Clinical Development HM15211

Clinical Study Protocol HM-TRIA-102

A PHASE 1 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF MULTIPLE DOSES OF HM15211 IN OBESE SUBJECTS WITH NAFLD

Sponsor:	
Sponsor Contact:	
Clinical Research Organization:	
Authors:	
Document type:	Clinical Study Protocol
IND number:	137766
Version number:	V5.0
Development phase:	1
Release date:	02-Jul-2019

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided.

1.2 Approval

Representatives of Sponsor and Coordinating Principal Investigator will sign the agreement on the protocol. Signatures of the responsible Investigator's at all participating sites will be collected in a separate protocol approval document.

1.3 Document History

Version	Revision Date	Revision Description
1.0	**27-Sep-2018**	**Original Document**
2.0 (Amendment 1)	**25-Oct-2018**	1. **Dose Escalation in Part 1 of the Study:** The starting dose of the study drug for cohort 1-1 in Part 1 will be 0.01 mg/kg. The proposed dose for cohort 1-2 will be 0.02 mg/kg and the dose for cohort 1-3 will not exceed 0.04 mg/kg, but dose escalation will not exceed a two-fold increase between doses/cohorts. *Section 2.0 Study Summary/Part 1, section 4.5 Dose Escalation Algorithm.* *2.* **Administrative Changes/ Correction of Typographical Errors:** 2.1 Addition of coagulation to SOEs. 2.2 Addition of footnote to SOEs. 2.3 Correction of typo in header of SOE for Part *Section 16.0 Appendix A.* 2.4 Update of exclusion criterion # 24 in Part 2, as a part of the sentence was inadvertently deleted. *Section 2.0 Study Summary/Part 2, section 7.4 Part 2 Exclusion Criteria* 2.5 Typo in measurement period for ABPM *Section 2.0 Study Summary* 2.6 Typo in email address on Investigator Approval Page *Section 1.2 Approval*

3.0 (Amendment 2)	**13-Feb-2019**	1. **Adjustment and Addition of Parameter for Laboratory Analysis:** Additional parameters will be analyzed to expand the assessment of the drug. CRP: Parameter will be added for analysis from blood samples taken on Day 3 in Part 1/Cohort 3 and in Part 2 of the study. For subjects who already participated in Part 1/ Cohort 1 or 2, back-up samples may be used for analysis. hs-CRP: Analysis of hs-CRP in Part 2 of the study will not be performed. Beta-hydroxybutyrate (BHB): Parameter will be added as exploratory endpoint and blood samples will be collected on Day 1 (pre-dose), Day 57 and Day 85 for Part 1/Cohort 3 and Part 2. For subjects who already participated in Part 1/Cohort 1 or 2, back-up samples may be used for analysis. Adiponectin: Parameter will be added as exploratory endpoint and blood samples will be taken on Day 1, Day 57 and Day 85 for Part 1/Cohort 3 and Part 2. For subjects who already participated in Part 1/Cohort 1 or 2, back-up samples may be used for analysis. *Section 2.0 Study Summary, sections 5.1.2 and 5.2.2 Exploratory Objectives and Endpoints, section 6.2 Study Description, section 9.1.17 Laboratory Pharmacodynamic Assessments, Table 9-2 and Table 9-3 Clinical Laboratory Assessments, section 9.1.22 Blood Volume, Table 12-1 and Table 12-2 Study Endpoints, Table 16-1 and Table 16-2 Schedule of Events.* 2. **Change of Sponsor Contact** Change of name and title of the person authorized to sign the protocol and the protocol amendments for the sponsor. *Title Page, Sponsor Protocol Approval Page* 3. **Incorporation of Administrative Letter # 1, dated 14 Nov 2018:** Clarification of body weight measurement on Day -1.

		Section 4.5 Dose Escalation Algorithm and section 16.0 Appendix A in Table 16-1 and 16-2 4. **Incorporation of Administrative Letter # 2, dated 03 Dec 2018:** Correction of typographical error and alignment/clarification of procedures and injection of study drug on outpatient visits. *Section 2.0 Study Summary and section 6.2 Study Description* 5. **Incorporation of Administrative Letter # 3, dated 25 Jan 2019:** a) Clarification to measurement of temperature in order to allow for oral and aural assessments. *Section 6.2 Study Design, section 9.1.6 Vital signs* b) Adjustment of language for immunogenicity sampling to align with the SOE and to clarify that sampling will be performed 30 min prior to dosing on Day 1, and post the first dosing on Day 22,50, 78, 85 and 99. Post first dose samples will be taken at the same time point of safety blood sampling or collection of other blood samples. *Section 9.1.20 Immunogenicity Assessments* c) Clarification around the measurement of blood pressure on Day 4 and 81. Blood pressure is to be taken prior to the PK sample, and is independent from the disconnection from the ABPM. *Section 9.1.6 Vital signs* 6. **Addition of example parameters for the assessment of heart rate variability (HRV)** SDANN and SDNN index added. *Section 3.0 List of Abbreviations, Table 12-1, Table 12-2, section 12.2.5 Safety Analysis and Endpoints* 7. **Correction of typographical errors and formatting** 5.1. Row "Week 3, Day 15" stated 2nd instead of 3rd dosing. *Table 9-3 PK Sampling Schedule* 5.2. Rows "Week" and "Day" were adjusted to

		include Day 77 to Week 11. 5.3. Row "PK Sampling": X mark deleted on Day 79, as PK sampling follows the PK Sampling Schedule in section 9.1.16. *Section 16.0 Appendix A in Table 16-1 and 16-2*
4.0 (Amendment 3)	**09-Apr-2019**	1. **Up to 3 additional cohorts may be added to Part 1 of the study. Cohort 1-4 will proceed with a dose of HM15211 of 0.06 mg/kg body weight.** Based on prediction from PK data for the second cohort, geometric mean weekly AUC_{0-t} will not exceed PK exposure limit determined in toxicology studies. Therefore, this protocol will be amended to enroll up to 3 additional cohorts to increase the dose of the study drug in increments. The increments will be determined at dose escalation meetings, up to a maximum of 0.12 mg/kg. Cohort 1-4 will proceed with a dose of 0.06 mg/kg *Section 4.4 Rationale for Starting and Maximum Dose, 4.5 Dose Escalation Algorithm, 6.1 Study Design ,6.4 Study Discontinuation and Stopping Criteria,* 2. **Addition of up to 2 study sites** As up to 3 additional cohorts, with up to n=36 additional subjects are added, up to 2 additional sites may be included in the study, if needed in order to fulfill enrollment needs. *Section 2.0 Study Summary* 3. **Addition of PK sampling timepoints starting with cohorts 1-3 (at week 12)** Four (4) additional samples will be collected. Blood volume will be adjusted. *Section 9.1.16 Pharmacokinetic Assessments and Schedule, section 9.1.22 Blood Volume* 4. **Prolongation of In-house Period 2** Due to the added PK sampling timepoint on Day 82, subjects in cohort 1-4 will not be released home on Day 81 but will stay overnight for the collection of the PK sample in the morning of Day 82. The extended In-house Period is

		optional for subjects that are already participating in cohort 1-3. *Section 2.0 Study Summary, 6.2 Study Description, Section 16.0 Appendix A in Table 16-3 Table 16-4* 5. **Extension of ABPM and Holter monitoring Period** Due to the added PK sampling timepoints around T_{max}, a consecutive extension of ABPM and Holter monitoring until Day 5 in week 1 and until Day 82 in week 12 will be added. *Section 2.0 Study Summary, 6.2 Study Description, section 9.1.6 Vital signs, section 9.1.11 ECG Procedure, Section 9.1.14 ABPM, Section 16.0 Appendix A in Table 16-3 and Table 16-4* 6. **Adjustment of ECG timepoint** Due to the extended ABPM and Holter monitoring period until Day 5 and Day 82, the ECG measurements are moved from Day 4 to Day 5 and from Day 81 to Day 82 as well, as they are supposed to be conducted after the ambulatory devices have been removed. *Section 9.1.11 ECG Procedure, Section 16.0 Appendix A in Table 16-2, 16-3 and 16-4* 7. **Part 2 of the study will not be conducted** Description of Part 2 and language referring to Study Part 2, will be deleted. Language in other parts of the protocol will be adjusted to reflect the changes, such as subject number, etc. As there is only one study part left, the specification "Part 1" will be deleted. *Title of the study, section 2.0 Study Summary, section 4.2 Rationale for the Proposed Study, section 4.5 Dose Escalation Algorithm, section 5.0 Study Objectives Part 2, 6.1 Study Design, 6.2 Study Description, 6.3 Rationale for Study Design and Endpoints, 7.0 Part 2 Inclusion and Exclusion Criteria, 8.6 Randomization and Blinding, 9.1.8 Procedures for Clinical Laboratory Samples, 9.1.17 Laboratory Pharmacodynamic Assessments, 9.1.18 MRI-*

		PDFF, 9.1.19 VCTE, 9.1.22 Blood Volume, 12.0 Statistical Methods 8. **Modification of Dose Escalation Stopping Criteria** Dose Escalation Stopping Criteria were modified for gastrointestinal (GI) criteria (emesis/ vomiting), as it is anticipated that the GI tolerability will be dose limiting. *Section 6.4 Study Discontinuation and Stopping Criteria* 9. **Addition of HbA1c as Parameter to Exploratory Endpoints** *Section 2.0 Study Summary, section 5.1.2 Exploratory Objectives and Endpoint, 9.1.17 Laboratory Pharmacodynamic Assessments* 10. **Adjustment of Rescreening Requirements** Allowing subjects who would otherwise qualify not be limited to 1 rescreen. Subjects who have screen failed due to out of window may be rescreened with CRO approval. *Section 9.1.2 Screening* 11. **Clarification around serum hCG pregnancy test** If FSH level in postmenopausal women is not corresponding to the stated postmenopausal status, a serum hCG pregnancy test may be performed out of the screening sample, if sampel is within stability range. *Section 9.1.9 Contraception* 12. **Clarification of Immunogenicity Sampling** In order to correct current inconsistencies of sampling volumes with actual sampling instructions, the section of the immunogenicity sampling will only reference the Immunogenicity Sample and Shipping Instructions. *Section 9.1.20 Immunogenicity Assessments* 13. **Clarification of the timing for the tolerability assessment** Specification of the timepoints for the assessment of injection site reactions to

		differentiate between dosing days and non-dosing days are inserted. *Section 9.1.21 Tolerability Assessment* 14. **Clarification of Language** a) Clarification of language for check-in criteria. *Section 9.1.12 Check-in Procedure* b) *Clarification of timepoint for body weight measurement through addition of a footnote.* *Section 16.0 Appendix A in Table 16-1 and 16-2* 15. **Formatting Adjustments** *Section 9.1.21 Tolerability Assessments* 16. **Adjustment of language for the responsibility of statistical services.** Adjustment of language to reflect that statistical services have already been delegated to Pharmapace, Inc.. *Section 12.1 Statistical and Analytical Plans*
5.0 (Amendment 4)	**02Jul-2019**	1. **Three additional exploratory objectives and endpoints added to the study** **a) Changes in liver steatosis and liver stiffness assessed by FibroScan® (VCTE), determined as absolute and percent change from baseline in controlled attenuation parameter (CAP) and liver stiffness measurements (LSM)** An additional FibroScan assessment will be performed on Day 85 for subjects participating in Cohort 1-4 and up, to assess a change from baseline assessment after 12 weeks of treatment. *Section 2.0 Study Summary, section 5.1.2 Exploratory Objectives and Endpoints, 6.2 Study Description, 9.1.19 VCTE, and 16.0 Appendix A in Table 16-4 and 16-5.* **b) Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI** For subjects participating in cohort 1-5 and up, assessment of visceral fat will be performed at Screening, and after 8 and 12 weeks of treatment via MRI. *Section 2.0 Study Summary, section 5.1.2 Exploratory Objectives and Endpoints, 6.2 Study*

		Description, 9.1.18 MRI/MRI-PDFF **c) Waist circumference/waist measurement** The measurement of the waist circumference is stated in the protocol in 2 different ways, as waist circumference and as waist measurement. In order to avoid confusion and to be consistent throughout the protocol, only the term waist circumference will be used. Measurements of waist circumference at Day 85 will be added for cohorts 1-3 and up, and will be performed at Screening, Day 85 and at the Follow-up Visit. *Section 9.1.5 Height, Weight, BMI and Waist Circumference and 16.0 Appendix A in Tables 16-1 to 16-5.*

Investigator Approval Page

Protocol Title:	**A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of HM15211 in Obese Subjects with NAFLD**
Protocol Number:	**HM-TRIA-102**
Protocol Version:	5.0
Date:	02-Jul-2019

The Principal Investigator agrees to conduct this study as outlined in this protocol in reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines described in the International Committee for Harmonization (ICH) Guidance document E6, the FDA regulations for clinical trials, 21 CFR 312, the Health Insurance Portability and Accountability Act (HIPAA), and the most current version of the Declaration of Helsinki. Any modification to the protocol must be agreed upon by both the Investigator and Sponsor and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing the Sponsor (including monitoring staff and auditors), to Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and/or to regulatory authorities.

Coordinating Principal Investigator:

Sponsor Protocol Approval Page

Protocol Title:	**A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of HM15211 in Obese Subjects with NAFLD**
Protocol Number:	**HM-TRIA-102**
Protocol Version:	5.0
Date:	02-Jul-2019

The Sponsor agrees to conduct the trial as outlined in this protocol in reference to national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines described in the International Committee for Harmonization (ICH) Guidance document E6, the FDA regulations for clinical trials, 21 CFR 312, the Health Insurance Portability and Accountability Act (HIPAA), and the most current version of the Declaration of Helsinki. Any modification to the Protocol must be agreed upon by both the Investigator and Sponsor and documented in writing. By written agreement to this protocol, the Sponsor agrees to allow direct access to all documentation, including source data, to authorized individuals representing the Sponsor (including monitoring staff and auditors), to Institutional Review Boards/Independent Ethics Committees (IRB/IEC) and/or to regulatory authorities.

