 3 -5 times vomiting within 24 hours (when vomiting interval is at a minimum 5 minutes or more, each vomiting event is counted.)
    - Severe: 6 times or more within 24 hours or requiring fluid injection via IV (intravenous) (when the vomiting interval is at a minimum 5 minutes or more, each vomiting event is counted.)

If one of the following criteria is met, an independent DMC will meet to assess safety in real-time and make dosing and cohort escalation assessments and recommendations, such as: IP administration and dose elevation should be stopped, or the dose level should be discontinued, suspended, or a dose modification or repetition should occur prior to proceeding to subsequent dosing, or dosing can continue. All decisions to increase the dose or discontinue dosing will be

decided by the DMC. The DMC will determine when the safety and/or tolerance limits have been reached.

1) Moderate or severe emesis occurred in 50% or more subjects in one cohort.
2) Severe emesis occurred in 25% or more subjects in one cohort.
3) At any time, if the subject dies (CTCAE grade 5 toxicity may be used as a grading scale) in one cohort.
4) If severe AEs (CTCAE grade ≥3 may be used as a grading scale) occurred in 2 subjects within one cohort.
5) If moderate AEs (CTCAE grade ≥2 may be used as a grading scale) occurred in 2 subjects within the one cohort for 7 days or more.
6) If a SAE occurred in 1 subject or more within the one cohort.
7) If clinically significant similar laboratory abnormalities, clinically significant ECGs or V/S abnormalities, or severe AEs in the same SOC (System organ class) occurred in 2 subjects or more receiving IP representing dose limiting toxicity (DLT).

As the DMC is unblinded, any potential stopping rule event occurring in subjects receiving placebo would not be considered as meeting the stopping rule. Additionally, AEs considered to be unrelated to HM15136 would not be considered as meeting the stopping rules.

A data review meeting will be held by sponsor, investigator and medical monitor to review safety data after the 9$^{th}$ subject of Cohorts 5 and 6 in Part 2 has completed their Day 43 visit. This time point is situated 6 weeks after the first dosing. Safety data review will guide the decision for dosing and cohort escalation recommendations.

Per DRM of Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit) to assess the safety data.

### 2.5. Study Stopping Criteria

In addition to the DMC, during the study the investigator and the sponsor may suspend the study after appropriate discussion, due to but not limited to, the following situations or events, and submit to the IRB a sufficient written statement of reasons for the termination of the study.

1) When any obvious or unacceptable risks to the subjects enrolled in this trial are found.
2) If the sponsor decides to suspend or hold the development of IP.

### 2.6. Study Procedures and Visit Structure

In the appendix, Table 2 describes the procedures and visit structure for this study. The PK sample schedule is also in the appendix as Table 3 and Table 4.

# 3. Study Objectives and Endpoints

## 3.1. Primary Objectives and Endpoints

### 3.1.1. Safety and Tolerability Objectives and Endpoints

To assess safety and tolerability of HM15136 after multiple subcutaneous doses for 12 weeks by assessing:

- Incidence of adverse events:
  - Potential unexpected adverse events include: cardiovascular events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal events, and gallstone formation.
- Incidence of clinical lab abnormalities:
  - Including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin. Only for female, LH (Luteinizing hormone) and FSH (follicle stimulating hormone) are additionally included.
- Immunogenicity: Anti-drug antibodies (ADAbs), neutralizing antibodies (nAbs), and anti-polyethylene glycol antibodies (anti-PEG)
- Incidence of clinically significant physical examination findings
- Change from baseline in vital signs:
  - Supine position blood pressure
  - Heart Rate
  - Respiratory rate
  - Tympanic temperature
- Change from baseline in blood pressure assessed by 24-hour ambulatory blood pressure monitoring
- Change from baseline in heart rate assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG)
- Change from baseline in 12-lead electrocardiogram parameters:
  - Primary electrocardiogram endpoint: QT corrected QTcF
- Presence of injection site reactions

### 3.1.2. Pharmacokinetic Objectives and Endpoints

To assess the PK profile of HM15136 after administration of multiple subcutaneous doses in obese subjects by, but not limited to:

- $C_{max}$: maximum concentration
- $T_{max}$: time to reach $C_{max}$
- $C_{trough}$: trough serum concentration
- AUC: area under the concentration-time curve
  - $AUC_{0-t}$
  - $AUC_{inf}$

- $K_{el}$: terminal elimination rate constant
- $t_{1/2}$: terminal half-life
- CL/F: apparent clearance
- Vz/F: apparent volume of distribution
- AR: accumulation ratio

### 3.2. Exploratory Objectives and Endpoints

#### 3.2.1. Pharmacodynamic Objectives and Endpoints

To evaluate the PD properties of HM15136 after multiple subcutaneous doses by assessing:

- Change from baseline in incretins/metabolic hormones:
  - Glucagon-like peptide-1 (GLP-1)
  - Gastric inhibitory polypeptide (GIP)
  - Glucagon
  - Fibroblast growth factor 21 (FGF 21)
  - Leptin
- Change from baseline and percent change from baseline in serum lipid profiles:
  - Total cholesterol
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Very low-density lipoprotein (VLDL)
  - Triglycerides
  - Free fatty acids (FFAs)
- Change from baseline in amino-acid profile
- Change from baseline in glucose metabolism parameters:
  - Fasting plasma glucose (FPG)
  - Fasting insulin, Fasting C-peptide
  - 7-point Self-monitoring of blood glucose (SMBG)
  - HbA1c
  - Fructosamine
  - Glycated albumin
- Change from baseline in insulin resistance:
  - Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)
- Change from baseline in insulin secretion function:
  - Homeostatic Model Assessment for β Cell Function (HOMA-β)
- Change from baseline (absolute) and percent change from baseline (relative) of liver fat via magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) (However, assessment of liver fat via MRI-PDFF will only be performed on day 85, if the liver fat prior to the first dose is ≥ 10%)
- Change from baseline and percent change from baseline in visceral fat volume, determined by absolute and relative percent change assessed by MRI

- Change from baseline and percent change from baseline in anthropomorphic measures:
  - Body weight
  - Body mass index (BMI)
  - Waist circumference
  - Hip circumference
  - Waist-to-hip ratio (WHR)
- Change from baseline in tympanic temperature
- Change from baseline in Inflammatory markers:
  - High-sensitive C-reactive protein (hs-CRP)
  - Adiponectin
- Change from baseline in ketone bodies:
  - β-hydroxybutyrate

## 4. Analysis Populations

### 4.1. Randomized Population

The randomized population will include all randomized subjects in the study. The randomized population will be used for disposition and analysis population summaries and listings.