Approved for the Sponsor by:

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

2.0 STUDY SUMMARY

Name of Study Drug	HM15211
Protocol Number	HM-TRIA-102
Protocol Title	**A PHASE 1 STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF MULTIPLE DOSES OF HM15211 IN OBESE SUBJECTS WITH NAFLD**
Study Overview	The study will include up to 6 cohorts with 12 obese subjects with nonalcoholic fatty liver disease (NAFLD) each (up to total n=72), to assess safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of HM15211 compared to placebo. Study drug will be administered weekly over a period of 12 weeks.
Phase of Development	1
Number of Study Sites	Up to 8 sites
Subjects	Obese Subjects with NAFLD in Part 1
Number of Subjects	Approximately up to 72 subjects, divided in up to 6 cohorts with 12 subjects per cohort.
Route of Administration	All study drugs will be administered by subcutaneous (SC) injection into the abdominal wall on a weekly basis.
Duration of Participation	The duration of participation in this study including Screening, Treatment and Follow-up will be approximately 23 weeks for each subject including 12 weeks of treatment period.
Primary Objectives and Endpoints	To assess safety and tolerability of HM15211 after administration of multiple SC doses in obese subjects with NAFLD by: • Incidence of adverse events (AEs) (cardiovascular [CV] events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal [GI] events, and gallstone formation [cholelithiasis] will be managed following separate AE guidance document) • Incidence of clinical lab abnormalities (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin)

	• Immunogenicity (Anti-drug antibodies [ADAbs], neutralizing antibodies [nAbs], anti-polyethylene glycol antibodies [anti-PEG]) • Incidence and severity of clinical findings on physical examination • Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature]); BP assessed by 24-hour ambulatory blood pressure monitoring (ABPM); HR assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG; central reader) • Change from baseline in 12-lead ECG parameters; the primary ECG endpoint will be QTcF • Injection site reactions To assess the pharmacokinetic (PK) profile of HM15211 after administration of multiple SC doses in obese subjects with NAFLD by, but not limited to: • Maximum concentration (C_{max}) • Time to reach C_{max} (t_{max}) • Trough plasma concentration (C_{trough}) • Area under the concentration-time curve (AUC), eg, AUC_{0-t} at steady state • Terminal elimination rate constant (k_{el}) • Terminal half-life (t1/2) • Apparent clearance (CL/F) • Apparent volume of distribution (Vz/F) To assess a reduction of liver fat after administration of multiple doses in obese subjects with NAFLD by: • Absolute and % changes of fat on magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF)
Exploratory Objectives and Endpoints	To assess additional PD properties of HM15211 after multiple SC doses in comparison to placebo by: • Incretins / metabolic hormones o Glucagon-like peptide-1 (GLP-1)

	○ Gastric inhibitory peptide (GIP) ○ Glucagon ○ Fibroblast growth factor 21 (FGF21) ○ Leptin • Body weight and body mass index (BMI) • Waist circumference • Serum lipid profile and particles ○ Total cholesterol ○ Low-density lipoprotein (LDL), LDL-C, LDL-P (particles), ○ High-density lipoprotein (HDL), HDL-C, HDL-P (particles) ○ Very low-density lipoprotein (VLDL), VLDL-C, VLDL-P (particles) ○ Triglycerides ○ Free Fatty Acids (FFAs) • Amino acid profile • Inflammatory markers ○ Adiponectin • Bone metabolism parameters ○ Fasting carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX-1) ○ Osteocalcin (OC) ○ Procollagen type 1 N-terminal propeptide (P_1NP) • Glucose metabolism parameters: ○ Fasting plasma glucose (FPG) ○ Fasting insulin, fasting C-peptide ○ HbA1c • Ketone bodies: ○ Beta-hydroxybutyrate (BHB) • Changes in liver steatosis and liver stiffness assessed by FibroScan® (VCTE), determined as absolute and percent change from baseline in controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) • Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI imaging

Summary of Study Design	The study includes a randomized, single-blind, placebo-controlled, multiple-ascending dose study to investigate the safety, tolerability, and PK of SC administration of HM15211 in approximately up to 72 (n=12/cohort) obese subjects with NAFLD. To assess the effect of multiple SC doses of HM15211 in obese subjects on: 1. Change in % liver fat, assessed by MRI-PDFF in obese subjects with pre-existing % liver fat >10% (determined by MRI-PDFF). The study will be conducted in up to 6 dosing cohorts that might partially overlap, enrolling 12 subjects per cohort. Subjects will be randomized to HM15211 or placebo in a ratio of 3:1 (9 on active, 3 on placebo). Dose escalation to the next dose will proceed based on safety and tolerability and available PK data. After 2-4 weeks treatments of at least 3/4 (n=9) active participating subjects of previous dose, safety and available blinded PK/PD data will be reviewed to decide on beginning the next cohort. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels. **Screening:** A Screening Visit will be performed up to 44 days prior to the first dosing to identify subjects for the study. All screening evaluations except MRI-PDFF will be performed. Only eligible subjects will undergo an MRI-PDFF for the assessment of liver fat within 30 days of randomization. Subjects who meet the inclusion criteria of >10% liver fat will proceed with the study and will be invited for the In-house Period 1. For subjects in cohort 1-5 and up: Only eligible subjects will undergo an MRI/MRI-PDFF for the assessment of liver fat and visceral fat within 30 days of randomization. Subjects who meet the inclusion criteria of >10% liver fat will proceed with the study and will be invited for the In-house Period 1. **In-house Period 1:** Day -2: Subjects will check in to the clinic in the morning on Day -2 for a 10-day In-house Period. They will receive standardized meals throughout their inpatient stay. Subjects will be connected to an ABPM system, and overnight measurements will be taken to

	familiarize the subjects with the device. ABPM measurements will continue throughout Day 5. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation. Day -1: In the morning, subjects will be connected to a Holter ECG for 24-hour measurements and will continue these until Day 5. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation. Subjects will be randomized to a weekly SC injection of HM15211 or placebo. Day 1: The active study drug or placebo, will be administered in the morning at approximately 08:00 hours (t=0), SC into the abdominal wall by qualified study staff. Measurements of vital signs, sampling for PK at pre-dose and 8 hours after dosing, and pre-dose sampling for laboratory parameters including incretins/metabolic hormones, lipid profiles and particles, amino acid panel, inflammatory marker, glucose metabolism parameters, ketone bodies and evaluations for safety parameters will be performed. ABPM and Holter ECG monitoring will be continued until the morning of Day 5 for the post-dose evaluation. Subjects will continue to stay in-house for safety evaluations and PK. They will be released from the clinical research unit (CRU) on Day 8, after the second dose of the weekly study drug is administered. They will return for multiple outpatient visits. **Outpatient Visits:** Subjects will return to the CRU every week (Days 10, 15, 22, 29, 36, 43, 50, 57, 64, 71) in order to undergo assessments as described in the SOE. Subjects will receive the injection of the study drug in an outpatient fashion to ensure compliance on days 15, 22, 29, 36, 43, 50, 57, 64 and 71. MRI/MRI-PDFF: Subjects will undergo an MRI/MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing. During all outpatient visits, blood samples for PK analysis, exploratory endpoints and safety assessments as stated in the SOE will occur. **In-house Period 2:**

	Day 77: Subjects will check in to the clinic in the morning on Day 77 for a 5-day In-house Period. They will receive standardized meals throughout their inpatient stay. Subjects will be connected to an ABPM system, and overnight measurements will be taken to familiarize the subjects with the device. ABPM measurements will continue throughout Day 82. Day 78 to Day 82: In the morning, subjects will be connected to a Holter ECG for 24-hour measurements and will continue these until Day 82. A sample for the assessment of PK will be collected pre-dose for PK_{trough}. Study drug will be administered. Measurements of vital signs, sampling for PK and sampling for laboratory parameters and evaluations for parameters for safety parameters will be performed. Subjects will continue to stay in-house for safety evaluations and PK. They will be disconnected from Holter monitoring and ABPM on Day 82 and will be released home in the morning of Day 82, after the PK sample has been collected. For subjects participating in cohort 1-3, the in-house stay until day 82 is optional. These subjects will continue to stay in-house for safety evaluations and PK until Day 81, after they are disconnected from Holter monitoring and ABPM. Subjects will undergo an MRI/MRI-PDFF assessment to assess liver fat during week 12, as close as possible to Day 85. For subjects in cohort 1-5 and up, visceral fat will be assessed additionally during the imaging procedure. Outpatient Visits: Subjects will return to the CRU during elimination phase of the drug on Days 85 and 99. On Day 85, measurements of vital signs, sampling for laboratory parameters including incretins/metabolic hormones, lipid profiles and particles, amino acid panel, bone metabolism parameters, glucose metabolism parameters, inflammatory marker, ketone bodies, local injection site evaluation, and evaluations for safety parameters will be performed for the assessment after 12 weeks of dosing. For subjects in cohort 1-4 and up, a FibroScan assessment will be performed additionally. On Day 99, sampling for PK, PD and safety will be performed as stated in the SOE. **Follow-up Visit:**

<table>
<tr><td></td><td>A follow-up visit will take place on Day 113 (± 2) to collect final safety assessments and the last PK sample.</td></tr>
<tr><td>Treatment</td><td>Sample Treatment Schedule:
<table>
<tr><th>Cohorts</th><th>Number of Subjects</th><th>Treatment Period</th></tr>
<tr><td rowspan="2">Cohort 1-1</td><td>N=9</td><td>HM15211 0.01 mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
<tr><td rowspan="2">Cohort 1-2</td><td>N=9</td><td>HM15211 0.02 mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
<tr><td rowspan="2">Cohort 1-3</td><td>N=9</td><td>HM15211 0.04 mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
<tr><td rowspan="2">Cohort 1-4</td><td>N=9</td><td>HM15211 0.06 mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
<tr><td rowspan="2">Cohort 1-5</td><td>N=9</td><td>HM15211 X mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
<tr><td rowspan="2">Cohort 1-6</td><td>N=9</td><td>HM15211 0.12 mg/kg</td></tr>
<tr><td>N=3</td><td>Matching Placebo</td></tr>
</table></td></tr>
<tr><td>Inclusion Criteria</td><td>Subjects who meet all criteria at Screening will be included in the study:

Adults ≥ 18 to ≤ 65 years.
Body mass index (BMI) ≥ 30 kg/m^2, with stable body weight by history for 3 months (defined as change < 5%).
Waist circumference ≤ 57 inches.
Fasting Plasma Glucose < 7 mmol/L (126 mg/dL).
HbA1c < 6.5%.
CAP ≥ 300 dB/m by FibroScan. (Subjects with matching results within 30 days prior to screening don’t need to undergo this procedure). Subjects with CAP 275-299 dB/m may proceed to MRI with CRO approval pending review of medical history and lab data.
Liver fat by MRI-PDFF ≥ 10%.
</td></tr>
</table>

	8. Female subjects must be non-pregnant and non-lactating. Females of child bearing potential must use highly effective contraceptive methods, stable at least 2 months prior to the screening. 9. Male subjects must be surgically sterile, abstinent or if engaged in sexual relations of child-bearing potential, the subject and his partner must use an acceptable method of contraception. 10. Ability and willingness to comply with all protocol procedures (e.g., correct handling of investigational product, compliance to visit schedule and dietary advice, and complete trial-related questionnaires).
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from the study: 1. Subjects with a history of or active chronic liver disease due to alcohol, auto-immune, HIV, HBV or active HCV-infection or NASH disease. 2. Any history of clinically significant chronic liver disease including esophageal varices, ascites, encephalopathy or any hospitalization for treatment of chronic liver disease; or Model for End Stage Liver Disease (MELD) ≥ 10. 3. Previous surgical treatment for obesity (bariatric surgery, gastric banding, etc.) or any other gastrointestinal surgery that may induce malabsorption, history of bowel resection > 20 cm, any malabsorption disorder, severe gastroparesis, any GI procedure for weight loss (including LAP-BAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe gastrointestinal reflux disease [GERD]) at Screening. 4. Pacemaker, implanted electronic devices, metal fragments, aneurysm clips in the brain that could interfere with the MRI examination. 5. Use of any prohibited concomitant medication (as listed in the table Prohibited Medication below) from time points specified until completion of the study. 6. Uncontrolled hypertension, defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening (reading may be repeated on a different day). (Subjects with uncontrolled hypertension

	may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy). 7. Any weight control treatment within 3 months prior to Screening. 8. Participation in an investigational study within 30 days prior to dosing or 5 half-lives within the last dose of investigational product whichever is longer. 9. Personal history or current diagnosis of acute or chronic pancreatitis or factors for pancreatitis, such as a history of cholelithiasis (without cholecystectomy) or alcohol abuse. 10. History of major depression, anxiety, suicidal behavior or attempts, or other psychiatric disorder (within 2 years of screening), requiring medical treatment, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, lithium. 11. History of any major surgery within 6 months prior to screening. 12. History of any serious adverse reaction or hypersensitivity to study drugs components. 13. History or current diagnosis of heart disease, defined as symptomatic heart failure (New York Heart Association class III or IV), myocardial infarction, unstable angina requiring medication, transient ischemic attack, cerebral infarct, or cerebral hemorrhage or invasive cardiovascular procedure, such as coronary artery bypass graft surgery (CABG), or angioplasty/percutaneous coronary intervention (PCI) within 6 months of screening. (A diagnostic cardiac catheterization without any intervention does not exclude the subject.) 14. Presence of clinically significant ECG findings (eg, QTcF > 450 msec for males, QTcF > 470 msec for females, LBBB) at Screening, or cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening. 15. Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2).

	16. Abnormal laboratory results: a) for fasting triglycerides >1000 mg/dL. Elevated values may be repeated once on a separate day. b) for pancreatic function, suggestive of pancreatic impairment (eg, amylase and lipase >3 x ULN). c) for calcitonin levels > 20 pg/mL. d) Transaminases (AST, ALT) > 3X ULN. 17. History of renal disease or abnormal kidney function tests at Screening (glomerular filtration rate [GFR] < 60 mL/min/1.73m^2 as estimated using the MDRD equation). 18. History of any active infection, other than mild viral illness within 30 days prior to dosing as judged by the Investigator. 19. History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year. Average daily drinking of ≥ 4 units/day for men and ≥ 3 units/day for women or are unwilling to stop alcohol consumption from 24 hours prior to each check-in for in-house and outpatient visits and throughout the in-house periods until discharged from the clinical research unit (CRU) and are unwilling to limit alcohol consumption during outpatient periods. Positive alcohol test at Screening. (One unit of alcohol equals about 250 mL of beer, 90 mL of wine, or 25 mL of spirits). 20. Daily use of more than 10 cigarettes/day, or 2 cigars/day, or equivalent use of any tobacco product within 6 weeks prior to Screening. 21. Frequent use of marijuana within 6 weeks, or clinically under the effect at Screening, as per Investigator evaluation. 22. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody. 23. Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study. 24. Presence of clinically significant physical exam, ECG or laboratory finding at screening that, in the opinion of the

Investigator, may interfere with any aspect of study conduct or interpretation of results.

25. Donation or loss of > 500 mL of blood or blood product within 56 days of dosing.
26. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
27. Is employed by Hanmi or [redacted] (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of Hanmi or [redacted], defined as a spouse, parent, sibling, or child, whether biological or legally adopted.

Prohibited Medication

Medication or Class	Indication/Reason	From time point specified until the end of the study
Antihypertensive medication	Hypertension	Excluded unless on stable dose for at least 3months prior to screening
Statins	Hyperlipidemia	Excluded unless on stable dose for at least 3 months prior to screening
Oral or systemic long-acting corticosteroids	Eg, chronic or acute non-infectious inflammatory conditions, auto-immune diseases	Within 3 months prior to screening
Antacids, anticholinergics, antispasmodics (eg, modafinil, phenytoin), 5HT3 antagonists, dopamine antagonists, or opiates, antiemetics	Reduction/modification of GI motility	Within 2 weeks prior to screening

	Orlistat, lorcaserin, sibutramine, etc., including over-the-counter and herbal supplements, or any medication with a labelled indication for weight loss or gain	Weight control treatment	Within 3 months prior to screening.
	Any anti-diabetic medication	Diabetes	Any prior treatment
	Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, lithium.	Depression, anxiety, psychiatric disorders	Current treatment
	Use of SSRIs and SNRIs (including bupropion)	For reasons other than active psychiatric indications (eg, migraine, weight loss, smoking cessation)	Within 3-month prior to screening.
Statistical Methods	Data analyses will follow a statistical analysis plan (SAP). PK and PD assessments for all dose groups will be analyzed using descriptive and comparative statistical methods. No formal sample size calculation will be performed. 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.		

3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ABPM	Ambulatory blood pressure measurement
ADAbs	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
Anti-PEG	Anti-polyethylene glycol antibody
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BG	Blood glucose
BHB	Beta-hydroxybutyrate
BMI	Body mass index
BUN	Blood urea nitrogen
BP	Blood pressure
BW	Body weight
CDM	Clinical data management
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRF	Case report form
CRO	Clinical Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CV	Coefficient of variation
DFT	Deviation from target
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic CRF
FDA	Food and Drug Administration
FFA	Free fatty acid
FGF	Fibroblast growth factor
FPG	Fasting plasma glucose
FSFV	First subject first visit
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose dependent insulinotropic polypeptide/ gastric inhibitory peptide
GLP-1	Glucagon-like peptide
HbA_{1C}	Glycosylated hemoglobin
HbsAg	Hepatitis B surface antigen

HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HR	Heart rate
HRV	Heart rate variability
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
lb	Pound
LBBB	Left brunch bundle block
LDL	Low-density lipoprotein
LS mean	Least square mean
LSM	Liver stiffness measurement
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
Mg	Milligram
MRI-PDFF	Magnetic resonance imaging-estimated proton density fat fraction
nAbs	Neutralizing antibodies
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCA	Non-compartmental analysis
NDA	New Drug Application
nmol	nanomol
NN	Normal to normal
PD	Pharmacodynamics
PE	Physical examination
PEG	Polyethylene glycol
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDANN	Standard deviation of the 5-minute average NN interval
SDNN	Standard deviation of all normal intervals

SDNN index	Mean of standard deviations of all NN intervals for all 5 min segments of the entire recording.
SOE	Schedule of event
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum serum concentration (in concentration time curve)
TSH	Thyroid-stimulating hormone
U	Unit
ULN	Upper limit of normal
US	United States
USP	Unites States Pharmacopeia
VCTE	vibration controlled transient elastography
VLDL	Very low-density lipoprotein
Vz/F	Apparent volume of distribution at terminal phase
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Excess weight has become an epidemic disease and impairs the health of more than 1.9 billion adults, of whom 650 million are obese, defined by a. BMI of ≥ 30kg/m^2. This represents about 13% of the world's adult population.[1]

Obesity impacts many organ systems. One affected system is the cardiovascular system, with an increased prevalence of heart failure, hypertension and coronary heart disease. Obstructive sleep apnea and asthma are also common in the obese. Non-alcoholic fatty liver disease (NAFLD), including non-alcoholic steatohepatitis (NASH), is on the rise and may soon become the leading cause of cirrhosis and hepatocellular carcinoma globally. Psychosocial and psychiatric consequences of obesity are also increasing.[2]

Dual agonists have been developed that co-target the glucagon and glucagon like peptide (GLP-1) receptors for obesity treatment.[3] Additionally, triple agonists, which have added a gastric inhibitory polypeptide receptor (GIPR) agonist to the combination, are under development in early phase clinical studies.