### 4.2. Safety Population

The safety population will include all randomized subjects in the study who received at least one dose of study medication, HM15136 or placebo. Subjects will be analyzed based on the actual treatment they received during the study. The safety population will be used for demographic, baseline characteristics, subject eligibility and safety summaries.

### 4.3. Pharmacokinetic Population

The PK population will include all randomized subjects who have at least one quantifiable HM15136 concentration measurement without important protocol deviations or violations that would have impact on the absorption, distribution, metabolism or excretion of HM15136. The PK population will be used for PK concentration and PK parameter summaries. As the study is double-blinded, a memo will be prepared to select the PK population based on dummy subject ID prior to treatment unblinding of Part 1 and Part 2.

### 4.4. Pharmacodynamic Population

The PD population will include all randomized subjects who have received at least one dose of study medication, HM15136 or placebo with sufficient evaluable PD data appropriate for the evaluation of interest without important protocol deviation or violation that would have an impact on the PD of HM15136. The PD population will be used for PD assessment and PD parameter summaries. Determination of the PD population will be documented in a memo prior to treatment unblinding of Part 1 and Part 2.

# 5. Study Subjects

## 5.1. Subject Disposition

Subject disposition will be summarized/listed for the randomized population by:

- Number and percentage of subjects who withdraw prior to receive randomized study medication
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who withdrew from the study; further summarized by the reason for withdrawal from the study.

## 5.2. Subject Eligibility

Subject eligibility, such as inclusion and exclusion criteria will be presented in listings.

## 5.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized descriptively for all subjects by treatment group for the safety population. Demographic and baseline characteristics include, but are not limited to: age, gender, ethnicity, race, body weight, height, body mass index (BMI), Liver fat via MRI-PDFF, Visceral fat via MRI, HbA1c, C-peptide, insulin, fasting plasma glucose, total cholesterol, HDL, LDL, VLDL, and triglycerides. The denominator of the percentage of subjects will be the number of subjects in the safety population at each cohort/dose level (placebo subjects will be pooled into one treatment group).

## 5.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 22.0) and summarized/listed by system organ class (SOC) and preferred term (PT) by cohort/dose level (placebo subjects will be pooled into one treatment group) for the safety population.

## 5.5. Study Drug Administration

Study drug administration data will be listed.

## 5.6. Extent of Exposure

Exposure will be summarized for the safety population. The summary of exposure will include the number of doses received, total dose administered, and the duration of exposure by cohort/dose level. Duration of exposure will be defined as the last dose date of treatment minus the first dose date of treatment.

Total duration of exposure to study drug (weeks) = (last dose date – first dose date +7)/7

### 5.7. Prior Medications and Concomitant Medications

Concomitant medication refers to medications that were administered after administration of the IP (includes the medication that start before IP and continue to be used together). Prior medication is defined as any medication that start and end before administration of the IP.

The WHO Drug Dictionary Enhanced (B3 WHO Drug Global version 2019 March) will be used to categorize the verbatim descriptions of medications into the 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 in the database.

The number and percentage of subjects receiving concomitant medications will be summarized by cohort/dose level, and by anatomical therapeutic chemistry (ATC) classification, ATC level 2 and level 4, for the safety population. Prior medications will only be listed.

### 5.8. Protocol Deviations

Protocol deviations will be listed. Category of the protocol deviations will be included in the listing.

## 6. Statistical Methods of Analysis

### 6.1. General Considerations

Summary and analysis of Part 1 and Part 2 will be separate. Placebo subjects within each part of the study will be pooled in summaries and listings. Exploratory analysis for subgroup of subjects being impacted by COVID-19, versus those not being impacted, may be conducted to assess missing data due to COVID-19. As the number of subjects in the subgroup analysis will be much smaller than the original planned population, caution should be taken when interpreting the inferential statistical results. Please refer to Sections 6.3 and 6.4 for COVID-19 subgroup analyses.

All data collected in the EDC and external data sets will be listed using the safety population.

#### 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, frequency and percentage 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 geometric CV is calculated as CV% = 100% $*$ $sqrt(\exp(\sigma^2) - 1)$, where σ is the standard deviation of the data on the natural log scale.

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. Minimum and maximum values will be rounded to the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values will be presented with 4 decimal places and values less than 0.0001 will be presented as <.0001.

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

### 6.1.2. Study Baseline

Baseline will be defined as the last non-missing observation obtained prior to the administration of the first dose of study medication, unless otherwise specified.

The mean value of the 3 baseline ECG measurements collected at Day -2 will serve as each subject's baseline for all post-dose comparisons.

### 6.1.3. Handling of Multiple Observations or Out of Window Observations

Per COVID-19, additional modifications were made to the visit schedule in protocol version 5.0; refer to Table 2 for schedule of events. It was noted that after the protocol amendment, the study might have 2 subjects from Cohort 4 and all subjects from Part 2 that follow the modified visit schedule.

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. For PD data with multiple observations on the same day and time point, the last observation will be used.

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. A footnote will be added to tables where unscheduled visits are used to impute missing scheduled visits. For vital signs data, if measurements are duplicated within the visit window, the data from the unscheduled visit will be used and the average of the scheduled and unscheduled visits will be taken for summary table. A footnote will be added to table to highlight the exception.

### 6.1.4. Handling of Missing or Partial Dates

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

- 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.

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

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

#### 6.1.5. Handling Outliers and Unquantifiable Measurements

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

- For individual PK concentration plots: BLQ values will not be displayed but will be flagged for reference in the by-subject listings.

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

For safety laboratory abnormality assessments, and potentially some PD variables:

- Values that are recorded with ">" (greater than) or "<" (lower than) the normal ranges, except some categorical variables, the numeric values will be used for descriptive statistical summary. For example, a value of >900 mg/dL will be set to 900 mg/dL for descriptive summary, and will be printed as ">900 mg/dL" on by-subject listing.
- Range result of "Low" will be assigned if the value is less than the lower limit of the normal range.
- Range result of "High" will be assigned if the value is greater than the upper limit of normal.

### 6.2. Safety Analysis

#### 6.2.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA, version 22.0.

AEs will be summarized for the safety population. 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. All of AEs will be listed.

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

An overall summary of TEAEs will be generated.

TEAEs will be summarized by:

- SOC and PT
- SOC, PT, and maximum severity by treatment group
- TEAEs that are related to study medication per investigator's decision
- TEAEs leading to study discontinuation
- TEAEs that are serious (treatment-emergent SAEs)
- Adverse events of special interest:
    - Necrolytic migratory erythema
    - Cholelithiasis

### 6.2.2. Local Tolerability

The number and percentage of subjects with any injection site reactions will be summarized by treatment group over the entire study and by visit and time point. 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.

### 6.2.3. Clinical Laboratory Assessments

All hematology, clinical chemistry, and urinalysis results (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin, eGFR) will be summarized. eGFR will be calculated using the following formula:

$175 \times (\text{creatinine in mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$

$175 \times (\text{creatinine in } \mu\text{mol/L divided by } 88.42)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$

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 (with clinical significance and without clinical significance) status changes from baseline. Percentages

of abnormal readings without clinical significance and abnormal readings with clinical significance will also be summarized.

### 6.2.4. Vital Signs

Observed values and the change from baseline in vital sign parameters such as, supine position blood pressure, heart rate, respiratory rate, and tympanic temperature, will be listed and summarized descriptively by cohort/dose level and time point.

### 6.2.5. Electrocardiograms

Observed values and the change from baseline in ECG parameters will be listed and summarized descriptively by cohort/dose level and time point. Overall interpretation of 12-lead ECG profiles over time will be summarized by categorical levels of normal, abnormal not clinically significant, and abnormal clinically significant; shift tables will summarize the shifts from baseline to each post baseline visit.

### 6.2.6. Physical Examination

The clinical findings during physical examination will be listed.

### 6.2.7. 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 and heart rate will be summarized for each day from Day -2 to Day 5 and Day 77 to Day 82 (Fagard 2008).

Baseline for 24 hour ABPM will be derived using the mean of the pre-dose measurements from Day -1 to Day 1.

### 6.2.8. 24 Hour Holter ECG Monitoring

Observed values from 24-Hour Holter ECG will be summarized by time point for each assessment day. 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.

### 6.2.9. Immunogenicity

Anti-drug antibodies (ADAbs, anti-HM15136 antibodies) will be summarized categorically, displaying the tier 1 (putative positive and negative) and tier 2 (positive and negative) tests by cohort/dose level 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.

## 6.3. Pharmacokinetic Analysis

PK analysis will be performed using the PK population. Additional COVID-19 subgroup analysis for those being impacted by COVID-19 versus those not being impacted may be provided for HM15136 concentrations over time and for HM15136 PK parameters using the descriptive statistical summary table and/or plots. However, unless necessary, the dose proportionality will not be explored for COVID-19 subgroups

### 6.3.1. HM15136 Pharmacokinetic Concentration Analysis

The concentration-time data of HM15136 will be summarized descriptively by cohort/dose level. Two line plots for mean concentration +/- standard deviation over time, one on original raw scale and the other on the logarithm scale, will be generated for the PK population with cohort/dose level overlaid. Graphical analysis using line plots of individual profiles will also be performed.

### 6.3.2. HM15136 Pharmacokinetic Parameter Analysis

The non-compartmental PK parameters of HM15136 will be summarized descriptively by cohort/dose level. AUC parameters, $AUC_{0\text{-}t}$ at steady state and $C_{max}$, will be log-transformed and geometric statistics will be included. Graphical analysis using box plots for PK parameters of $AUC_{0\text{-}t}$ at steady state and $C_{max}$ will be performed. To calculate AUC, for the absorption phase, the linear rule will be used; and for the elimination phase, the logarithmic rule will be used.

### 6.3.3. Dose Proportionality Analysis

Dose proportionality will be assessed using log-transformed PK parameters, $AUC_{0\text{-}t}$ at steady state and $C_{max}$, and a linear regression approach to log-transformed dose levels. The power model will be used to analyze the dose proportionality. 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:

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

Where

$PK_i$ is the PK parameter ($C_{max}$ or $AUC_{0\text{-}t}$ at steady state) observation for the subject $i$.

α is the population intercept.

β is the population slope.

$dose_i$ is the dosage for the subject $i$.

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

The assumption for the power model is that the underlying relationship between log(PK parameter) and log(dose) is linear. The dose proportionality corresponds to the ratio of dose normalized geometric means ($R_{dnm}$), 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.

Log(PK parameter) and log(dose) will be plotted in a line plot for $AUC_{0\text{-}t}$ at steady state and $C_{max}$.

### 6.4. Pharmacodynamic Analysis

PD analysis will be performed using the PD population. Additional COVID-19 subgroup analysis for those being impacted by COVID-19 versus those not being impacted may be provided for PD endpoints using the descriptive statistical summary table and/or inferential statistics, if deemed necessary.

#### 6.4.1. Analysis of Exploratory Incretins/Metabolic Hormone Endpoints

The observed values and the change from baseline in incretins/metabolic hormone endpoints, such as GLP-1, GIP, glucagon, FGF21 and leptin, will be summarized descriptively by cohort/dose level and time point.

A mixed model repeated measures analysis will be performed with the change from baseline in incretins/metabolic hormone endpoint as the dependent variable, treatment group, analysis visit and the interaction between treatment group and analysis visit as factors, and the baseline of the dependent variable as a covariate. Repeated measures on each subject, at each visit, 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 least squares (LS) mean, standard error of LS mean and 95% confidence interval will be presented by treatment group for each post baseline analysis visit. The LS mean difference between active treatment group minus pooled placebo, standard error of the LS mean difference from placebo, and the 95% confidence interval will be presented by analysis visit.

### 6.4.2. Analysis of Exploratory Serum Lipid Profiles Endpoints

The observed values and the change from baseline and percent change from baseline in serum lipid profile endpoints, total cholesterol, LDL, HDL, VLDL, triglycerides and FFA, will be summarized descriptively by cohort/dose level and time point.

A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline and percent change from baseline in serum lipid profile endpoints.

### 6.4.3. Analysis of Exploratory Amino-Acid Profile Endpoint

The observed values and the change from baseline in amino-acid profile will be summarized descriptively by cohort/dose level and time point.

### 6.4.4. Analysis of Exploratory Glucose Metabolism Parameter Endpoints

Fasting plasma glucose, glucose via YSI, insulin, c-peptide, HbA1c, fructosamine, and glycated albumin measurements and change from baseline will be summarized by dosage and visit. A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline and percent change from baseline in each of these parameters.

Individual SMBG measurements of each time point, as the daily/weekly mean, the daily/weekly pre-meal mean and daily/weekly post-meal mean measurements will be presented in a listing. Subject SMBG of each time point, the daily/weekly mean of pre-meal and post-meal SMBG will be summarized by part/cohort/dose level as well as change from baseline. Mean SMBG (+/- SD) at each time point of baseline, Week 1 and Week 12 will be plotted.