HM15211 is a novel long-acting triple incretin agonist. It is a chemical conjugate of a chimeric peptide (GLP-1/Glucagon/GIP triple agonist; named TA15211) and human immunoglobulin G4 Fc fragment (named HMC001) linked via a bifunctional [redacted] linker molecule.

[redacted]

HM15211 is a long-acting GLP-1/Glucagon/GIP triple agonist with an extended half-life through reduced renal clearance and possibly by vascular endothelial recycling via FcRn binding. HM15211 showed triple-agonistic properties with potent glucagon activity in addition to balanced GLP-1 and GIP activity.

According to series of in vivo pharmacologic studies, HM15211 can be an attractive treatment option for obese patients based on its potent body weight loss efficacy from

energy intake inhibition and energy expenditure enhancement. Glucagon activity provides potent body weight loss primarily from fat mass reduction as shown in efficacy studies in diet-induced obesity (DIO) mice. Furthermore, GLP-1/GIP activities negate a possible hyperglycemic risk as demonstrated in intra-peritoneal glucose tolerance test (ipGTT) studies in normal and DIO mice.

Above all, liver preferential distribution, and subsequent hepatic lipid metabolism improvement, renders HM15211 a suitable therapeutic option for NASH and hepatic fibrosis. Therefore, HM15211 is expected to have favorable therapeutic profiles in both obesity and NASH as well as convenience in its weekly clinical dosing regimen.

For further information please refer to the Investigator's brochure (IB).

4.2 Rationale for the Proposed Study

The aim of this multiple ascending dose study is to investigate safety and tolerability of the drug as well as the PK and PD profiles in obese subjects with NAFLD. Up to 6 cohorts in obese subjects with NAFLD will compare HM15211 to placebo.

Adverse effects observed in the ongoing single ascending dose study (HM-TRIA-101), include so far GI events of nausea and vomiting. The management of any cardiac event, dermatitis, cholelithiasis and GI events will follow a specific adverse event management plan as provided in section 17.0.

Based on the pre-clinical data and the conducted single ascending dose study (HM-TRIA-101), the intended potential target populations will ensure that a robust and relevant set of safety, PK and PD data can be generated.

4.3 Summary of Pre-Clinical/Clinical Studies

In vitro activity of HM15211 was evaluated using respective receptors, human GLP-1 receptor (hGLP-1R), human glucagon receptor (hGlucagonR), and human GIP receptor (hGIPR). HM15211 showed dose-dependent activation of all three receptors with potent glucagon activity in addition to balanced GLP-1 and GIP activity. Simultaneous activation of three incretin receptors could provide synergistic metabolic benefits on body weight loss and lipid profile improvement whilst avoiding hyperglycemic risk.

Further in vitro studies confirmed that since HM15211 includes an aglycosylated Fc moiety derived from human IgG4, there are minimal immune-mediated effector functions. In addition, due to Fc moiety, HM15211 retained pH-dependent FcRn binding property, which is essential for vascular endothelial recycling.

In vivo pharmacology studies using obese mice showed that HM15211 enables potent body weight loss from both food intake inhibition and enhanced energy expenditure. The body weight loss was mainly from fat mass reduction, along with lowered serum lipid profile. Glucagon action increased energy expenditure and thus enhanced body weight loss; hyperglycemic risk by glucagon was effectively buffered by actions of GLP-1/GIP. In NASH-induced models, HM15211 effectively reduced hepatic triglycerides (TG),

oxidative stress and inflammatory markers. Furthermore, HM15211-treated animals showed significant reduction in NAFLD activity score and hepatic fibrogenic markers, suggesting HM15211 is an effective pharmacotherapy for NASH with hepatic fibrosis.

Safety pharmacology studies were conducted to evaluate the effects on the cardiovascular, respiratory, central nervous systems and in vitro hERG channel assay. No significant effect was observed in the safety pharmacology studies and in vitro human ether-a go-go related gene (hERG) channel assay.

In pharmacokinetic studies, HM15211 exhibited a prolonged half-life (t½) after subcutaneous (SC) or intravenous (IV) dosing, which ranged from approximately 42.7 to 85.6 hours in mice, 74.7 to 86.0 hours in rats, and 35.7 to 79.7 hours in dogs, indicating that HM15211 is a long acting triple-agonist. HM15211 is preferentially distributed in the liver, making HM15211 a favorable treatment option for dysfunction in lipid metabolism specifically in the liver.

The toxicity studies of HM15211, repeat dose toxicity up to 4 weeks in rats and monkeys, and in vitro genotoxicity studies, were conducted. Local tolerance of HM15211 was investigated in 4-week repeated rat and monkey studies. Additional studies were conducted with HMC001 (inactive ingredient) in rat and monkey up to 4 weeks repeat dose toxicity studies.

No target organ was identified during the 4 weeks repeat dose toxicity studies of HM15211. All changes were completely or partially reversible during the recovery period.

The majority of findings were related to fasting effect or pharmacological effect of glucagon. No adverse test article-related findings at the injection sites were noted. No adverse events were observed in HMC001 studies.

Treatment emergent adverse events observed in the HM-TRIA-101 study and thought to be related to study drug are primarily gastrointestinal, specifically nausea and vomiting. Most GI adverse events were mild in severity; no cardiac or drug-related dermatologic adverse events have been noted up to this point.

4.4 Rationale for Starting and Maximum Dose

Doses up to 0.12 mg/kg were evaluated in the single dose HM-TRIA-101 study. The steady state weekly AUC (AUC_{168SS}) after multiple dosing can be approximated to the AUC_{inf} after single dosing. From the HM-TRIA-101 study, the maximum AUC_{inf} after single dosing in the 0.12 mg/kg group was 126,281 ng*h/mL. In the 13 week rat toxicology study, the AUC_{168} exposure during the 13^{th} week was 297,000 ng*h/mL at the rat NOAEL dose of 0.4 mg/kg. At the highest proposed dose in this study, the ratio would be (297,000/126,281) = 2.4

Moreover, clinical issues including skin lesions, gastrointestinal adverse events (nausea and vomiting) and an elevation in fasting plasma glucose are known to occur as

exaggerated pharmacology with glucagon agonists such as HM15211. All of these clinical signs and symptoms are easily monitored, and are reversible.

4.5 Dose Escalation Algorithm

The proposed dose escalation algorithm may include the following steps:

Table 4-1 Treatment Allocation and Dose Escalation (NAFLD)

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

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

Each subject will be randomized to HM15211 or placebo according to the table above. The dose for the weekly dosing in cohort 1-1 will be 0.01 mg/kg, based on the body weight measured prior to the first dosing on Day -1. For dose calculation and rounding, please refer to the Operations Manual/Pharmacy Manual.

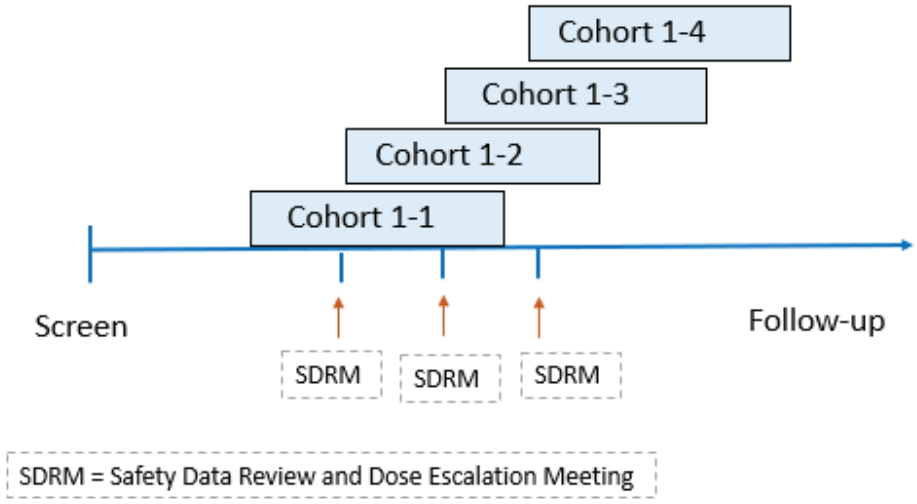
After at least ¾ (n=9) of the subjects participating in one cohort have completed 2-4 weeks of treatment (2 weeks of treatment is reached at Visit week 3), an interim data review meeting will be held which may include a dose escalation decision. Safety and available blinded PK and/or PD data will be reviewed, and predictions based on results

from the previous study and PK/PD data modelling will be used for a dose decision/ dose escalation decision for the subsequent cohort. The dose decision will be made by the Sponsor, medical monitor and the coordinating Principal Investigator. Dose escalation will not exceed a 2-fold increase. If there are no safety concerns, the next cohort may start and may partially overlap with the previous one. An additional data review meeting may be held at the end of the completed cohort. The maximum dose for cohort 1-3 will not exceed 0.04 mg/kg. The dose for cohort 1-4 will be 0.06 mg/kg. The maximum dose for the study will not exceed 0.12 mg/kg.

Following the dose escalation decision, the procedures for the subsequent cohorts will be identical to those described above. Therefore, all cohorts could be performed in parallel.

The blind of the study will be maintained throughout. If dose escalation is stopped, dose de-escalation may occur for additional cohorts, to further refine the dose.

Figure 4-1 Dose Escalation Schematic



Optional adjustments

Optional adjustments to the number of cohorts:

If the first 3 cohorts do not provide sufficient data for the dose selection, optional cohorts may be added. The optional cohorts may proceed with a higher dose or a lower dose. If deemed appropriate, another cohort with the repetition of the same dose may be conducted.

Optional adjustments to the study visits and sampling schedule:

Depending on the safety and tolerability and/or on available PK/PD results of the first cohorts, additional study visits might be performed, or existing visit schedule or PK/PD sampling schedule may be adjusted/rescheduled for following cohorts.

5.0 STUDY OBJECTIVES

5.1.1 Primary Objectives and Endpoints

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

- Incidence of adverse events (AEs) (cardiovascular [CV] events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal [GI] events, and gallstone formation [cholelithiasis] will be managed following separate AE guidance document)
- Incidence of clinical lab abnormalities (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin)
- Immunogenicity (Anti-drug antibodies [ADAbs], neutralizing antibodies [nAbs], anti-polyethylene glycol antibodies [anti-PEG])
- Incidence and severity of clinical findings on physical examination
- Change from baseline in vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and temperature]);
  BP assessed by 24-hour ambulatory blood pressure monitoring (ABPM);
  HR assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG; central reader)
- Change from baseline in 12-lead ECG parameters; the primary ECG endpoint will be QTcF
- Injection site reactions

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

- Maximum concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Trough plasma concentration (C_{trough})
- Area under the concentration-time curve (AUC), eg, AUC_{0-t} at steady state
- Terminal elimination rate constant (k_{el})
- Terminal half-life (t1/2)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V_z/F)

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

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

5.1.2 Exploratory Objectives and Endpoints

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

- Incretins / metabolic hormones
  - Glucagon-like peptide-1 (GLP-1)
  - Gastric inhibitory peptide (GIP)
  - Glucagon
  - Fibroblast growth factor 21 (FGF21)
  - Leptin
- Body weight and body mass index (BMI)
- Waist circumference
- Serum lipid profile and particles
  - Total cholesterol
  - Low-density lipoprotein (LDL), LDL-C, LDL-P (particles),
  - High-density lipoprotein (HDL), HDL-C, HDL-P (particles)
  - Very low-density lipoprotein (VLDL), VLDL-C, VLDL-P (particles)
  - Triglyceride
  - Free Fatty Acids (FFAs)
- Amino acid profile
- Inflammatory marker
  - Adiponectin
- Bone metabolism parameters
  - Fasting carboxy-terminal crosslinked telopeptide of type $_1$ collagen (CTX-$_1$)
  - Osteocalcin (OC)
  - Procollagen type $_1$ N-terminal propeptide (P_1NP)
- Glucose metabolism parameters:
  - Fasting plasma glucose (FPG)
  - Fasting insulin, fasting C-peptide
  - HbA1c
- Ketone bodies
  - Beta-hydroxybutyrate

- Changes in liver steatosis and liver stiffness assessed by FibroScan® (VCTE), determined as absolute and percent change from baseline in controlled attenuation parameter (CAP) and liver stiffness measurements (LSM)
- Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI imaging

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a randomized, placebo-controlled, multiple-ascending dose study to investigate the safety, tolerability, PK and PD of SC administration of HM15211, conducted in 1 part.

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

Based on available safety, tolerability, and PK data of each cohort, and following a safety review and dose escalation meeting between the investigator and the sponsor, dose escalation to the next cohort may proceed. Cohorts will start in sequential order but may overlap partially during execution. Replacement of dropouts and withdrawals may take place.
Each subject will undergo a screening visit, 2 in-house/ treatment periods and multiple outpatient visits. A final follow-up visit that will conclude subject study participation.

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

Figure 6-1 Study Design Schematic Cohorts 1-1 to 1-3

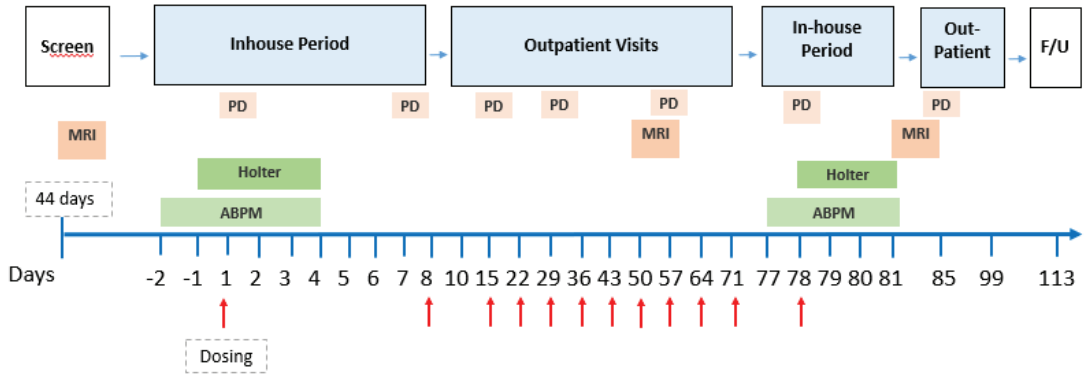
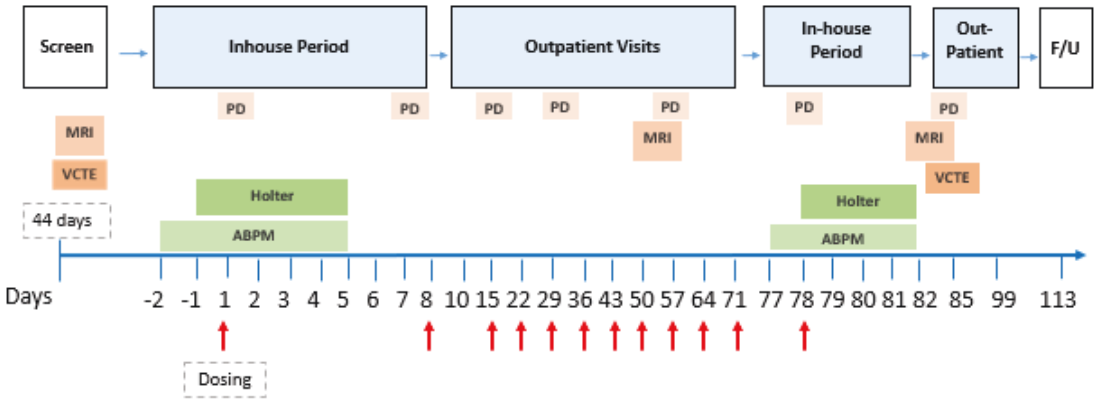


Figure 6-2 Study Design Schematic Cohort 1-4 and up



***Day 82 is optional for subjects in cohort 1-3**

6.2 Study Description

Each subject will undergo the following procedures during the study:

Screening Visit:

Before the screening takes place, potential subjects for the trial will be provided with written and oral information about the trial and the procedures involved. Subjects must sign the informed consent form (ICF) prior to entering the study. Please see section 9.1.1 for further details.

The screening visit will be performed up to 44 days prior to the first dosing day, to identify eligible subjects for the study. All assessments performed at the screening visit are stated in Table 16-1 and will be recorded in the electronic case report form (eCRF). Please see section 9.1.2 and 11.2 for further details.

Subjects' screening lab parameters and VCTE (CAP) scores will be evaluated to identify subjects who are likely to have a liver fat content of > 10% at MRI-PDFF. Depending on the outcome/results of these values, the subjects will proceed to MRI/MRI-PDFF. For further details on parameters and outcome for the determination to proceed to MRI/MRI-PDFF see the Operations Manual. Subjects who are not able to proceed to MRI-PDFF will be recorded as screening failures.

In-house Period 1:

Day -2: Subjects will check in to the clinic in the morning of Day -2 for a 10-day in-house period. They will receive standardized meals throughout their in-house stay. A 12-lead standard ECG will be performed. Subjects will be connected to an ABPM system for measurement of blood pressure (BP), and measurements will be started overnight on Day -2 to familiarize the subjects with the device. Measurements will continue until the morning of Day 5.

Day -1: In the morning of Day -1, subjects will get connected to a Holter ECG for continued measurement of the heart rate activity until the morning of Day 5.

Only 24-hour monitoring data from Day -1 to Day 1 will be used for the monitoring evaluation as baseline assessments for ABPM and Holter ECG monitoring. For measuring timepoints, please see sections 9.1.14 and 9.1.15.

Subjects will be randomized to weekly SC injections of HM15211 or placebo. Randomization will take place as close to the drug administration as possible.

Day 1: On Day 1, after an ≥ 10 h overnight fast, subjects will be dosed with HM15211or placebo at approximately 08:00 hours (t=0), through SC injection into the abdominal wall by qualified study staff. Measurements of vital signs, blood sampling for PK at pre-dose and 8 hours after dosing and sampling for laboratory parameters including incretins/metabolic hormones, lipid profiles and particles, amino acid panel, bone metabolism parameters, glucose metabolism parameters, ketone bodies, local injection site evaluation, and evaluations for safety parameters will be performed, at timepoints stated in Table 16-1.

ABPM and Holter ECG monitoring will be continued until the morning of Day 5 for the post-dose evaluation.

Subjects will continue to stay in-house for safety evaluations, PK and PD assessments as stated in the SOE. They will be released from the CRU in the morning of Day 8, after the second dose of the weekly study drug is administered. They will return for multiple outpatient visits.

Outpatient Visits:

Subjects will return to the CRU every week (Days 10, 15, 22, 29, 36, 43, 50, 57, 64, 71) in order to undergo assessments as described in Table 16-1. Subjects will receive the injection of the study drug in an outpatient fashion to ensure compliance on Days 15, 22, 29, 36, 43, 50, 57, 64 and 71.

MRI/MRI-PDFF: Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing.

During all outpatient visits, blood samples for PK analysis, exploratory endpoints and safety assessments will be performed as stated in the Table 16-1.

In-house Period 2:

Day 77: Subjects will check in to the clinic in the morning on Day 77 for a 5-day In-house Period. They will receive standardized meals throughout their inpatient stay. Subjects will be connected to an ABPM system, and overnight measurements will be taken to familiarize the subjects with the device. ABPM measurements will continue throughout Day 82.

Day 78 to 82: In the morning of Day 78, subjects will get connected to a Holter ECG for 24-hour measurements and will continue these until Day 82. Sample for the assessment

of PK will be collected pre-dose for PK_{trough}. Study drug will be administered. Measurements of vital signs, sampling for PK, sampling for laboratory parameters and evaluations for safety parameters will be performed as stated in the SOE

Subjects will continue to stay in-house for safety evaluations and PK. They will be disconnected from Holter monitoring and ABPM on Day 82 and will be released home in the morning of Day 82, after the PK sample has been collected.

For subjects participating in cohort 1-3, the in-house stay until day 82 is optional. These subjects will continue to stay in-house for safety evaluations, PD and PK until Day 81, after they are disconnected from Holter monitoring and ABPM.

Subjects will undergo an MRI/MRI-PDFF assessment to assess liver fat during week 12, as close as possible to Day 85. For subjects in cohort 1-5 and up, visceral fat will be assessed additionally during the imaging procedure.

Outpatient Visits:

Subjects will return to the CRU during elimination phase of the drug on Days 85 and 99. On Day 85, measurements of vital signs, sampling for laboratory parameters including incretins/metabolic hormones, lipid profiles and particles, amino acid panel, bone metabolism parameters, glucose metabolism parameters, inflammatory markers, ketone bodies, local injection site evaluation, and evaluations for safety parameters will be performed for the assessment after 12 weeks of dosing. For subjects in cohort 1-4 and up, a FibroScan assessment will be performed additionally, as stated in the SOE.

On Day 99, sampling for PK, PD and safety will be performed as stated in the SOE.

Follow-up Visit:

A Follow-up Visit will be performed on Day 113 (± 2) to collect final safety assessments and the last PK sample. Please see Table 16-1 Schedule of Events for details.

Sampling and Assessment:

Time points for study procedures and sample collection are specified in the Table 16-1.

Safety assessments will occur throughout the duration of the study, including monitoring of adverse events (AEs), clinical laboratory tests (eg, chemistry, hematology, coagulation, amylase, lipase and urinalysis), vital signs measurements (blood pressure, heart rate, respiration rate, and aural/oral temperature), 12-lead electrocardiograms (ECGs), ABPM, Holter ECG monitoring, and physical examinations.

Local tolerability assessments will be performed by injection site inspection at specific time-points as stated in the Table 16-1.

Immunogenicity samples for assessment of ADAbs, nAbs and anti-PEG will be taken prior to first dosing on Day 1, on Days 22, 50, 78, 85 and 99 as stated in the Table 16-1.

The PK samples will be taken in accordance with the PK sampling schedule in section 9.1.16. Sampling may be adjusted based on the results of the SDRM.

The PD samples will be taken in accordance with the PD sampling schedule in section 9.1.17. Sampling time points may be adjusted based on the results of the SDRM.

Follow-up Visit:

A follow-up visit will take place on Day 113 (± 2) in order to collect final safety assessments and the last PK sample.

6.3 Rationale for Study Design and Endpoints

This MAD study will assess the safety and tolerability, PK and PD of HM15211 in obese subjects with NAFLD compared to placebo.

Cohorts will be assessed in ascending order, but may overlap, to determine a clinically appropriate dose for the subjects and will include the comparison with placebo.

Randomization is used to avoid bias introduced through an association between study drug allocation order and subject characteristics.

A single-blind design has been chosen to avoid bias and to maintain the blind between the administration of the study drug and placebo for subjects and clinical staff.

Obese subjects with NAFLD will participate in the study, as these subjects are an important target population for the novel triple agonist. Enrollment criteria will favor the target population. Liver fat will be determined by MRI-PDFF and body mass index of ≥ 30 kg/m^2.

Measurements for the assessment of cardiovascular events will start right after dosing and will continue until Day 5.

The proposed PK endpoints are well-established, commonly used parameters to characterize pharmacological profiles of drugs. For the PK endpoints, blood samples for determination of HM15211 will be analyzed using a validated assay.

This is an exploratory study. No formal sample size calculation and no statistical hypothesis testing will be performed.

6.4 Study Discontinuation and Stopping Criteria

6.4.1 Dose Escalation Criteria

Dose decision algorithms:

- The primary tolerability criterion for decision-making will be emesis/vomiting (= GI tolerability).
- As emesis has been shown to be associated with pharmacological doses of GLP-1 agonists and glucagon, the severity of emesis is defined as follows for this study:

- Moderate: 3 to 5 episodes in 24 hours (individual episodes separated by at least 5 min)
- Severe: ≥ 6 episodes in 24 hours (individual episodes separated by at least 5 min) or requiring iv fluids

6.4.2 Dose Escalation Stopping Criteria

Dose escalation will be stopped if one of the following conditions apply:

- 50% or more of the subjects in the cohort have experienced moderate or severe emesis;
- 25% or more of the subjects in the cohort have experienced severe emesis;
- Death of a subject in one cohort, at any time, that is considered related to the IP, judged by the Investigator;
- One (1) or more of the subjects in a cohort have experienced a serious adverse event (SAE), that is considered related to the IP, judged by the Investigator, following discussion with the medical monitor and breaking the blind;
- Two (2) or more of the subjects in a cohort have experienced severe or medically significant adverse events (eg, common terminology criteria for adverse events [CTCAE] ≥ grade 3 may be used as a grading scale at the discretion of Investigator), that is considered related to the IP, judged by the Investigator;
- Two (2) or more of the subjects in a cohort have experienced moderate adverse events for more than 7 days (eg, common terminology criteria for adverse events [CTCAE] ≥ grade 2 may be used as a grading scale at the discretion of Investigator), that is considered related to the IP, judged by the Investigator;
- Two (2) or more subjects receiving HM15211 develop similar clinically significant laboratory, significant ECG or vital signs abnormalities, or severe AEs in the same organ class, indicating dose-limiting intolerance. Dose escalation may proceed if after review of the data by the Investigator and discussion with Sponsor, it is concluded that the events are not drug related;
- It is determined that the limit of safety and/or tolerability has been reached. Decision will be made between Sponsor and the Coordinating Investigator.
- All dose escalation and stopping decisions will be made following a discussion between the Coordinating Investigator and Sponsor.

6.4.3 Criteria for Early Termination of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied

- Violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Failure to meet expected enrollment goals
- Administrative Reasons

In case that the Sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.4.4 Criteria for Early Termination of Individual Subjects

Subjects may withdraw their consent to participate in the study at any time.

If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subjects will be encouraged to remain in the clinic for safety assessments until the Investigator deems that it is safe for the subject to be discharged. Subject data will be included in the analysis up to the date of the consent withdrawal.

- AE or SAE that requires discontinuation at the discretion of the Investigator
- Protocol violation: If protocol violation or concurrent illness occurs, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the study by interfering pharmacokinetically or pharmacodynamically with the investigational products, subject will be withdrawn by the Investigator.
- Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
- Voluntary withdrawal of consent (mandatory removal from study)
- Discretion of Investigator (document reason on CRF)
- Subject becomes pregnant or begins breastfeeding (mandatory)
- Study discontinuation by Sponsor

Wherever possible, the tests and evaluations, including those listed for the Follow-up Visit should be performed for all subjects who discontinue prior to the completion of the study.

In the event the Investigator determines to terminate a subject participation in the Clinical Study, the Investigator must notify the Sponsor of such decision and rationale immediately in writing. In all cases, the appropriate IRB/IEC and other applicable regulatory authorities shall be informed.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Subjects who meet all criteria at Screening will be included in the study:

1. Adults ≥ 18 to ≤ 65 years.
2. Body mass index (BMI) ≥ 30 kg/m^2, with stable body weight by history for 3 months (defined as change < 5%).
3. Waist circumference ≤ 57 inches.
4. Fasting Plasma Glucose < 7 mmol/L (126 mg/dL).
5. HbA1c < 6.5%.
6. CAP ≥ 300 dB/m by FibroScan. (Subjects with matching results within 30 days prior to screening don't need to undergo this procedure). Subjects with CAP 275-299 dB/m may proceed to MRI with CRO approval pending review of medical history and lab data.
7. Liver fat by MRI-PDFF ≥ 10%.
8. Female subjects must be non-pregnant and non-lactating. Females of child bearing potential must use highly effective contraceptive methods, stable at least 2 months prior to the screening. Male subjects must be surgically sterile, abstinent or if engaged in sexual relations of child-bearing potential, the subject and his partner must use an acceptable method of contraception.
9. Ability and willingness to comply with all protocol procedures (e.g., correct handling of investigational product, compliance to visit schedule and dietary advice, and complete trial-related questionnaires).

7.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subjects with a history of or active chronic liver disease due to alcohol, auto-immune, HIV, HBV or active HCV-infection or NASH disease.
2. Any history of clinically significant chronic liver disease including esophageal varices, ascites, encephalopathy or any hospitalization for treatment of chronic liver disease; or Model for End Stage Liver Disease (MELD) ≥ 10.
3. Previous surgical treatment for obesity (bariatric surgery, gastric banding, etc.) or any other gastrointestinal surgery that may induce malabsorption, history of bowel resection > 20 cm, any malabsorption disorder, severe gastroparesis, any GI procedure for weight loss (including LAP-BAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe gastrointestinal reflux disease [GERD]) at Screening.

4. Pacemaker, implanted electronic devices, metal fragments, aneurysm clips in the brain that could interfere with the MRI examination.
5. Use of any prohibited concomitant medication (as listed in the table Prohibited Medication below) from time points specified until completion of the study.
6. Uncontrolled hypertension, defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening (reading may be repeated on a different day). (Subjects with uncontrolled hypertension may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy).
7. Any weight control treatment within 3 months prior to Screening.
8. Participation in an investigational study within 30 days prior to dosing or 5 half-lives within the last dose of investigational product whichever is longer.
9. Personal history or current diagnosis of acute or chronic pancreatitis or factors for pancreatitis, such as a history of cholelithiasis (without cholecystectomy) or alcohol abuse.
10. History of major depression, anxiety, suicidal behavior or attempts, or other psychiatric disorder (within 2 years of screening), requiring medical treatment, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, lithium.
11. History of any major surgery within 6 months prior to screening.
12. History of any serious adverse reaction or hypersensitivity to study drugs components.
13. History or current diagnosis of heart disease, defined as symptomatic heart failure (New York Heart Association class III or IV), myocardial infarction, unstable angina requiring medication, transient ischemic attack, cerebral infarct, or cerebral hemorrhage or invasive cardiovascular procedure, such as coronary artery bypass graft surgery (CABG), or angioplasty/percutaneous coronary intervention (PCI) within 6 months of screening. (A diagnostic cardiac catheterization without any intervention does not exclude the subject.)
14. Presence of clinically significant ECG findings (eg, QTcF > 450 msec for males, QTcF > 470 msec for females, LBBB) at Screening, or cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening.
15. Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2).
16. Abnormal laboratory results:
    a) for fasting triglycerides >1000 mg/dL. Elevated values may be repeated once on a separate day.
    b) for pancreatic function, suggestive of pancreatic impairment (eg, amylase and lipase >3 x ULN).

c) for calcitonin levels > 20 pg/mL.
d) Transaminases (AST, ALT) > 3X ULN

17. History of renal disease or abnormal kidney function tests at Screening (glomerular filtration rate [GFR] < 60 mL/min/1.73m^2 as estimated using the MDRD equation).
18. History of any active infection, other than mild viral illness within 30 days prior to dosing as judged by the Investigator.
19. History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year. Average daily drinking of ≥ 4 units/day for men and ≥ 3 units/day for women or are unwilling to stop alcohol consumption from 24 hours prior to each check-in for in-house and outpatient visits and throughout the in-house periods until discharged from the clinical research unit (CRU) and are unwilling to limit alcohol consumption during outpatient periods. Positive alcohol test at Screening. (One unit of alcohol equals about 250 mL of beer, 90 mL of wine, or 25 mL of spirits).
20. Daily use of more than 10 cigarettes/day, or 2 cigars/day, or equivalent use of any tobacco product within 6 weeks prior to Screening.
21. Frequent use of marijuana within 6 weeks, or clinically under the effect at Screening, as per Investigator evaluation.
22. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody.
23. Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study.
24. Presence of clinically significant physical exam, ECG or laboratory finding at screening that, in the opinion of the Investigator, may interfere with any aspect of study conduct or interpretation of results.
25. Donation or loss of > 500 mL of blood or blood product within 56 days of dosing.
26. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
27. Is employed by Hanmi or [redacted](permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of Hanmi or [redacted], defined as a spouse, parent, sibling, or child, whether biological or legally adopted.