### 6.4.5. Analysis of Exploratory Homeostatic Model Assessment Endpoints

Observed values and the change from baseline in HOMA endpoints such as, HOMA-IR and HOMA-β, will be summarized descriptively by cohort/dose level and time point.

A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline in HOMA endpoints.

### 6.4.6. Analysis of Exploratory MRI Endpoints

Observed values and the change from baseline (absolute) and percent change from baseline (relative) in MRI endpoints such as of liver fat via MRI-PDFF and visceral fat volume, will be summarized descriptively by cohort/dose level and time point. **Note:** MRI-PDFF at Day 85 is only measured if the Day -1 or Baseline visit is ≥ 10% liver fat.

A Wilcoxon Mann Whitney test will be performed to test the change from baseline and the percent change from baseline in MRI endpoints by treatment group. The p-value from the Wilcoxon Mann Whitney test will be presented. In addition, the estimate of the median and the exact 95% confidence limits estimated by the Hodges-Lehmann estimator will be presented.

In addition, an analysis of variance (ANOVA) model will be performed; the difference between each HM15136 dose group and placebo and its associated 95% confidence interval and p-value will be presented.

### 6.4.7. Analysis of Exploratory Anthropomorphic Measure Endpoints

The observed values and the change from baseline and percent change from baseline in anthropomorphic measures such as, body weight, BMI, waist circumference, hip circumference, WHR, will be summarized descriptively by cohort/dose level and time point.

A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline and percent change from baseline in anthropomorphic measure endpoints.

### 6.4.8. Analysis of Tympanic Temperature

The observed values and the change from baseline and percent change from baseline in tympanic temperature will be summarized descriptively by cohort/dose level and time point for 4AM, 6PM, and combined.

A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline and percent change from baseline in tympanic temperature for 4AM, 6PM, and combined.

### 6.4.9. Analysis of Exploratory Inflammatory Markers and Ketone Body Endpoints

The observed values and the change from baseline in inflammatory markers, such as hs-CRP and adiponectin, and the observed values and the change from baseline in ketone bodies such as β-hydroxybutyrate, will be summarized descriptively by cohort/dose level and time point.

A similar mixed model repeated measures analysis as described previously will be performed for the change from baseline in inflammatory markers and ketone body endpoints.

## 7. Interim Analysis

An interim analysis will be performed for administrative purposes, to aid in the planning of future studies in the development program after all healthy subjects in Part 1 have been finalized. Part 1 includes all subjects in Cohorts 1-3. As COVID-19 may lead to challenges in the collection of data, only partially validated data might be available for the planned interim analysis. This interim analysis will be performed for administrative purpose prior to database lock of Part 1. Unblinding will occur prior to the database lock for Part 1. Designated personnel not involved in the study conduct will perform the above stated interim analysis. Only authorized members who are listed in the Interim Analysis Unblinding and Information Dissemination Plan will have access to review the summary tables or figures of the interim analysis results, in which the information is presented in a grouped fashion with the actual treatment, e.g., mean treatment effect. The interim analysis will include an assessment of all efficacy, safety, and PK variables of Part 1.

An additional interim analysis will be performed after database lock for Part 1, which is the final analysis of Part 1. The final analysis results of part 1 will be included in the final CSR along with the final analysis of Part 2.

Both analyses for Part 1 may occur, while Part 2 will continue in a blinded fashion. The study will be conducted as outlined in this protocol. Part 2 will be performed independently from the conduct/results of the Part 1 and will not lead to changes to the conduct of the protocol. After Part 2 (T2DM cohorts) has been completed, a final analysis, that only includes the results of Part 2, will be conducted after data base lock of Part 2. For details on the interim analysis based on semi-clean data, please refer to the Interim Analysis Unblinding and Information Dissemination Plan.

## 8. Statistical Software

All statistical analyses will be performed using SAS® version 9.4. PD parameters will be derived with SAS® version 9.4. PK parameters will be derived with standard non-compartmental methods using WinNonlin v5.2 or higher.

## 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

### Schedule of Events (Part 1)

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Administration IP | | | | X | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | | X | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Procedure of Screening | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent process | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| In/Exclusion criteria | X | X[1] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior medication and medical history taking | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Infection of HBV, HCV and Anti-body, infection of HIV | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (Urine) | X | X | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | X |
| Serum FSH (Only Postmenopausal female) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| eGFR | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug abuse urine screening and alcohol exhalation test | X | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | X | X |
| Dietary education | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | | |
| Diet diary distribution | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | | |
| Diet diary review | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | |
| Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TSH | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Amylase, lipase | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Calcitonin | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| LH, FSH (Only female) | | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Physical examination | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Abbreviated Physical examination | | X | | | | | | | | | | | X | | | | X | | | | X | | | X | | | | | | X | X | X |
| Vital sign[2] | 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 | X | X | X | X | X |
| 12-lead ECG[3] | X | X | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | X | X |
| ABP monitoring[4] | | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Holter monitoring[4] | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | X | | | |
| Clinical laboratory test (Hematological, Chemistry[5], Blood coagulation, Urine analysis) | X | X | X | X[5] | X | X | X | X | X | X | X | | X | | | X | X | X | X | X | X[5] | X | X | X | X | X | X | X | X | X[5] | X | X |
| Other Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | 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 | X | X | X | X | X |
| Adverse events | 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 | X | X | X | X | X |
| Injection site reactions | | | | 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 | | |
| Pharmacodynamics (PD) assessment[6] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MRI/MRI-PDFF[7] | | | X[7] | | | | | | | | | | | | | | | | | | | | | | | | | | | X[7] | | |
| Body weight, BMI | X | X | X | X | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | X | X | | | | | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tympanic temperature (2x/day)[10] | | | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |

| Assessment | V 1 | V 2 | | | | | | | | V 3-15 | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | OPD | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Waist circumference, Hip circumference, Waist-to-hip ratio (WHR) | X | X | | X | | | | | | X | | | X | | | | X | | | | X | | | X | X | | | | | X | X | X |
| 7-point Self-monitoring of blood glucose (SMBG)[8] | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | | | | |
| Glucose measure (via YSI)[11] | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| HbA1c | X | X | | | | | | | | | | | | | | | | | | | X | | | | | | | | | X | | X |
| Fructosamine, glycated albumin | | | | X | | | | | | | | | | | | | X | | | | X | | | | | | | | | X | | X |
| Fasting plasma glucose (FPG) | 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 | X | X | X | X | X |
| Fasting insulin, Fasting C-peptide | 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 | X | X | X |
| HOMA-IR, HOMA-β | | | | X | | | | | | | | | | | | | | | | | X | | | | | | | | | X | | |
| Incretins / metabolic hormones | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Amino-acid profile | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Serum lipid profiles | X | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Inflammatory markers | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| β-hydroxybutyrate | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Pharmacokinetic (PK), Immunogenicity assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Immunogenicity (ADAbs, nAbs, anti-PEG) | | | | X | | | | | | | | | X | | | | X | | | | X | | | | X | | | | | X | | X |
| PK assessment[9] | | | | 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 | X |

1 Only that are eligible for in-house period and past medications (stated as #1-5 in section 10.1.1-3) in-house period.

2 Sampling for PK assessment and V/S to be measured on the day should be conducted before each PK sampling (prior to the collection of Pre-dose Samples on Day 1 and Day 78).