7.3 Prohibited Medications

Use of the agents listed in Table 7-1 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 7-1 Prohibited Medications

Medication or Class	Indication/Reason	From time point specified until the end of the study
Antihypertensive medication	Hypertension	Excluded unless on stable dose for at least 3 months prior to screening
Statins	Hyperlipidemia	Excluded unless on stable dose for at least 3 months prior to screening
Oral or systemic long-acting corticosteroids	Eg, chronic or acute non-infectious inflammatory conditions, auto-immune diseases	Within 3 months prior to screening
Antacids, anticholinergics, antispasmodics (eg, modafinil, phenytoin), 5HT3 antagonists, dopamine antagonists, or opiates, antiemetics	Reduction/modification of GI motility	Within 2 weeks prior to screening
Orlistat, lorcaserin, sibutramine, etc., including over-the-counter and herbal supplements, or any medication with a labelled indication for weight loss or gain	Weight control treatment	Within 3 months prior to screening.
Any anti-diabetic medication	Diabetes	Any prior treatment
Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, lithium.	Depression, anxiety, psychiatric disorders	Current treatment
Use of SSRIs and SNRIs (including bupropion)	For reasons other than active psychiatric indications (eg, migraine, weight loss, smoking cessation)	Within 3-month prior to screening.

7.4 Check in Criteria

Subjects will be educated about influencing factors, such as to refrain from strenuous exercise throughout the entire course of the study, to avoid alcohol and herbal supplements, (especially 24 hours prior to dosing), caffeinated drinks (caffeine containing food and beverages 24 hours prior to dosing), smoking or medication and illness/infection.

At check-in for any in patient period(s) and outpatient visit(s), a subject will not be allowed to check in if they meet any of the following criteria and the treatment period may be rescheduled one time per Investigator discretion. The Sponsor will be notified about the rescheduling in a timely manner.

1. Positive alcohol breath test.
2. Positive urine drug screen test.
3. Positive urine pregnancy test in female subjects.
4. Any use of medicine other than any allowed concomitant medications within the last 24 hours.
5. Any medical condition that could interfere with the study, as judged by the Investigator.

8.0 STUDY MATERIALS

8.1 Investigational Products (IPs)

8.1.1 HM15211

A sterile solution of HM15211 contained in 0.52 mL pre-filled syringes will be provided. The concentration of HM15211 is 10 mg/mL as protein. HM15211 is manufactured by Hanmi Pharmaceuticals, Seoul, South Korea.

8.1.2 Placebo

Placebo is a sterile, matching solution (all components except drug substance) and free of visible particles. Placebo solution will be supplied in 0.52 mL pre-filled syringes by Hanmi Pharmaceuticals, Seoul, South Korea. Storage: 2 ℃ to 8 ℃.

8.2 Packaging, and Labeling of Investigational Products

The Sponsor or designee will provide the Investigator with the labeled IPs in accordance with specific country regulatory requirements.

The IP will be packaged and shipped to the clinical research unit (CRU) in an open label manner. Hanmi will prepare each syringe and place them in an independent paper box/carton.

For details please see the Operations Manual.

8.3 Storage and Drug Accountability of Investigational Products

All clinical material will be kept in an appropriate, limited-access, secure location.

The investigational product, and its storage and preparation instructions, will be provided by the Sponsor. The IP must be stored securely at 2 ℃ to 8 ℃ (36 °F to 46 °F) and should not be exposed to excessive heat and never be frozen. It should be protected from direct sunlight and therefore should be kept in its carton until ready to be used.

HM15211 is stable at room temperature up to 4 hours.

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drugs and supplies provided by or on behalf of the Sponsor. The CRU will destroy all used syringes of HM15211 and placebo at the CRU by the end of the study. Unused syringes of HM15211 and placebo will be processed as requested by the Sponsor by the end of the study.

The Investigator or Investigator’s authorized staff must ensure the availability of proper storage conditions. The temperature of all study drugs will be monitored over 24 hours a day, 7 days a week (24/7). In case of incorrect storage, the Sponsor and monitor must be contacted without delay.

No study drugs may be dispensed to any person not enrolled in the study.

8.4 Dose Regimen

The IPs, HM15211 or placebo will be administered after an ≥ 10 h overnight fast, by qualified staff while subjects are in the CRU. The products will be administered weekly by SC injection into a lifted skin fold of the abdominal wall. The injection needle should be placed at a 45° to 90° angle and kept in the skin fold for 5-10 seconds. Aim is to dose at approximately the same clock time (eg, at approximately 08:00 h) for all subjects. The actual clock time of dosing is defined as t=0. The actual time of each dosing will be recorded in the source documents and on the eCRFs.

Subjects who miss a dose by > 1 day, must be approved by the medical monitor before they continue with the study.

8.5 Overdose

If a study medication error occurs, it should be documented as Protocol Deviation. A brief description should be provided in the deviation, including whether the subject was symptomatic (list symptoms) or asymptomatic and whether the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the subject takes a dose of IP that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported.

Should an overdose occur, the Investigator or designee should contact the Sponsor or designee within 24 hours.

8.6 Randomization and Blinding

Subjects who meet all inclusion and exclusion criteria or check-in criteria will be assigned a subject randomization number via an Interactive Web Response System (IWRS). The system will randomize in a 3:1 ratio to HM15211 or placebo. Randomization will continue until a total of up to 72 subjects have completed the study (or until 12 subjects per cohort have completed the study).

If a subject fails to start dosing, or if a subject can't be randomized, the reason will be entered into the screening disposition page. The IWRS must be notified within 2 days that the subject was not randomized.

In the event of an emergency, e.g. when it becomes necessary for the investigator to know which study drug the subject is taking, the subject code can be broken by the investigator, preferably after consultation with the medical monitor. Emergency code breaks can be performed using the IWRS, see section 8.7.

As the study is single-blind, subjects and the clinical staff caring for the subjects are blinded to treatment. Staff involved in the data management, statistical analyses and staff from Pharmaceutical Services who are responsible for preparing the IP, will be unblinded. Unblinded staff will not be involved in the subjects' care.

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

8.7 Breaking of Blinded Code

The code for a subject may be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment decision of the subject or if demanded by the subject. The emergency code break can be performed using the IWRS.

Whenever a code is broken, the person breaking the code must record the time, date, and reason as well as his/her initials in the source documents. During un-blinding procedure in case of medical emergency, it should be ensured that no study personnel is unblinded to other subjects. Study site personnel and Sponsor personnel directly associated with the conduct of the study will not be unblinded.

If the study site needs to break the code, the sponsor should, if possible, be contacted prior to breaking the blind. In all cases, the Trial Monitor must be notified within 24 hours after an emergency unblinding.

All codes (whether broken or not) must be kept throughout the trial period. Accountability of all broken or unbroken codes (hard copy or electronic) will be performed at or after trial closure and will be maintained in the Trial Investigator's File (TIF) at the site.

9.0 STUDY PLAN

9.1 Study Procedures

9.1.1 Informed Consent and HIPAA Release

Written informed consent will be obtained from each subject prior to performing any study-specific evaluations. The HIPAA release is embedded in the informed consent document. The informed consent document is subject to review and approval by the Sponsor and will be approved by a qualified IRB. The IRB-approved document must contain, at minimum, the eight basic elements of informed consent set forth in applicable law. Only the most recently IRB-approved informed consent document must be used to consent prospective study subjects. The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, will fully inform the potential study subject of all pertinent aspects of the Clinical Study, including written information given approval/favorable opinion by the IRB/IEC.

Prior to the potential subject's participation in the Clinical Study, the written informed consent form must be signed, name filled in and personally dated by the subject and by the person who conducted the informed consent discussion, and by the Investigator. One copy of the signed and dated informed consent document will be given to the subject and the original retained by the Investigator/CRU.

9.1.2 Screening

Investigators must account for all subjects who sign informed consent forms.

Screening number will be provided and will include a 3-digit site number followed by 3-digit sequential number (i.e. 101 001).

The Investigator will keep a Subject Screening and Enrollment Log at the investigational site. Subjects who have screen failed due to laboratory abnormalities may be allowed to re-screen once at the discretion of the Investigator. Subjects who have screen failed due to out of window may be rescreened with CRO approval. A new screening number will be assigned.

If subjects are fasting (only water for ≥10 hours), all screening laboratory assessments may be done on the same day. If subjects are not fasting, they will be invited to return for a second screening visit to complete any missing screening procedures.

Subjects screening lab parameter and VCTE (CAP) will be evaluated to identify subjects who are likely to have a liver fat content of > 10% at MRI-PDFF. Depending on the outcome/results of these values, the subjects will proceed to MRI/MRI-PDFF or not. For further details on parameters and outcome for the determination to proceed to MRI-PDFF see the Operations Manual.

Subjects MELD score will be calculated according to the following formula:

MELD(i) = 0.957 × ln(Cr) + 0.378 × ln(bilirubin) + 1.120 × ln(INR) + 0.643

Then, round to the tenth decimal place and multiply by 10. For further details see the Operations Manual.

Subjects who meet all inclusion criteria and none of the exclusion criteria are eligible for this study and will be invited for the in-house period. Subjects will be instructed on influencing factors, such as refraining from strenuous exercise throughout the entire course of the study, restrictions on of alcohol and herbal supplements during the study, caffeinated drinks, smoking or medication and illness/infection as stated in section 7.4.

9.1.3 Demographics and Medical History

Demographic information and medical history, including smoking status, alcohol consumption and medication history will be obtained at Screening.

9.1.4 Physical Examination

The baseline physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat, neck, thyroid; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system, mouth; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) central and peripheral nervous system and (10) lymph nodes.

An abbreviated physical exam (based on symptoms and including examination of cardiovascular, respiratory, and gastrointestinal system) will be performed by the Investigator (or a qualified physician at the CRU) at time points indicated in the Table 16-1. A complete physical examination may be performed in case the subjects have symptoms or at the discretion of the Investigator.

9.1.5 Height, Weight, BMI and Waist Circumference

Height (without shoes) will be measured once, during the Screening visit.

Weight (without shoes) will be measured fasting in the morning, with light clothing and post void at time points indicated in the Table 16-1.

BMI (kg/m2) will be calculated from height and weight.

Waist circumference (inches) will be measured at Screening, Day 85 and at Follow-up Visit.

9.1.6 Vital Signs

Vital signs will include body temperature (*aural or oral*), supine blood pressure (supine BP after 5 minutes resting), respiration rate and pulse rate (after 5 minutes resting). The method of temperature (aural or oral) should be consistent throughout the study per subject from baseline through end of study. Vital sign measurements will be performed at days indicated in the Table 16-1. Vital signs measurements will be performed at PK

sampling timepoints (as stated in the PK sampling schedule), and the vital sign should be measured before PK sample is collected.

Body temperature: Assessments will be performed as stated in the Table 16-1. Measurements may be taken more frequently, if deemed necessary by the Investigator. Measurement on Day -1 will be performed as baseline assessment. Measurements will continue throughout the study. Timepoints must not interfere with ABPM measurement timepoints.

Blood pressure:
Supine assessments will be performed. Measurements will be taken at Screening. Measurements on Day -2 and day 77 will be taken prior to connecting the subjects to the ABPM. Measurements on Day 4, 5, 81 and 82 will be taken prior to the PK sample. Measurements will be performed on the arm that is not connected to the ABPM system. Timepoints must not interfere with the ABPM measurements.

Pulse rate and respiration rate: Assessments will be performed as stated in the Table 16-1 at timepoints for blood pressure measurements.

9.1.7 Concomitant Illness and Therapy

Concomitant therapy is any medication given in addition to the investigational product (including over-the-counter medications, herbal medications, and vitamin supplements) administered between screening and follow-up.

Concomitant illness is any significant medical condition or disease that is present at study start (signing of informed consent). This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at Screening examination.

Details of all concomitant illnesses and therapies must be recorded at study entry and must be recorded on the subject's CRF. Any changes in concomitant medication must be recorded at each visit. If the change influences the subject's eligibility to continue in the study, the Sponsor must be informed. The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing, and indication.

AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples (Table 9-1) will be taken as described in the Schedule of Events.

Table 9-1 Clinical Laboratory Assessments at Screening

Hematology	Serum Chemistry	Urinalysis
CBC with Differential: Hematocrit Hemoglobin Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC) Red Cell Distribution Width (RDW) Percentage and Absolute Differential Counts Platelet Count Red Blood Cell Count (RBC) White Blood Cell Count (WBC)	**Hepatic Function Panel:** Alanine Aminotransferase (ALT/SGPT) Alkaline Phosphatase, Serum Aspartate Aminotransferase (AST/SGOT) Bilirubin, Direct Bilirubin, Total Protein, Total, Serum Gamma Glutamyl Transferase, Serum **Renal Function Panel:** Albumin, Serum BUN BUN: Creatinine Ratio Calcium, Serum Carbon Dioxide, Total Chloride, Serum Creatinine, Serum Phosphorus, Serum Potassium, Serum Sodium, Serum **Lipid Panel:** Cholesterol, Total High-Density Lipoprotein (HDL) Cholesterol Low-Density Lipoprotein (LDL) Cholesterol (Calculated) Triglycerides Very Low-Density Lipoprotein (VLDL) Cholesterol (Calculated) **Additional Parameters:** Amylase Lipase Calcitonin Alpha-2 Macroglobulin Lactic Acid Dehydrogenase (LDH) Magnesium Uric Acid Free Fatty Acid (FFA) C-reactive protein (CRP)	**Routine urinalysis with microscopic examination on positives**[(a)]: Color Appearance, Specific Gravity PH Protein Glucose Ketones Occult Blood Leukocyte Esterase Nitrite Bilirubin Urobilinogen

Diagnostic Screening		
Serum/Plasma/Whole Blood	**Urine**	**Breath**

Viral Serology: HBsAg Anti-HCV Anti-HIV-1 Anti-HIV-2 **Coagulation:** Partial thromboplastin time (PTT) PT International normalized ratio (INR) Thyroid-stimulating hormone (TSH)[(b)] HbA1c Serum Insulin FPG	**Drug Screen Profile** Urine drug screen (12 panel) via commercial kit at the site. **Female Subjects Only** human chorionic gonadotropin (hCG) performed at Screening. Follicle-stimulating hormone (FSH) test for postmenopausal women (defined as amenorrheic female subjects <60 years of age and not surgically sterile) at Screening. Urine pregnancy testing via commercial kit at the site will at timepoints stated in the Schedule of Events. Urine pregnancy testing may be performed per Investigator's discretion at additional timepoints during the study, if there is reason to believe the subject might be pregnant.	Alcohol breath test at timepoints stated in the SOE at the site

(a) Microscopic analysis should be performed only if urine evaluations are abnormal.
(b) In the event of abnormal TSH, Free T3/T4 may be collected at Investigator discretion.

Table 9-2 Clinical Laboratory Assessments during the Study

Hematology	Serum Chemistry	Urinalysis
CBC with Differential: Hematocrit Hemoglobin Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC) Red Cell Distribution Width (RDW) Percentage and Absolute Differential Counts Platelet Count Red Blood Cell Count (RBC) White Blood Cell Count (WBC)	**Hepatic Function Panel:** Alanine Aminotransferase (ALT/SGPT) Alkaline Phosphatase, Serum Aspartate Aminotransferase (AST/SGOT) Bilirubin, Direct Bilirubin, Total Protein, Total, Serum Gamma Glutamyl Transferase, Serum **Renal Function Panel:** Albumin, Serum BUN BUN: Creatinine Ratio Calcium, Serum Carbon Dioxide, Total Chloride, Serum Creatinine, Serum Phosphorus, Serum Potassium, Serum Sodium, Serum **Additional Parameters:** Amylase Lipase Lactic Acid Dehydrogenase (LDH) Magnesium Uric Acid C-reactive protein (CRP)	**Routine urinalysis with microscopic examination on positives**[a]: Color Appearance, Specific Gravity PH Protein Glucose Ketones Occult Blood Leukocyte Esterase Nitrite Bilirubin Urobilinogen

Serum/Plasma/Whole Blood	Urine	Breath
Lipid profile and particles: Cholesterol, Total HDL-C (Cholesterol) HDL-P (Particles) LDL-C LDL-P VLDL-C VLDL-P Triglycerides FFA Thyroid-stimulating hormone (TSH)[b] **Coagulation:**	**Drug Screen Profile** 12 panel urine drug screen as stated in the SOE via commercial kit at the site. **Female Subjects Only** Urine pregnancy testing via commercial kit at site will be performed at timepoints stated in the SOE. Urine pregnancy testing may be performed per Investigator's discretion at additional timepoints during the study, if there is reason to believe the subject might be pregnant.	Alcohol breath test at timepoints stated in the SOE at the site.