3 At the screening visit, a 12-lead ECG is conducted 1 time. All other 12-lead ECGs should be repeated 3 times. Additional measurements of the 12-lead ECG may be conducted during the following specified in-house period, which is also repeated 3 times.
The ECG measurements are collected on Day -2 and Day 77 before the subject is connected to the ABP monitoring device and on the Day 5 and Day 82 after the subject is disconnected to the ABP monitoring device.

4 Measurement time point may be adjusted after PK assessment.

5 Serum ferritin in the chemistry laboratory test is measured on the Day 1 before the administration, Day 57, Day 85.

6 All PD assessment endpoints are collected at the same time on fasting conditions at the time of PK Sample collection (Pre-dose Sample collection on Day 1 and Day 78). In the case of fasting conditions, the test subject should be kept in a state of being maintained for about 10 hours.

7 MRI/MRI-PDFF assessment marked for Day -1 can be performed prior to Day -1, after subject's eligibility for the study is confirmed (MRI may be performed while Screening calcitonin results are pending). MRI-PDFF measurements marked for Day 85 should be conducted as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling, and on Day 85 of the MRI-PDFF measurement, the MRI-PDFF will only be performed if the MRI-PDFF on Day -1 showed equal or more than 10% liver fat. MRI assessment will be performed as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling.

8 The 7-point SMBG is measured 15 minutes before the meal (± 10 minutes), 2 hours after the meal starts (± 15 minutes), and 15 minutes before the evening snack (± 10 minutes)s. For the Day 1 and Day 78 of the test, 5 times, except before and after breakfast, should be conducted.

9 The time of PK sampling may be adjusted between cohorts if PK data showing that other time points are more advantageous can be obtained when the sample for pharmacokinetic analysis is collected. Specific PK sampling timeline for analysis follows the PK sampling schedule table.

10 During the in-house periods, tympanic temperature will be measured 2 x /24 hours.

11 FPG will be measured via YSI in addition to the FPG measure that is included in clinical laboratory assessments. The measurement of glucose via YSI should be performed for all subjects and for all outpatient visits.

## Schedule of Events (Part 2)

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Administration IP | | | | X | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | | X | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Procedure of Screening | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent process | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| In/Exclusion criteria | X | X[1] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior medication and medical history taking | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Infection of HBV, HCV and Anti-body, infection of HIV | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (Urine) | X | X | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | X |
| Serum FSH (Only Postmenopausal female) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| eGFR | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug abuse urine screening and alcohol exhalation test | X | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | X | X |
| Dietary education | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | | |
| Diet diary distribution | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | | |
| Diet diary review | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | X | | | |
| Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TSH | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Amylase, lipase | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Calcitonin | X | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| LH, FSH (Only female) | | | | X | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Physical examination | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Abbreviated Physical examination | | X | | | | | | | | | | | X | | | | X | | | | X | | | X | | | | | | X | X | X |
| Vital sign[2] | 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 | X | X | X | X | X |
| 12-lead ECG[3] | X | X | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | X | X |
| ABP monitoring[4] | | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Holter monitoring[4] | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | X | | | |
| Clinical laboratory test (Hematological, Chemistry[5], Blood coagulation, Urine analysis) | X | | | X[5] | | X | | | | X | X | | X | | | X | X | X | X | X | X[5] | X | X | | X | | X | | X[5] | X | X |
| Other Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | 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 | X | X | X | X | X |
| Adverse events | 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 | X | X | X | X | X |
| Injection site reactions | | | | 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 | | |
| Pharmacodynamics (PD) assessment[6] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MRI/MRI-PDFF[7] | | | X[7] | | | | | | | | | | | | | | | | | | | | | | | | | | | X[7] | | |
| Body weight, BMI | X | X | X | X | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | X | X | | | | | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tympanic temperature (2x/day)[10] | | | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Waist circumference, Hip circumference, Waist-to-hip ratio (WHR) | X | X | | X | | | | | | X | | | X | | | | X | | | | X | | | X | X | | | | | X | X | X |
| 7-point Self-monitoring of blood glucose (SMBG)[8] | | | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | | | | |
| Glucose measure (via YSI)[11] | | | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | | | | |
| HbA1c | X | X | | | | | | | | | | | | | | | | | | | X | | | | | | | | | X | | X |
| Fructosamine, glycated albumin | | | | X | | | | | | | | | | | | | X | | | | X | | | | | | | | | X | | X |
| Fasting plasma glucose (FPG) | 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 | X | X | X | X | X |
| Fasting insulin, Fasting C-peptide | 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 | X | X | X |
| HOMA-IR, HOMA-β | | | | X | | | | | | | | | | | | | | | | | X | | | | | | | | | X | | |
| Incretins / metabolic hormones | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Amino-acid profile | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Serum lipid profiles | X | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Inflammatory markers | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| β-hydroxybutyrate | | | | X | | X | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |

| Assessment | V 1 | V 2 | | | | | | | | | V 3-15 | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | In-house Period 1 | | | | | | | | | OPD | | | | | | | | | | | | In-house Period 2 | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Visit(day) | -35 to -3 | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6-7 | 8 | 10 | 11 | 15 | 17 | 18 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77 | 78 | 79 | 80 | 81 | 82 | 85 | 99 | 113 |
| Visit window | | | | | | | | | | | | | ±1 | | | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | | | | | | | ±2 | ±2 | ±2 |
| Sequestered in clinic/unit | | X | X | X | X | X | X | X | X | X | | | | | | | | | | | | | | X | X | X | X | X | X | | | |
| Pharmacokinetic (PK), Immunogenicity assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Immunogenicity (ADAbs, nAbs, anti-PEG) | | | | X | | | | | | | | | X | | | | X | | | | X | | | | X | | | | | X | | X |
| PK assessment[9] | | | | 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 | X |

1 Only that are eligible for in-house period and past medications (stated as #1-5 in section 10.1.1-3) in-house period.

2 Sampling for PK assessment and V/S to be measured on the day should be conducted before each PK sampling (prior to the collection of Pre-dose Samples on Day 1 and Day 78).