Partial Thromboplastin Time
(PTT)
PT
International Normalized Ratio
(INR)

Amino acid panel:
Taurine
Aspartate
Hydroxyproline
Threonine
Serine
Asparagine
Glutamate
Glutamine
Sarcosine
Alpha-Aminoadipate
Proline
Glycine
Alanine
Citrulline
Alpha-Aminobutyrate
Valine
Cystine
Methionine
Homocitrulline
Cystathionine
Alloisoleucine
Isoleucine
Leucine
Tyrosine
Phenylalanine
Argininosuccinate
Beta-Alanine
Beta-Aminoisobutyrate
Homocysteine
Gamma-Aminobutyrate
Tryptophan
Hydroxylysine
Ornithine
Lysine
Histidine
Arginine

Incretins:
GLP-1
GIP
Glucagon
FGF21
Leptin

Glucose Metabolism
Parameter:
FPG
Fasting Insulin
Fasting C-Peptide
HbA1c

Inflammatory Biomarker:
Adiponectin

Bone Metabolism Parameter:
CTX-1
OC
P1NP

Ketone bodies:
BHB

Immunogenicity Parameter:
ADAbs
nAbs
anti -PEG

Additional Parameters:
Calcitonin

(a) Microscopic analysis should be performed only if urine evaluations are abnormal.
(b) In the event of abnormal TSH, Free T3/T4 may be collected at Investigator discretion.

The responsible laboratory will perform all necessary laboratory tests listed above. Specialty labs may be responsible for specific PD parameter. The results of safety laboratory tests will be sent to the appropriate Investigator or designee, who is responsible for reviewing these results. All laboratory safety data will be faxed or transferred electronically.

Laboratory reports must be signed and dated by the Investigator or designee indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

All clinically significant laboratory abnormalities must be recorded as an AE. A clinically significant laboratory abnormality may be verified by retesting and may be followed upon discretion of the Investigator.

9.1.9 Contraception

Females must be non-pregnant and non-lactating, and either surgically sterile (eg, tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal for >12 months. If females' sterility or postmenopausal status is confirmed, no pregnancy testing is required during the study. The site will make an effort to retrieve medical records to document the sterility, however, the absence of records will not exclude the subject. In case that medical records cannot be obtained, serum pregnancy testing will be conducted at Screening, and urine pregnancy testing will be conducted throughout the study. Postmenopausal status will be confirmed through testing of FSH levels outside the normal range (as specified by responsible lab) at screening for amenorrheic female subjects < 60 years of age.

Female subjects who state they are postmenopausal at the screening visit but have an FSH value that does not correspond with a postmenopausal FSH level, may have a serum hCG pregnancy test performed on a separate day. If screening sample is within stability range, the serum hCG pregnancy test may be performed out of the same sample. If test is negative and the subject agrees to be on a highly effective contraceptive method, subject may be enrolled in the study at the discretion of the Investigator.

Female subjects of child-bearing potential must use highly effective contraceptive methods. Highly effective contraceptive methods are considered those with failure rate less than 1% undesired pregnancies per year, including hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner. Oral hormonal contraceptives have to be taken at least 2 months prior to Screening until 30 days after the last Follow-up Visit.

During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed for sterilized women, when medical records are not available. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at check-in to in-house periods.

Males must be surgically sterile (at least 1-year post vasectomy), abstinent or if engaged in sexual relations of child-bearing potential, the subject and his partner must be using an acceptable contraceptive method from screening and for a period of 30 days after the last Follow-up visit. Acceptable methods of contraception are the use of condoms together with spermicidal foam/gel/film/cream/suppository. In addition, they must be advised not to donate sperm during this period. Male subjects must also encourage their female partner to use effective contraception. Effective contraceptive for the female partner includes surgical sterilization (e.g., bilateral tubal ligation, bilateral salpingectomy, bilateral oophorectomy), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/ suppository. The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator.

9.1.10 Pregnancy

In the event a subject becomes pregnant during the study, she should be withdrawn. However, the subject will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy.

In addition, any pregnancies in the partner of a male subject during the study or for 60 days after the last dose should also be recorded.

If the pregnancy occurs at any time during the study and the 60 days of last dose of active study medication, the pregnancy should be reported immediately to the Sponsor, using a pregnancy notification form.

Study subjects will give consent on enrollment that the Investigator will report any pregnancy during the study to the Sponsor and that they will be asked to provide information about her pregnancy, delivery, and the health of her infant until age one month. Payment for all aspects of obstetrical care, child, or related care will be the subject's responsibility.

All reported pregnancies will be followed up to final outcome, using the pregnancy and pregnancy follow-up forms. The outcome, including any premature termination, will be reported to the Sponsor. An evaluation after the birth of the child may also be conducted.

Pregnancy complications must be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

9.1.11 ECG Procedure

All ECG's throughout this study will be performed as standard triplicate 12-lead ECG's, except the ECG at Screening. ECG's will be recorded after 5 minutes in a supine position. Only the Triplicate ECG's will be recorded at least 1 minute apart from each other, not exceeding a time period of 5 minutes for the completion of all three ECG's.

The Investigator (or designee) will interpret the ECG's by use of an electronic measurement using the following categories: within normal limits, abnormal but not clinically significant, or abnormal with clinical significance. ECG's are performed according to the Table 16-1. The following parameters will be recorded from the subject's ECG trace: heart rate, QT interval, PR interval, QRS interval, R-R interval, and QTcF (corrected) using the Fridericia correction (QTcF = QT ÷ cube root of the R-R interval [where R-R is the duration of the entire cardiac cycle]).

When ECGs are to be collected at the same time point as a blood collection, ECGs should be collected first to avoid any artificially increased heart rates due to the blood collection.

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. ECG measurements are to be collected during screening and on Day -2 and 77 before subjects are connected to the ABPM device. Additionally, ECG measurements are taken on Day 5 and Day 82, after ambulatory devices (Holter and ABPM) are removed.

In some cases, it may be appropriate to repeat abnormal ECGs. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if the Investigator's interpretation determines that the QTc value is in the acceptable range.

9.1.12 Check-in Procedure

All subjects will check in to the clinic in the morning for the In-house Periods 1 and 2. Eligibility will be confirmed, and the following will be assessed:

1. Positive alcohol breath test.
2. Positive urine drug screen.
3. Positive urine pregnancy test for WOCBP.
4. Any use of prescription or non-prescription medicine other than the allowed concomitant medications within the last 12 hours.
5. Any medical condition that could interfere with glucose metabolism, as judged by the Investigator.

Subjects who fulfill one or more of the stated criteria at check–in, will not be able to continue onto the treatment period. The treatment period will be rescheduled. Each treatment period may be rescheduled no more than twice. After that, the subject will be excluded from the study. Replacement of subjects for the dosing period may be permitted to enroll sufficient subjects into the study after discussion with Sponsor and Investigator.

9.1.13 Standardized Meals

During in-house period, subjects will receive standardized meals. The standardized weight maintaining meals will be provided using estimated BMR× activity factor of 1.5 to determine daily caloric intake.

9.1.14 ABPM

The 24-hour blood pressure will be measured by an ABPM device. A validated, reliable, automated, and accurate monitor will be used with a storage function. Blood pressure measurements will be started overnight on Day -2 to familiarize the subjects with the device. During this period, measurements will be taken every 2 hours until the morning of Day -1.

The baseline assessment period will start in the morning of Day -1 until Day 1. Measurements will be taken hourly up to 14 hours and then 2-hourly until 24 hours.

The post-dose assessment period will start in the morning of Day 1. Measurements will be taken hourly up to 14 hours and then 2-hourly until 24 hours every day (for every 24-hour period), until the morning of Day 5.

Additionally, subjects will be connected to the ABPM system again on Day 77. Blood pressure measurements will be started overnight on Day 77 to familiarize the subjects with the device. During this period, measurements will be taken every 2 hours until the morning of Day 78.

The post-dose assessment period will start in the morning of Day 78. Measurements will be taken hourly up to 14 hours and then 2-hourly until 24 hours every day (for every 24-hour period), until the morning of Day 82.

Time points stated in the Table 16-1. Adequate cuff size will be documented for each subject, after determination of the patient's non-dominant arm circumference. Subject's bedtime and awakening will be recorded to divide the downloaded data into diurnal and nocturnal values. Depending on available PK and safety data, timepoints for measurements may be adjusted for the following cohorts.

Specifications about the ABPM model will be described in the Operations Manual and ABPM Procedure Manual, as well as detailed instructions of blood pressure frequency, data management and medical review.

9.1.15 Holter Monitoring

24-hour heart rate activity will be continuously recorded with an ambulatory Holter monitoring system (eg, Mortara surveyor). Holter electrodes (12 lead, 3-channel placement) will be placed to the subject's chest and will be attached to a small recording monitor. The Holter monitor will be carried in a pocket or small pouch. Subject's activities or exercises will be recorded while wearing the monitor.

Specifications about the Holter model will be described in the Operations Manual and Holter Procedure Manual, as well as detailed instructions of data management and medical review.

9.1.16 Pharmacokinetic Assessments and Schedule

Blood for PK analysis of the study drugs will be collected at the time points indicated in the Table 16-1 Schedule of Events and follow the PK sampling schedule Table 9-3. One 2-mL sample per scheduled time point will be collected to provide a minimum of 500 µL of serum for PK measurements and 500 µL of serum as a secondary back-up sample. Instructions for sample processing and shipment will be provided in the PK Sample and Shipping Instructions. Pre-dose sampling will be taken within 10 minutes before dosing. Dosing should occur at approximately 08:00 h on every dosing day. The actual time of PK sampling should not deviate from the nominal time by more than ± 5 minutes during the Inpatient Period, and by more than ± 2 days for the Elimination Period and Follow-up Visit. If Visit during elimination period or follow-up visits will be performed on a different day, the time point for the sampling will still be in the morning, preferably at the same time (at approximately 08:00h). The actual time of dosing, actual sampling dates and times should be recorded.

Table 9-3 PK Sampling Schedule for cohorts 1-1 and 1-2

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

Table 9-4 PK Sampling Schedule starting from cohort 1-3

PK sampling schedule			
Treatment Period	Week 1	Day 1	Pre-dose 1st dosing
			8 h after 1st dosing
		Day 2	24 h after 1st dosing
		Day 3	48 h after 1st dosing
		Day 4	72 h after 1st dosing
		Day 5*	96 h after 1st dosing
	Week 2	Day 8	Pre-dose 2nd dosing
		Day 10	48 h after 2nd dosing
	Week 3	Day 15	Pre-dose 3rd dosing
	Week 4	Day 22	Pre-dose 4th dosing
	Week 5	Day 29	Pre-dose 5th dosing
	Week 6	Day 36	Pre-dose 6th dosing
	Week 8	Day 50	Pre-dose 8th dosing
	Week 9	Day 57	Pre-dose 9th dosing
	Week 12	Day 78	Pre-dose 12th dosing
			8 h after 12th dosing
		Day 79	24 h after 12th dosing
		Day 80	48 h after 12th dosing
		Day 81	72 h after 12th dosing
		Day 82**	96 h after 12th dosing
Elimination Period (±2)	Week 13	Day 85	168 h after 12th dosing
	Week 15	Day 99	504 h after 12th dosing
F/U (±2)	Week 17	Day 113	840 h after 12th dosing

*Sampling on Day 5 will start with Cohort 1-4 and will not be taken for cohort 1-3.
** Sampling on Day 82 will be optional for cohort 1-3 but will be taken in cohort 1-4.

Available PK data will be utilized for decision making in dose escalation meeting. Based on results, the PK sampling schedule may be adjusted. The total number of blood sampling events will not exceed the total number of blood sampling events originally planned.

9.1.17 Laboratory Pharmacodynamic Assessments

Blood for analyses of PD assessments will be collected at the time points indicated in the Table 16-1 and Table 16-2. Sampling for incretins/ metabolic hormones (GLP-1, GIP,

Glucagon, FGF21, Leptin), serum lipid profiles and particles (total cholesterol, LDL-C, LDL-P (particles), HDL-C, HDL-P (particles), VLDL-C, VLDL-P (particles), Triglyceride, Free Fatty Acids), amino acid profile (taurine, aspartate, hydroxyproline, threonine, serine, asparagine, glutamate, glutamine, sarcosine, alpha-aminoadipate, proline, glycine, alanine, citrulline, alpha-aminobutyrate, valine, cystine, methionine, homocitrulline, cystathionine, alloisoleucine, isoleucine, leucine, tyrosine, phenylalanine, argininosuccinate, beta-alanine, beta-aminoisobutyrate, homocystine, gamma-aminobutyrate, tryptophan, hydroxylysine, ornithine, lysine, histidine, arginine), glucose metabolism parameter (FPG, Fasting insulin, fasting c-peptide, HbA1c), inflammatory marker (Adiponectin), ketone bodies (BHB) and bone metabolism parameters ($CTX\text{-}_1$, OC, P_1NP) will be collected.

Instructions for sample processing and shipment will be provided in the laboratory manual. All samples, including pre-dose sampling on Day 1 will be taken within 30 minutes before dosing.

9.1.18 MRI/MRI-PDFF

Magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) deems as a noninvasive, quantitative, and accurate measure of liver fat content/ hepatic steatosis grade in this study to identify the study population and assess the treatment response in subjects with NAFLD. For subjects in cohort 1-5 and up, the assessment of visceral fat will also be assessed via MRI imaging at Screening, during week 8 and week 12, together with the MRI-PDFF assessment.

MRI-PDFF will be performed using a standardized imaging acquisition calibration protocol and the results a will be determined by central reader at screening (as baseline value) and during week 8 (close to Day 57 as possible, but prior to dosing on Day 57), and week 12 (close to Day 85 as possible, but after ABPM and Holter are disconnected on Day 82; but prior to the PK sampling on Day 85).

For details please see the Operations Manual.

9.1.19 VCTE

One-dimensional vibration controlled transient elastography (VCTE) assessed via eg, FibroScan (EchoSens™, Paris, France) will be used in this study.

At Screening, subjects will be examined with the FibroScan to assess the controlled attenuation parameter (CAP) in order to qualify for the inclusion in the study.

For subjects participating in cohort 1-4 and up, FibroScan assessments will be performed on Day 85 to assess a change from baseline in CAP and LSM.

It is a device, that uses non-invasive, one-dimensional vibration controlled transient elastography (VCTE). The device generates a low-frequency shear wave from a probe applied to the subject's skin between the ribs. The speed of the wave spread is then measured between two points within the liver to allow the livers stiffness to be

quantified. The wave will travel more rapidly through stiff tissue. An examination using the FibroScan consists of ten signal acquisitions at a single point; the whole process lasts around 15 minutes. The results are instantly displayed on a screen and the value for stiffness can be matched to a fibrosis stage.

For details please see the Operations Manual.

9.1.20 Immunogenicity Assessments

Blood samples will be acquired to determine ADAbs, nAbs and anti -PEG within 30 min prior to the first dosing on Day 1, post first dosing on Day 22, 50, 78, 85 and 99. Post first dose samples will be taken at the same time point of safety blood sampling or collection of other blood samples.

Instructions for sample processing and shipment will be provided in the PK/Immunogenicity Sample and Shipping Instructions.

9.1.21 Tolerability Assessments

After injection of the study drug, the injection site will be marked with an indelible marker/pen. Assessment of study drug injection site will be performed within 30 minutes of pre-dose, at 4 and 12-hour post-dose on Day 1 with a window of ± 30 minutes. Assessment of study drug injections on the other dosing days will be performed at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days. Last injection site inspection will be performed on Day 85.

The local reaction from the injection site will be evaluated quantitatively using a Draize scale or similar scale. If an injection site reaction like pain on palpation, itching, erythema, edema, induration is observed, it must be recorded as an AE and then will be evaluated using the following scale:

Erythema will be evaluated as follows:

- 0 – No erythema
- 1 – Very slight erythema (barely perceptible)
- 2 – Well-defined erythema
- 3 – Moderate to severe erythema
- 4 – Severe erythema (beet redness) to slight eschar formations (injuries in depth)

Edema will be evaluated as follows:

- 0 – No edema
- 1 – Very slight edema (barely perceptible)
- 2 – Slight edema (edges of area well defined by definite raising)
- 3 – Moderate edema (raised approximately 1 mm)

- 4 – Severe edema (raised more than 1 mm and extending beyond the area of exposure)

For the irritation assessment, all irritation events will be documented as AEs. The diameter of the affected area will be measured with a paper measuring tape in centimeter (cm) and the condition of the injection site will be recorded. Digital photography will be used to document all positive injection site reactions. In case of clinically significant injection site reactions, subjects may undergo a dermatological consultation and/or cutaneous biopsies for further histological examination of the injection site reaction. Biopsies will be performed using a 4-mm punch biopsy centered on the injection site. The biopsy area will be anesthetized with lidocaine prior to the biopsy. Wound closure will be performed with Steristrips. If stitches are necessary to close the punch area, they will be removed approximately 2 weeks later. The time between injection and biopsy will be recorded. Microscopic and histological examination of the punch biopsies will be performed at a qualified lab.