3 At the screening visit, a 12-lead ECG is conducted 1 time. All other 12-lead ECGs should be repeated 3 times. Additional measurements of the 12-lead ECG may be conducted during the following specified in-house period, which is also repeated 3 times.
The ECG measurements are collected on Day -2 and Day 77 before the subject is connected to the ABP monitoring device and on the Day 5 and Day 82 after the subject is disconnected to the ABP monitoring device.

4 Measurement time point may be adjusted after PK assessment.

5 Serum ferritin in the chemistry laboratory test is measured on the Day 1 before the administration, Day 57, Day 85.

6 All PD assessment endpoints are collected at the same time on fasting conditions at the time of PK Sample collection (Pre-dose Sample collection on Day 1 and Day 78). In the case of fasting conditions, the test subject should be kept in a state of being maintained for about 10 hours.

7 MRI/MRI-PDFF assessment marked for Day -1 can be performed prior to Day -1, after subject's eligibility for the study is confirmed (MRI may be performed while Screening calcitonin results are pending). MRI-PDFF measurements marked for Day 85 should be conducted as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling, and on Day 85 of the MRI-PDFF measurement, the MRI-PDFF will only be performed if the MRI-PDFF on Day -1 showed equal or more than 10% liver fat. MRI assessment will be performed as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling.

8 The 7-point SMBG is measured 15 minutes before the meal (± 10 minutes), 2 hours after the meal starts (± 15 minutes), and 15 minutes before the 15 minutes before the evening snack (± 10 minutes). For the Day 1 and Day 78 of the test, 5 times, except before and after breakfast, should be conducted.

9 The time of PK sampling may be adjusted between cohorts if PK data showing that other time points are more advantageous can be obtained when the sample for pharmacokinetic analysis is collected. Specific PK sampling timeline for analysis follows the PK sampling schedule table.

10 During the in-house periods, tympanic temperature will be measured 2 x /24 hours.

11 FPG will be measured via YSI in addition to the FPG measure that is included in clinical laboratory assessments. The measurement of glucose via YSI should be performed for all subjects and for all outpatient visits.

## Schedule of Events (Part 1 and Part 2 COVID-19 Modification)

| Assessment | V 1 | V 2 | | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | OPD | | | | | | | | | | OPD | | | | | | | | | | | | | OPD | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | | 2 | 2 | | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | 13 | 15 | 17 |
| Phone visit (P) (assessments at home)[11] | | | P | | P | | P | | P | P | | | | | | | | | | | | | | | P | | P | | P | | | | |
| Visit(day) | -35 to -3 | -2[11] | -1[11] | 1 | 2[11] | 3[11] | 4[11] | 5[11] | 6[11] | 7[11] | 8 | 10 | 11[11] | 15 | 17 | 18[11] | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77[11] | 78 | 79[11] | 80[11] | 81[11] | 82[11] | 85 | 99 | 113 |
| Visit window | | ±1 | ±2 | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | | ±1 | ±2 | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±2 | ±2 | ±2 |
| **Administration IP** | | | | X | | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | | X | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Procedure of Screening | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed consent process | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| In/Exclusion criteria | X | X[1] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Prior medication and medical history taking | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Infection of HBV, HCV and Anti-body, infection of HIV | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (Urine) | X | X | | | | | | | | | | | | | | | | | | | | | | | | X | | | | | | | X |
| Serum FSH (Only Postmenopausal female) | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| eGFR | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug abuse urine screening and alcohol exhalation test | 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 |
| Dietary education | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | | | |
| Diet diary distribution | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | | | |
| Diet diary review | | | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | | |
| Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TSH | X | | | X | | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Amylase, lipase | X | | | X | | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |
| Calcitonin | X | | | X | | | | | | | | | | X | | | | X | | | | X | | | | | | | | | X | | X |

| Assessment | V 1 | V 2 | | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | OPD | | | | | | | | | | OPD | | | | | | | | | | | | | OPD | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | 13 | 15 | 17 | | |
| Phone visit (P) (assessments at home)[11] | | | P | | P | | P | | P | P | | | | | | | | | | | | | P | | P | | P | | | | | |
| Visit(day) | -35 to -3 | -2[11] | -1[11] | 1 | 2[11] | 3[11] | 4[11] | 5[11] | 6[11] | 7[11] | 8 | 10 | 11[11] | 15 | 17 | 18[11] | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77[11] | 78 | 79[11] | 80[11] | 81[11] | 82[11] | 85 | 99 | 113 |
| Visit window | | ±1 | ±2 | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | | ±1 | ±2 | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±2 | ±2 | ±2 |
| LH, FSH (Only female) | | | | X | | | | | | | | | | X | | | | X | | | | X | | | | | | | | X | | X |
| Physical examination | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Abbreviated Physical examination | | X | | | | | | | | | | | | X | | | | X | | | | X | | | X | | | | | X | X | X |
| Vital sign[2] | 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[3] | X | X | | | | | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | | | X | X | X | X |
| ABP monitoring[4] | | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | X | | | |
| Instructions on ABPM at home | | X | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Holter monitoring[4] | | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | | X | X | X | X | X | | | |
| Instructions on Holter monitoring at home | | X | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| Clinical laboratory test (Hematological, Chemistry[5], Blood coagulation, Urine analysis) | X | | | X[5] | | X | | | | | X | X | | X | | | X | X | X | X | X | X[5] | X | X | | X | | X | | X[5] | X | X |
| Other Safety assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant medications | 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 | X | X | X | X | X | X |
| Adverse events | 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 | X | X | X | X | X | X |
| Injection site reactions | | | | 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 | X | | |
| Pharmacodynamics (PD) assessment[6] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MRI/MRI-PDFF[7] | | X[7] | | | | | | | | | | | | | | | | | | | | | | | | | | | | X[7] | | |
| Body weight, BMI | X | X | | X | | | | | | | X | | | X | | | X | X | X | X | X | X | X | X | | X | | | | | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| Assessment | V 1 | V 2 | | | | | | | | | | V 3-15 | | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | OPD | | | | | | | | | | OPD | | | | | | | | | | | | | OPD | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | 2 | 2 | | 3 | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | | 13 | 15 | 17 |
| Phone visit (P) (assessments at home)[11] | | | P | | P | | P | | P | P | | | | | | | | | | | | | P | | P | | P | | | | |
| Visit(day) | -35 to -3 | -2[11] | -1[11] | 1 | 2[11] | 3[11] | 4[11] | 5[11] | 6[11] | 7[11] | 8 | 10 | 11[11] | 15 | 17 | 18[11] | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77[11] | 78 | 79[11] | 80[11] | 81[11] | 82[11] | 85 | 99 | 113 |
| Visit window | | ±1 | ±2 | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | | ±1 | ±2 | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±2 | ±2 | ±2 |
| Waist circumference, Hip circumference, Waist-to-hip ratio (WHR) | X | X | | X | | | | | | | X | | | X | | | | X | | | | X | | | X | | | | | X | X | X |
| 7-point Self-monitoring of blood glucose (SMBG)[8,12] | | | X | X | X | X | X | X | X | | | | | | | | | | | | | | | | X | X | X | X | | | | |
| Instructions on 7-point SMBG and FPG at home | | X | | | | | | | | | | | | | | | | | | | | | X | | | | | | | | | |
| SMBG and fasting blood glucose (FPG) diary distribution | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | | | |
| Glucose measure (via YSI)[10,12] | | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | X |
| HbA1c | X | X | | | | | | | | | | | | | | | | | | | | X | | | | | | | | X | | X |
| Fructosamine, glycated albumin | | | | X | | | | | | | | | | | | | | X | | | | X | | | | | | | | X | | X |
| Fasting plasma glucose (FPG) (per clinical lab assessment)[9,12] | X | X | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | X |
| FBG at home (via glucometer)[12] | | | | | | | | | X | X | | | | | | | | | | | | | | X | | | | | | | | |
| Fasting insulin, Fasting C-peptide | X | | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | X | X |
| HOMA-IR, HOMA-β | | | | X | | | | | | | | | | | | | | | | | | X | | | | | | | | X | | |
| Incretins / metabolic hormones | | | | X | | X | | | | | X | | | X | | | | X | | | | X | | | X | | X | | | X | | |
| Amino-acid profile | | | | X | | X | | | | | X | | | X | | | | X | | | | X | | | X | | X | | | X | | |