9.1.22 Blood Volume

Total blood sampling volume for subjects will approximately be 435 mL for subjects participating in the study.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE is any undesirable and unintended medical event occurring to a subject in a clinical study, whether or not related to the study products. This includes events from the first study related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first study related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures
- Pre-existing events that has not worsened in intensity or frequency from baseline

10.1.2 Treatment Emergent Adverse Event (TEAE)

A treatment-emergent AE (TEAE) is defined as any clinically significant event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

10.1.3 Adverse Events of Special Interest (AESI)

AEs of special interest (AESI) are selected, non-serious adverse events. They will be reported to the sponsor within the same timeframe that applies to SAE, using SAE report form.

AESIs in this study include the following:

- Necrolytic migratory erythema
- Cholelithiasis
- Pancreatitis

10.1.4 Clinical Laboratory Event

A clinical laboratory AE is any clinically significant laboratory abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of study product, more frequent follow-up, or diagnostic investigation).

A laboratory re-test and/or continued monitoring of an abnormal value is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

10.1.5 Adverse Reaction

An adverse reaction is defined as any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

10.1.6 Suspected Adverse Reaction

Suspected adverse reaction is defined as a subset of any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lower degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Reasonable possibility is given if:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
- One or more occurrences of an event, that is not commonly associated with drug exposure, but otherwise uncommon in the population exposed to the drug
- An aggregate analysis of specific events observed in a clinical study that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

10.1.7 Unexpected Adverse Event/ Unexpected Suspected Adverse Reaction

An unexpected AE/unexpected suspected adverse reaction is an AE or suspected adverse reaction that is not listed in the Investigator Brochure, as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation, or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

10.1.8 Serious Adverse Event (SAE)/ Serious Suspected Adverse Reaction

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life threatening.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.

4. Results in persistent or significant disability/incapacity.
5. Leads to a congenital anomaly/birth defect.
6. Is an important medical event that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.1.9 Life-Threatening Adverse Event/Life-Threatening Suspected Adverse Reaction

A life-threatening AE/life-threatening suspected adverse reaction, in the view of either the Investigator or Sponsor, places the patient or suspect at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death.

The determination of whether an AE is life threatening can be based on the opinion of the Investigator or Sponsor. If either, the Sponsor or investigator believes that the event is serious or life threatening, the event must be considered serious and evaluated by the Sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

10.2 Severity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient, easily tolerated by the subject and does not affect the subject's daily activities.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual daily activities.
Severe:	The event is incapacitating and causes considerable interference with the subject's usual activities.

10.3 Relationship to Study Treatment

The relationship of each AE to the study drug(s) will be assessed by the Investigator or Sub-Investigator on the basis of his/her clinical judgment and the following definitions:

1= **Related**:
The AE follows a reasonable temporal sequence from the study product administration and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications).

The AE follows a reasonable temporal sequence from the investigational product administration and represents a known reaction to the drug under study or other drugs in its class or is predicted by the known pharmacological properties of the drug.

The AE resolves with discontinuation of the investigational product and/or recurs with rechallenge, if applicable.

If a relationship to an AE is not assessable, it should be recorded as Related.

2 = **Not Related**:
The AE does not follow a reasonable temporal sequence from investigational product administration or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

10.4 Procedures

10.4.1 Collection and Recording of AEs

Collection of all AEs (serious AEs and non-serious AEs) will commence from the time the subject signs the informed consent to participate in the study until the post-treatment follow-up visit. Throughout the in-house treatment period and outpatient visits, the Investigator will assess whether any subjective AEs have occurred. In order to avoid bias in eliciting AEs, a non-specific question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored and given appropriate medical treatment at the discretion and judgement of the Investigator until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the Investigator concludes that the event is related to the drug treatment. The event term, start and stop dates, severity, action taken with study drug and outcome, will be documented, along with the Investigator's opinion of the causal relationship between the event and the study drug.

10.4.2 Collection and Reporting of SAEs and AESIs

When an SAE and AESI occur, it should be reported according to the following procedure:

An SAE form must be completed immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum a short description of the event and the reason why the event is categorized as serious, subject identification number, Investigator's name, name of the study medication and a causality assessment.

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs and AESIs (regardless of their relationship to study drug) should be reported to the Sponsor or a designated qualified vendor within 24 hours of the Study Center's first knowledge of the event.

The collection of SAEs and AESIs will begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period. An Initial Serious Adverse Event Form should be completed, and a copy should be faxed to the Sponsor or designated qualified vendor.

All serious and unexpected adverse event reporting will adhere to 21 CFR 312.32 for IND drugs and 21 CFR 314.80 for marketed drugs (15-day alerts). The Institutional Review Board (IRB) and all Investigators will be notified of the alert reports per FDA regulations.

10.5 Anticipated Adverse Events

Normal precautions taken for a human study, including the provision of emergency equipment, will be taken during this study. Qualified and well-trained physicians and medical staff will instruct the subjects.

In case any drug related AEs occur, they will be managed according to the AE guidance document in section 17.0.

Procedure related AEs:

The study procedures involve the use of adhesive to secure the placement medical equipment. The adhesive may cause an allergic reaction, redness, swelling or itching when in contact with the skin.

Subjects will participate in several blood draws throughout the course of the study which have the potential to cause a venous line-vasovagal response, bruising, tenderness, and rarely infection.

10.6 Follow-up of AEs and SAEs

All AEs should be followed up and subjects will be rendered appropriate medical care and treatment at the discretion of the Investigator until resolution or until the Investigator and Sponsor concludes that "further follow-up is not necessary". If the AE has not resolved by the post-treatment follow-up visit, the stop date will be recorded as "ongoing."

All SAEs and AESIs should be followed up until resolution or permanent outcome of the event or until the Investigator and Sponsor judge that further follow-up is not necessary.

If information is not available at the time of the first report and becomes available later, the Investigator should complete a follow-up SAE form at the earliest possible or provide other written documentation and fax it immediately within 24 hours of receipt of information to the Sponsor or designee. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent accordingly.

All other non-serious AEs must be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered", or until the end of the post-

treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AE's have been resolved.

10.6.1 Safety Reporting to IRBs or IECs, and Regulatory Authorities

The Sponsor or designated qualified vendor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted.

Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations.

The Sponsor or designated qualified vendor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the investigational product administration or in the overall conduct of the study. The investigational site will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

Reporting responsibilities of Investigator under 21 CFR 312.64(b) and Sponsor under 21 CFR 312.32(c)(1)(i) for serious and unexpected suspected adverse reactions will be followed.

11.0 DATA HANDLING AND MANAGEMENT

Clinical Data Management (CDM), is the responsibility of [redacted]. With permission of the Sponsor, CDM may be delegated under an agreement of transfer of responsibilities to a qualified vendor of [redacted].

11.1 Data Management

The full details of procedures for data handling will be documented in the Data Management Plan (DMP).

AEs and medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) WHODrug Global.

Unique numbers will identify the subject and the biological material obtained from the subject. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human subjects in all presentations and publications as required by local/regional/national requirements.

Data from screening failures will be entered into the database.

Laboratory data from the central laboratory will be electronically transferred to [redacted] for database reconciliation purposes. The electronic laboratory data will be considered source data. In cases where sensitive non-PK laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The laboratory will provide one copy of the laboratory reports to the CRU staff. The staff will receive all laboratory data electronically or based on FAX reports directly from the laboratory. An Investigator must review, evaluate, sign and date the laboratory print-outs upon receipt. The signed print-out of the laboratory reports are source data.

All other results, including PK, PD data, and laboratory tests will be transferred electronically to the responsible Data Management Unit.

11.2 CRFs (Electronic)

11.2.1 Clinical Data Management Workflow

Electronic CRFs will be developed by the CDM department, in collaboration with the clinical study team at [redacted] and statistician. CDM will document the process workflow in the DMP. After data entry, monitor(s) will source data verify (SDV) the eCRFs against the source documents. Queries may be issued to clarify the data entered. The PI will electronically sign the eCRFs after all data have been entered, all queries have been resolved and all external data has been reconciled with the eCRF data. If corrections and/or resolution of queries are required after PI approvals, those eCRFs affected by changes will be re-signed by the PI. The database may be locked after the PI approvals are completed.

After database lock, CDM study design documentation and locked eCRFs (PDF) will be created and will be provided to the Sponsor, if requested.

11.2.2 Data Entry of eCRFs

Data required for analyses and subject safety assessments will be entered from source documentation into eCRFs. Instructions for data entry will be provided in the eCRF Completion Guidelines, developed by the CDM department. All staff involved with entering data into the eCRFs will be trained prior to gaining access to the study database.

11.2.3 Corrections to eCRFs

Queries may be generated by the eCRF system during data entry, and queries may be generated by CDM staff, monitors, and other data reviewers during the course of the study. Only specific CRU personnel will be authorized to make corrections to the eCRFs; CDM will train personnel prior to granting access in the eCRF system. Corrections will be made directly in the eCRF – by modifying existing data, adding new data, or deleting data, as appropriate. All data corrections will be logged in the electronic audit trail.

11.2.4 PI Approval of eCRF Data

The Investigator or Investigator's authorized staff must ensure that all information derived from source documentation is consistent with the source information and accurately reflected in the eCRFs. By electronically signing the eCRFs, the Investigator confirms that the information is complete and correct.

11.3 Retention of Documents

At the completion of the study, all records created by and under the supervision of the Investigator should be maintained in accordance with the requirements of the regulatory authority guideline and the GCP Guideline. These will be available for inspection at any time by the Sponsor or the FDA.

Clinical study documents are archived upon completion of the study and maintained for at least 15 years from the study closure or longer in accordance with local regulation and applicable regulatory authority guidelines, and the study sponsor will be notified prior to destruction of study records.

Current FDA guidelines require records to be retained for a period of 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated. If no application is filed or if the application for the investigated indication is not approved, documents will be kept until 2 years after the investigation is discontinued and the FDA is notified. It is the sponsor's responsibility to inform [ ] as to when essential documents are no longer needed to be retained.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

Statistical services is delegated under an agreement of transfer of responsibilities to Pharmapace, Inc., a qualified vendor of the Sponsor.

An SAP will be prepared that will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. It will also provide any changes or additions to the analyses that are not apparent in the protocol. Procedures for accounting for missing, unused, or spurious data will be discussed in detail in the SAP

12.2 Study Endpoints

The study endpoints or derived parameters used to assess whether the study objectives have been met. The endpoints for this study are shown in Table 12-1. Additional endpoints may be added to the SAP as needed to address the needs of the study.

Table 12-1 Study Endpoints

Primary Endpoints (Safety Endpoints)		**Primary Endpoints**		**Exploratory Endpoints**
To assess the safety of HM15211	**To assess the local tolerability of HM15211**	**To assess the PK profiles of HM15211**	**To assess the reduction of liver fat by MRI-PDFF**	**To assess the PD properties of HM15211 compared to placebo**
Adverse events	**Injection site reaction**	**Cmax**	**Absolute change from baseline**	**Incretins / metabolic hormones** **-GLP-1** **-GIP** **-Glucagon** **-FGF21** **-Leptin**
Clinical laboratory abnormalities (including serum amylase, lipase, coagulation, TSH, calcitonin)		**tmax**	**% change from baseline**	**Body weight and BMI**
Immunogenicity (ADAbs, nAbs, anti-PEG)	·	**C_{trough}**		**Lipid metabolism (Total cholesterol, --LDL, LDL-C, LDL-P** **-HDL, HDL-C, HDL-P**

Primary Endpoints (Safety Endpoints)		Primary Endpoints		Exploratory Endpoints
				-VLDL, VLDL-C, VLDL-P **-Triglycerides** **-FFA**
Clinical findings on physical examination		**AUC, eg., AUC_{0-t} at s.teady state**		**Amino acid profile**
Vital signs (BP, respiratory rate, temperature, and HR)		**kel**		**Glucose metabolism parameters:** **-FPG** **-Fasting insulin** **-fasting C-peptide** **-HbA1c**
24-hour ABPM (Mean day- and night time systolic/diastolic BP)		**$t_{1/2}$**		**Bone metabolism parameters:** **-CTX-1** **-OC** **-P_1NP**
24-hour Holter ECG (HR, HRV (e.g. mean heart rate, difference between day and night HR, mean NN intervals, SDNN, SDANN, SDNN index)		**CL/F**		**Inflammatory markers:** **-Adiponectin**
12-lead ECG parameters (the primary ECG endpoint will be QTcF)		**V_z/F**		**Ketone bodies:** **-BHB**
				Waist circumference
				Changes in liver steatosis and liver stiffness assessed by FibroScan® (VCTE), determined as absolute and

Primary Endpoints (Safety Endpoints)		Primary Endpoints		Exploratory Endpoints
				percent change from baseline in controlled attenuation parameter (CAP) and liver stiffness measurements (LSM)
				Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI imaging

12.2.1 Analysis Sets

12.2.1.1 Safety Set

The Safety analysis set will include all subjects who received study medication (HM 15211 or Placebo). The Safety analysis set will be used for demographic, baseline characteristics and safety summaries.

12.2.1.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will include all subjects who received HM 15211 or placebo with sufficient evaluable PK data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism, or excretion of HM 15211). The PK analysis set will be used for analysis of PK endpoints.

12.2.1.3 Pharmacodynamics (PD) Analysis Set

The PD analysis set will include all subjects who received HM 15211 or placebo with sufficient evaluable PD data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the PD of HM 15211). The PD analysis set will be used for analysis of PD endpoints.

12.2.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects overall and by cohort and treatment. Summary statistics (e.g., number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, ethnicity, and race).

12.2.3 Analysis of the Pharmacokinetic Endpoints

The planned analyses will be described in more detail in the statistical analysis plan (SAP).

The serum pharmacokinetic (PK) concentration profiles will be graphically presented. The PK endpoints will be derived from the individual serum HM15211 profiles during the elimination phase using the non-compartmental models. C_{trough} will be derived from the pre-dosing PK samples on Day 78. The PK parameters will be summarized by dose.

12.2.4 Analysis of the Pharmacodynamic Endpoints

All PD parameters including but not limited to MRI-PDFF will be summarized using appropriate descriptive statistics (e.g., n, mean or geometric mean, CV, min, median, max) by treatment dose and collection day. The placebo group will be pooled across cohorts in the summary tables.

Exploratory PD parameters including but not limited to FPG, insulin, C-peptide, GCG, leptin, GLP1, GIP, FGF21, Leptin, as well as CRP, lipid profiles and particles, FFA, BMI, and body weight, etc. will be summarized by treatment dose. The placebo group will be pooled across cohorts in the summary tables.

12.2.5 Safety Analysis and Endpoints

Safety and tolerability of the study drugs will be assessed by collection and review of adverse events, tolerability, laboratory parameters, physical examination, vital signs, and ECG parameters throughout the duration of the study. Immunogenicity of HM15211 will be assessed by the development of ADAbs, nAbs and anti-PEG.

Safety analysis will involve examination of the descriptive statistics and individual subject listings for any effects of study treatment on clinical tolerability and safety. Placebo patients will be pooled across cohorts in the safety analysis.

The 24-hour blood pressure (day and night time systolic/diastolic BP) collected from ABPM, and 24-hour Holter ECG (HR, HRV [eg, difference between day and night HR, NN intervals, SDNN, SDANN, SDNN index]) will be summarized descriptively by treatment dose.

All AEs will be coded using the most current MedDRA version. AEs will be summarized using preferred term and primary system organ class using the safety analysis set by treatment dose.

Adverse event summaries will include the overall incidence (by system organ class and preferred term), events by maximum intensity, event by relationship to study treatment, events leading to discontinuation of study drug, and serious adverse events. Physical exam, vital signs, blood pressure assessed by ABPM, heart rate assessed by Holter ECG, 12-lead ECG data, and laboratory parameters (hematology, chemistry, and urinalysis) will be summarized descriptively by treatment.

12.3 Interim Analysis

No formal interim analysis is planned.

12.4 Determination of Sample Size

Due to the exploratory nature of this study, a sample size of 12 subjects per cohort is empirically determined and consistent with typical sample sizes used for similar studies to assess PK and safety data.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The study will be monitored by [redacted] monitor.

Monitoring visits to the study sites will be made periodically during the study to ensure that all aspects of the protocol and GCP are followed, CRFs are completed correctly, and drug accountability is monitored. The Monitor will visit the sites at least once before First Subject First Visit (FSFV) (Initiation Visit), at least once during the clinical part of the study, and at least once after Last Subject Last Visit (LSLV). Furthermore, the Monitor must be available for discussions by telephone.

[redacted] may assign additional Clinical Research Associates (CRAs)/Monitors on an ad hoc basis for training purposes and to meet required timelines. In addition, if study timelines are modified for any reason, e.g., delays in recruitment or accelerated enrollment, [redacted] may use additional CRAs at its discretion to ensure study expectations are met.

The Monitor must be given direct access to source documents, such as original documents, data, and records. Direct access includes permission to examine, analyze, verify any record(s) and report(s) that are important to evaluation of the clinical study. The study will be monitored to verify integrity and validity of the data. Monitoring will follow a Monitoring Plan.

Additional QC monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by qualified staff of [redacted]

13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other circumstances arise that will require deviation from protocol-specified procedures, unless there is an emergency or immediate need, the Investigator should contact the medical monitor and Sponsor to review and discuss the implications of the deviation and determine the appropriate course of action. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the subject and/or the study. The documentation must be kept in the Investigator's Study File and the Sponsor's Study Master File.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted in accordance with the Protocol, the International Conference on Harmonization (ICH), Guideline for Good Clinical Practice: Consolidated Guidance (E6) and applicable regulatory requirements including clinical research guidelines established by the Basic Principles defined in the U.S. 21 CFR Parts 50, 56, and 312 and the principles enunciated in the Declaration of Helsinki (revised version Fortaleza 2013).[7,8]

14.1 Institutional Review Board and/or Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, subject information/informed consent form, any other written information to be provided to the subject, subject recruitment procedures, information about payments and compensation available to subjects if not mentioned in the subject information, the Investigator's current CV and/or other documentation evidencing qualifications, and other documents as required by the local Independent Ethics Committee (IEC)/Institutional Review Board (IRB) should be submitted. The submission letter should clearly identify (by study identification number, including version, title and/or date of the document) which documents have been submitted to the IEC/IRB. Written approval/favorable opinion must be obtained from IEC/IRB prior to commencement of the clinical study start.

During the study, the Investigator must promptly report the following to the IEC/IRB: Updates to IB, unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the study status and other documents as required by the local IEC/IRB.

Substantial amendments must not be implemented before approval/favorable opinion, unless necessary to eliminate hazards to the subjects.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC/IRB. The records should be filed in the Investigator's Study File and copies must be provided to the Sponsor.

14.2 Regulatory Authorities

Regulatory Authorities will receive the Clinical Study Application, Protocol, Amendments to the Protocol, reports on SAEs and the Integrated Clinical Study Report according to national regulations.

14.3 Responsibilities of the Investigator

The Investigator will conduct this clinical study in compliance with all applicable national, state, local or regional laws and regulatory requirements of the countries in

which the clinical study is performed. The Investigator will align his or her conduct in accordance with the "Responsibilities of the Investigator".

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigators" (Form FDA 1572), which must be completed and signed before the Investigator may participate in this study.

14.4 Informed Consent

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

14.5 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Subject records will be kept private except when ordered by law. The following individuals will have access to study subject records: Principal Investigator and designees, study Sponsor, monitors and auditors, the FDA, other government offices and the IRB.

Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

The Investigator must agree to permit the Sponsor's monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's source data or documents, including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process. The confidentiality of the verified data and the protection of the subjects must be respected during these inspections.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed.

14.6 Publication, Disclosure, and Clinical Study Registration Policy

The Investigator will provide the Sponsor with truthful, accurate and complete test results and all data derived from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

[ ] or its designee will be responsible for preparing the Clinical Study Report. When all data has been fully analyzed, [ ] or Sponsor will communicate the results of the Clinical Study to the Investigator(s).

The Investigator or qualified designee agrees to use this information only and strictly in connection with this Clinical Study and must not use it for other purposes without the prior written permission from the Sponsor. Prior to any publication, the Sponsor must be given the opportunity to review and comment upon any manuscript, poster, or paper that contains data derived or generated from this study in order to be aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

To ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable law, regulation and guidance, this study may be registered on Clinicals.gov or other publicly accessible websites before study initiation.

14.7 Insurance and Compensation for Injury

The Sponsor shall carry applicable insurance in the types and amounts necessary to cover its obligations herein in accordance with local laws and requirements and/or guidelines for conducting clinical studies in any country, unless others have shown negligence. The Sponsor renounces liability in the event of negligence or any other liability by the clinics or doctors conducting experiments or by persons for whom the said clinic or doctors are responsible. The Sponsor accepts liability in accordance with all applicable regulations per the Code of Federal Regulations (CFR) and all other applicable federal or state regulations.

Each subject in the study must be insured in accordance with the regulations applicable to the study site where the subject is participating.

If a subject becomes ill or injured due to an adverse event directly resulting from use of the study drug or a study procedure in the course of their participation in this Clinical Study, medical treatment will be provided. Sponsor will pay the costs of such treatment.

15.0 REFERENCES

1. Obesity and overweight fact sheet (2016). http://www.who.int/mediacentre/factsheets/fs311/en/
2. Finer N. Medical consequences of obesity (2003). Medicine, Vol 43: 2, pp 88-93
3. Sanchez-Garrido MA, Brandt SJ, Clemmensen C et al (2017). GLP-1/glucagon receptor co-agonism for treatment of obesity. Diabetologia Vol 60, pp 1851-1861
4. Choi IY, Lee JS, Kim JK, et al. (2017). Potent body weight loss and therapeutic efficacy in a NASH animal model by a novel long-acting GLP-1/GIP/Glucagon tri-agonist (HM15211). Diabetologia, Vol 60: Supplement 1, pp 1-564
5. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, Food and Drug Administration. Center for Drug Evaluation and Research, July 2005.
6. European Medicines Agency guidance: Guidelines on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products, Committee for Medicinal Products for Human Use (CHMP), July 2007
7. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002.and Note of clarification on paragraph 30 by the WMA General assembly, Tokyo 2004
8. International Conference on Harmonization. ICH Harmonized Tripartite Guideline. Good Clinical Practice. 01-May-1996

16.0 APPENDIX A

Table 16-1 Schedule of Events Cohorts 1-1 and 1-2

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

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

[1]Confirmation of eligibility.
[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points
[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.
[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from the ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule in section 9.1.16.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1.

[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 16-2 Schedule of Events, Cohort 1-3 (not including Day 82)

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

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

[1]Confirmation of eligibility.
[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points
[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.
[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 4 and 81 after subject have been disconnected from the ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).

[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule in section 9.1.16. Cohort 3 will start to collect additional PK sample with start of Day 78.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1.
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits on non-dosing days in the morning, approximately at the time of the dosing on dosing days
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 16-3 Schedule of Events, starting with Cohort 1-3 (including Day 82)

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

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

[1]Confirmation of eligibility.
[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points
[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from the ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule in section 9.1.16. Cohort 1-3 will start to collect additional PK sample with start of Day 78. .
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits in the morning, approximately at the time of the dosing on non dosing days
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.
* Day 82 is optional for subjects already participating in cohort 1-3.

Table 16-4 Schedule of Events, Cohort 1-4

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

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

[1]Confirmation of eligibility.
[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points
[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from the ambulatory device.
[5]Subjects will undergo an MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule in section 9.1.16.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits in the morning, approximately at the time of the dosing on non-dosing days
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

Table 16-5 Schedule of Events, Cohort 1-5 and up

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

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

[1]Confirmation of eligibility.
[2]Serum pregnancy test only at screening, urine pregnancy tests at all other time points
[3]Measurements of vital signs on PK sampling days will follow the PK sampling schedule and should be measured prior to every PK sample.

[4]ECG at screening not triplicate. ECG measurements are to be collected on Day-2 and 77 before subjects are connected to the ABPM and on Day 5 and 82 after subject have been disconnected from the ambulatory device.
[5]Subjects will undergo an MRI/MRI-PDFF assessment during week 8, as close as possible to Day 57, but prior to the Day 57 (week 9) Dosing and during week 12, as close as possible to Day 85, but prior to the Day 85 PK sampling (week 13).
[6]All incretins will be collected at the same time points together with the PK sample collection.
[7]Subjects need to be in fasting condition for collection.
[8]PK sampling will follow the PK sampling schedule in section 9.1.16.
[9]Injection site will be inspected pre-dose, at 4 and 12-hour post-dose on Day 1. Assessment of injection site on the other dosing days at least 30 minutes post-dose, and then daily during the in-house periods and at outpatient visits in the morning, approximately at the time of the dosing on non-dosing days
[10]CRP only, on Day 3. CRP is also measured at SCR/D1/D8/D15/D29/D36/D57/D78/D85/D99 in chemistry panel.
[11]Inflammatory biomarkers will be collected at the same time points together with the PK sample collection.
[12]To be measured prior to dosing.
[13]Weight to be collected in the morning, fasting and post void. On all dosing days, weight should be measured pre-dose.

17.0 APPENDIX B

Adverse Event Guidance Document

General Statement

As any new investigational product may have unexpected adverse events, the following guidance is offered for potential, but unexpected, toxicities for HM15211. The following diagnostic work-up and procedures are suggested actions and should be tailored to the clinical presentation as assessed by the Investigator.

1. Cardiovascular Toxicity

Definitions:

Signs and symptoms may include:

chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, fatigue

Diagnostic Workup:

At baseline:

- Electrocardiogram
- Cardiac biomarkers (creatine kinase and troponin)

Depending on presentation:

- Inflammatory biomarkers (ESR, CRP, WBC count)
- O_2 Saturation
- BNP
- Emergency room/hospital transfer
- Cardiology consultation
- Chest x-ray

Additional testing to be guided by cardiology and may include:

- Echocardiography
- Stress test
- Cardiac catheterization
- Cardiac MRI

<table>
<tr><th>Grading*</th><th>Management</th></tr>
<tr><td>G1: Asymptomatic abnormal cardiac biomarker testing, including abnormal ECG</td><td rowspan="3">All grades warrant workup and intervention given potential for cardiac compromise

Please consider the following:
• Hold therapy and permanently discontinue after G1
• Management of cardiac symptoms according to ACC/AHA guidelines
• Transfer patient to the emergency room at the hospital for further evaluation and management for any grade > G1
• Cardiology consultation</td></tr>
<tr><td>G2: Mild symptoms consistent with cardiotoxicity with or without abnormal cardiac biomarkers</td></tr>
<tr><td>G3: Moderate symptoms consistent with cardiotoxicity and/or clinically significant abnormal cardiac biomarkers</td></tr>
<tr><td>G4: Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions</td><td></td></tr>
<tr><td colspan="2">Qualifying Statement: Treatment recommendations are based on local standards of care and the life- threatening nature of cardiovascular complications. Holding therapy is recommended for complication grades greater than G2. The appropriateness of rechallenging remains unknown.</td></tr>
</table>

* Not associated with CTCAE grading system

2. Rash/Inflammatory Dermatitis and Other Skin Disorders

Definitions:

- Erythema multiforme major and minor (a targetoid reaction in the skin and mucous membranes usually triggered by infections, such as Herpes Simplex Viruses, but can be associated with an immune-related drug eruption and if progresses to EM major, it can be a harbinger of SCAR, such as SJS)
- Lichenoid (resembling the flat-topped, polygonal and sometimes scaly or hypertrophic lesions of lichen planus)
- Eczematous (Inflammatory dermatitis characterized by pruritic, erythematous, scaly or crusted papules or plaques on the skin, which is vulnerable to superinfection)
- Psoriasiform (resembling the well-demarcated, erythematous and scaly papules and plaques of psoriasis)
- Morbilliform (a non-pustular, non-bullous measles-like exanthematous rash of the skin often referred to as "maculopapular" and without systemic symptoms or lab abnormalities, excluding occasional isolated peripheral eosinophilia
- Palmoplantar erythrodysaesthesia (PPE) (hand-foot syndrome) (redness, numbness/burning/itching and superficial desquamation of the palms and soles)
- Neutrophilic dermatoses (e.g. sweet's syndrome)
- Others

Diagnostic Workup for Skin Disorders above and Others Considered to be Possibly IP-related:

- Pertinent history and physical exam
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug or a skin condition linked to another systemic disease or unrelated primary skin disorder
- If needed, a biological checkup including a blood cell count, liver and kidney tests
- Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody test, SSA/Anti-Ro, SS-B/Anti-La if predominantly photodistributed/photosensitivity, anti-histone, ds-DNA and other relevant serologies. Consider expanding serologic studies or diagnostic work up if other autoimmune conditions are considered based on signs, symptoms.
- Dermatology consultation with skin biopsy
- Consider clinical monitoring with use of serial clinical photography, if IRB approved and subject has consented

- Review full list of patient medications to rule out other drug-induced cause for photosensitivity

Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	**Management**
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	• Consider continuing therapy for mild localized reaction, e.g., injection site erythema • Consider treatment with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.	• Dermatology consultation with possible biopsy • Consider holding therapy and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 • Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at 4 weeks In addition, treat with topical emollients, oral antihistamines and medium-to-high potency topical corticosteroids
G3: As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis.	• Hold therapy and consult with dermatology to determine appropriateness of resuming • Treat with topical emollients, oral antihistamines and high potency topical corticosteroids • Initiate oral prednisone or equivalent (0.5-1 mg/kg/day) tapering over at least 4 weeks

G4: All severe rashes not manageable with prior intervention	• Immediate hold therapy and consult dermatology to determine appropriateness of resuming therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10mg or less. • Systemic steroids: IV (methyl)prednisolone (or equivalent) dosed at 1–2mg/kg with slow tapering when the toxicity resolves • Monitor closely for progression to Severe Cutaneous Adverse Reaction • Should admit patient immediately with an urgent consult by dermatology

3. Gallstones (Cholelithiasis), Biliary Cholic or Cholecystitis

Definition:

Asymptomatic gallstones/ asymptomatic common bile duct stones: Stones that are found incidentally, as a result of imaging investigations unrelated to gallstone disease in people who have been completely symptom free for at least 12 months before diagnosis.

Symptomatic gallstones/ symptomatic common bile duct stones: Stones found on gallbladder imaging, regardless of whether symptoms are being experienced currently or whether they occurred sometime in the 12 months before diagnosis.

When should symptomatic gallbladder stones be suspected?

The characteristic symptoms of gallbladder stones, i.e. episodic attacks of severe pain in the right upper abdominal quadrant or epigastrium for at least 15-30 minutes with radiation to the right back or shoulder and a positive reaction to analgesics, should be identified by medical history and physical examination

- **Diagnostic Workup for Symptoms Suggestive of Gallstone-related Disorders:**
- Liver function tests and ultrasound for suspected gallstone disease, and for individuals with abdominal or gastrointestinal symptoms that have been unresponsive to previous management.
- Consider magnetic resonance cholangiopancreatography (MRCP) if ultrasound has not detected common bile duct stones but the:
    - ✓ bile duct is dilated and/or
    - ✓ liver function test results are abnormal.
- Consider endoscopic ultrasound (EUS) if MRCP does not allow a diagnosis to be made.
- Consider holding therapy and consulting gastroenterology.
- Refer people for further investigations if conditions other than gallstone disease are suspected.

4. Gastrointestinal Events

Definition: Nausea and vomiting are anticipated adverse events with this protocol. The initial assessment needs to include consideration of other differentials including pancreatitis and cholelithiasis. Laboratory assessments of amylase, lipase and liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) or imaging (ultrasound, CT or MRI) should be considered and pursued if indicated.

Severity of symptoms should be assessed as following:

Grading (Not associated with CTCAE grading system)	**Management**
G1: Mild symptoms that do not interfere with quality of life	• No intervention
G2: Mild to moderate symptoms that may need intervention based on Investigator.	• Patient observation • Consider initiating antiemetic medication
G3: Moderate to severe symptoms that need medical intervention.	• Hold therapy; resume therapy only if symptoms are fully resolved • Treat with antiemetic medication as indicated • Treat with IV fluid • Treat with parenteral nutrition if no oral intake sustained beyond 7 days
G4: Life-threatening symptoms	• Immediately discontinue therapy • Systemic IV fluids • Treat with antiemetic medication as indicated • Treat with parenteral nutrition • Should admit patient immediately with an urgent consult