| Assessment | V 1 | V 2 | | | | | | | | | | V 3-15 | | | | | | | | | | | | V 16 | | | | | | V 17-19 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | OPD | | | | | | | | | | OPD | | | | | | | | | | | | OPD | | | | | | OPD (F/U) | | |
| Visit(Week) | -5 to -1 | | | 1 | | | | | | | 2 | 2 | | 3 | | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 11 | 12 | | | | | 13 | 15 | 17 |
| Phone visit (P) (assessments at home)[11] | | | P | | P | | P | | P | P | | | | | | | | | | | | | | P | | P | | P | | | | |
| Visit(day) | -35 to -3 | -2[11] | -1[11] | 1 | 2[11] | 3[11] | 4[11] | 5[11] | 6[11] | 7[11] | 8 | 10 | 11[11] | 15 | 17 | 18[11] | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 77[11] | 78 | 79[11] | 80[11] | 81[11] | 82[11] | 85 | 99 | 113 |
| Visit window | | ±1 | ±2 | | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | | ±1 | ±2 | ±1 | ±1 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±2 | ±1 | | ±1 | ±1 | ±1 | ±1 | ±2 | ±2 | ±2 |
| Serum lipid profiles | X | | | X | | X | | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Inflammatory markers | | | | X | | X | | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| β-hydroxybutyrate | | | | X | | X | | | | | X | | | X | | | | X | | | | X | | | | X | | X | | | X | | |
| Pharmacokinetic (PK), Immunogenicity assessment | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Immunogenicity (ADAbs, nAbs, anti-PEG) | | | | X | | | | | | | | | | X | | | | X | | | | X | | | X | | | | | X | | | X |
| PK assessment[9] | | | | X | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X | X | X | X |

1 Only that are eligible for past medications (stated as #1-5 in section 10.1.1-3).

2 Sampling for PK assessment and V/S to be measured on the day should be conducted before each PK sampling (prior to the collection of Pre-dose Samples on Day 1 and Day 78).

3 At the screening visit, a 12-lead ECG is conducted 1 time. All other 12-lead ECGs should be repeated 3 times. Additional measurements of the 12-lead ECG may be conducted during the OPV days, which is also repeated 3 times. The ECG measurements are collected on Day -2 and Day 78 before the subject is connected to the ABP monitoring device and on the Day 5 and Day 82 after the subject is disconnected to the ABP monitoring device.

4 Measurement time point may be adjusted after PK assessment.

5 Serum ferritin in the chemistry laboratory test is measured on the Day 1 , Day 57, Day 85.

6 All PD assessment endpoints are collected at the same time on fasting conditions at the time of PK Sample collection (Pre-dose Sample collection on Day 1 and Day 78). In the case of fasting conditions, the test subject should be kept in a state of being maintained for about 10 hours.

7 MRI/MRI-PDFF assessment marked for Day -2 can be performed after subject's eligibility for the study is confirmed (MRI may be performed while Screening calcitonin results are pending), but MRI must be completed prior to first dosing. MRI-PDFF measurements marked for Day 85 should be conducted as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling, and on Day 85 of the MRI-PDFF measurement, the MRI-PDFF will only be performed if the MRI-PDFF prior to the first dosing showed equal or more than 10% liver fat. MRI assessment will be performed as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling. If MRI/MRI-PDFF assessment is not possible during the stated time period, due to COVID- restrictions, MRI/MRI-PDFF may be performed at a later timepoint, but prior to the last visit on Day 113. If MRI/MRI-PDFF assessment is not possible due to restricted access of MRI center under COVID-19 restrictions, the missing assessment will be documented in the CRFs (specific information will be captured that explains the basis of the missing data due to COVID-19).The missing assessment will be documented as a protocol deviation (with reason due to COVID-19 stated).

8 The 7-point SMBG is measured 15 minutes before the meal (± 10 minutes), 2 hours after the meal starts (± 15 minutes), and 15 minutes before the 15 minutes before the evening snack (± 10 minutes). For the Day 1 and Day 78 of the test, 5 times, except before and after breakfast, should be conducted. During OPD, subjects will perform SMBG at stated times. Measurements may partly be performed in the clinic and partly at home on that day. On days with a phone visit, subjects will only measure the 7-point profile at home. All meal-times and corresponding SMBG values will be recorded in a subject diary.

9 The time of PK sampling may be adjusted between cohorts if PK data showing that other time points are more advantageous can be obtained when the sample for pharmacokinetic analysis is collected. Specific PK sampling timeline for analysis follows the PK sampling schedule table.

10 FPG will be measured via YSI in addition to the FPG measure that is included in clinical laboratory assessments. The measurement of glucose via YSI should be performed for all subjects and for all outpatient visits. If OPV is adjusted to a phone visit, subjects will measure fasting glucose in the morning (prior to any breakfast). Capillary blood will be used for the fasting blood glucose assessment (FBG), which will be performed by subjects at home via glucometer instead of FPG with YSI at the site. Other fasting glucose measures are already covered by the assessment of the 7-point profiles.

11 If OPVs and/or phone visits are not feasible on the specified visit days (only as an example, Day 1 being on a Monday and visit is therefore scheduled to take place on a weekend/holiday),visits can be moved within the visit window and OPV and phone visit (on day prior to OPV or day after OPV) can be combined into one visit (as example, combined visit for Day 5 and 6) to keep the schedule for the following visits. If the visit is moved/combined, all other visits between the corresponding dosing visits will be performed as scheduled, to ensure that weekly dosing can be performed as scheduled.

12 -Summary of the various measurement methods that involve assessment of glucose:

- 7-point SMBG will be measured on Day -1, 1, 2, 3, 4, 5, 78, 79, 80, and 81 (original time points kept, regardless of the changes in visit type).
- FBG at home (via glucometer): Day 6, 7, and 77.
- FPG at clinic (blood sample for LabCorp analysis): at every visit in the clinic (D-2, Day 1, 3, 5, 8, and all OPD V3-15 assessments, 78, 80, 82, 85, 99, and 113)
- Glucose measure (via YSI): at every visit in the clinic.

**Table 3: PK Sampling Schedule**

| PK sampling schedule | | | | | Time window |
|---|---|---|---|---|---|
| Treatment period | In-house Period 1 | Week 1 | Day 1 | Pre-dose 1st dosing | -60 min |
| | | | | 8 h after 1st dosing | ±10 min |
| | | | Day 2 | 24 h after 1st dosing | ±30 min |
| | | | Day 3 | 48 h after 1st dosing | ±30 min |
| | | | Day 4 | 72 h after 1st dosing | ±30 min |
| | | | Day 5 | 96 h after 1st dosing | ±30 min |
| | | Week 2 | Day 8 | Pre-dose 2nd dosing | -60 min |
| | OPD | Week 2 | Day 10 | 48 h after 2nd dosing | ±30 min |
| | | | Day 11 | 72 h after 2nd dosing | ±30 min |
| | | Week 3 | Day 15 | Pre-dose 3rd dosing | -60 min |
| | | | Day 17 | 48 h after 3rd dosing | ±30 min |
| | | | Day 18 | 72 h after 3rd dosing | ±30 min |
| | | Week 4 | Day 22 | Pre-dose 4th dosing | -60 min |
| | | Week 5 | Day 29 | Pre-dose 5th dosing | -60 min |
| | | Week 6 | Day 36 | Pre-dose 6th dosing | -60 min |
| | | Week 7 | Day 43 | Pre-dose 7th dosing | -60 min |
| | | Week 8 | Day 50 | Pre-dose 8th dosing | -60 min |
| | | Week 9 | Day 57 | Pre-dose 9th dosing | -60 min |
| | | Week 10 | Day 64 | Pre-dose 10th dosing | -60 min |
| | | Week 11 | Day 71 | Pre-dose 11th dosing | -60 min |
| | In-house Period 2 | Week 12 | Day 78 | Pre-dose 12th dosing | -60 min |
| | | | | 8 h after 12th dosing | ±10 min |
| | | | Day 79 | 24 h after 12th dosing | ±30 min |
| | | | Day 80 | 48 h after 12th dosing | ±30 min |
| | | | Day 81 | 72 h after 12th dosing | ±30 min |
| | | | Day 82 | 96 h after 12th dosing | ±30 min |
| F/U | OPD | Week 13 | Day 85 | 168 h after 12th dosing | ±2 days |
| | | Week 15 | Day 99 | 504 h after 12th dosing | ±2 days |
| | | Week 17 | Day 113 | 840 h after 12th dosing | ±2 days |

## PK Sampling Schedule (Parts 1 and 2) – COVID-19 Modification

| PK sampling schedule | | | | | Time window | Added Time window |
|---|---|---|---|---|---|---|
| Treatment period | OPD | Week 1 | Day 1 | Pre-dose 1st dosing | -60 min | |
| | | | | 4 h after 1st dosing | ±10 min | |
| | | | Day 3 | 48 h after 1st dosing | ±30 min | ±1 day |
| | | | Day 5 | 96 h after 1st dosing | ±30 min | ±1 day |
| | | Week 2 | Day 8 | Pre-dose 2nd dosing | -60 min | |
| | | Week 2 | Day 10 | 48 h after 2nd dosing | ±30 min | ±1 day |
| | | | Day 11 | 72 h after 2nd dosing | ±30 min | ±2 days |
| | | Week 3 | Day 15 | Pre-dose 3rd dosing | -60 min | |
| | | | Day 17 | 48 h after 3rd dosing | ±30 min | ±1 day |
| | | | Day 18 | 72 h after 3rd dosing | ±30 min | ±2 days |
| | | Week 4 | Day 22 | Pre-dose 4th dosing | -60 min | |
| | | Week 5 | Day 29 | Pre-dose 5th dosing | -60 min | |
| | | Week 6 | Day 36 | Pre-dose 6th dosing | -60 min | |
| | | Week 7 | Day 43 | Pre-dose 7th dosing | -60 min | |
| | | Week 8 | Day 50 | Pre-dose 8th dosing | -60 min | |
| | | Week 9 | Day 57 | Pre-dose 9th dosing | -60 min | |
| | | Week 10 | Day 64 | Pre-dose 10th dosing | -60 min | |
| | | Week 11 | Day 71 | Pre-dose 11th dosing | -60 min | |
| | | Week 12 | Day 78 | Pre-dose 12th dosing | -60 min | |
| | | | | 4 h after 12th dosing | ±10 min | |
| | | | Day 80 | 48 h after 12th dosing | ±30 min | ±1 day |
| | | | Day 82 | 96 h after 12th dosing | ±30 min | ±1 day |
| F/U | OPD | Week 13 | Day 85 | 168 h after 12th dosing | ±2 days | |
| | | Week 15 | Day 99 | 504 h after 12th dosing | ±2 days | |
| | | Week 17 | Day 113 | 840 h after 12th dosing | ±2 days | |