Clinical Development HM15211

Clinical Study Protocol HM-TRIA-101

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

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided.

1.2 Approval

Representatives of Sponsor and Principal Investigator will sign the agreement on the protocol.

1.3 Document History

Version	Revision Date	Revision Description
1.0	**08-Dec-2017**	**Original Document**
2.0	**04-Feb-2018**	**FDA Review Based Revisions:** **1. Addition of Maximum Dose and Dose Escalation Steps** The maximum human dose is determined by the exposure seen at the NOAEL in the 4-week toxicology study in the rat which corresponds to approximately 0.16 mg/kg in a human according to pharmacokinetic (PK) prediction. Doses between cohorts will not exceed a 2-fold increase relative to the specified doses stated below. The maximum dose for each cohort will be defined as: Cohort 1 - Starting dose 0.01 mg/kg; Cohort 2 – Dose will not exceed 0.02 mg/kg; Cohort 3 – Dose will not exceed 0.04 mg/kg; Cohort 4 – Dose will not exceed 0.08 mg/kg; Cohort 5 – Dose will not exceed 0.16 mg/kg. Dose escalation will be based on clinical safety and available PK data. *Section 2.0 Study Summary, section 4.4 Rationale for Starting and Maximum Dose, section 4.5 Dose Escalation Algorithm* **Additional Revisions:** **2. Correction of Placebo Description** Placebo is a sterile, matching solution (all components except the drug substance) and free of visible particles. *Section 8.1.2 Placebo*

		3. Safety Review and Dose Escalation Meetings Safety Review and Dose Escalation Meeting to be held after all subjects of one cohort have completed at least the D10 Visit. Therefore, cohorts may overlap. After PK modeling from preclinical 3 animal species, human C_{max} is expected to be reached approximately 3 days after dosing. As dose limiting adverse events occur at or around C_{max}, safety data beyond Day 10 are not critical for a dose escalation decision. *Section 2.0 Study Summary, section 4.5 Dose Escalation Algorithm, section 6.1 Study Design, Figure 6-2 Dose Escalation Schematic, section 6.3 Rationale for Study Design and Endpoints* **4. Change of Principal Investigator (PI)** PI change from Dr. Rodriguez to Dr. Morrow due to Sponsor preference. *Investigator Approval Page (page 5)* **5. Addition of Biomarkers to Exploratory Endpoints** Incretin secretion: Glucagon-like peptide-1 (GLP-1) and Gastric inhibitory polypeptide (GIP) are added to exploratory endpoints. GLP-1 and GIP will be collected at timepoints of glucagon (GCG) collection and analysis. These additional biomarkers will be analyzed to expand the PD assessment of the drug. *Section 2.0 Study Summary, section 5.2 Exploratory Objectives and Endpoints, section 9.1.17 Pharmacodynamic Assessments and Schedule, Table 9-3 PD Sampling Schedule, Table 12-1 Study Endpoints, section 12.2.4 Analysis of the Pharmacodynamic Endpoints and Table 16-1 Schedule of Events.* **6. Addition of timepoints for the existing PD endpoint fasting plasma glucose (FPG) analyses** Blood samples for the analysis of FPG will be collected and analyzed on a daily basis during In-house Period, Outpatient Visits and Follow-up Visit to expand the assessment of this PD parameter. *Section 9.1.17 Pharmacodynamic Assessments and Schedule, Table 9-3 PD Sampling Schedule and Table 16-1 Schedule of Events*

		7. Adjustment of Blood Volume. Due to revisions # 4 and 5, but combination of analyses, additional blood volume of approximately 20 mL is necessary per subject. *Section 9.1.20 Blood Volume* **8. Clarifications:** **a) Markers in Schedule of Events (SOE)** 'Lipid panel, incl. FFA', and 'FPG' rows in the SOE: Timepoints for analyses of the parameters are to be performed per protocol at Screening, but fields in table were not marked with an 'X'. Adjustment of footnotes. *Table 16-1 Schedule of Events* **b) Urine Pregnancy Test** Urine pregnancy testing via commercial kit at CRU will be performed 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. *Table 9-1 Clinical Laboratory Assessments* **c) Correction of Typographical Error** Screening period stated with 30 days instead of 28 days. *Figure 6-1 Study Design Schematic*
3.0	**09-Feb-2018**	**FDA Review Based Revisions:** **1. Change of Storage Condition for Investigational Product** Recommended storage condition at room temperature is up to 4 hours instead of up to 12 hours, considering the potential risk of biological products and formulations. *Section 8.3 Storage and Drug Accountability of Investigational Product.*
4.0	**06-Apr-2018**	**Revisions for this Amendment:** **1. Change of Dose Escalation** The dose escalation decision for subsequent cohorts can be made after a minimum of 6 subjects (at least 4 subjects on active drug) have completed at least Day 10, and safety and available PK data have been

		reviewed. Four subjects are sufficient for the initial assessment of safety risks and for the selection of the drug dose for the next cohort. *Section 4.5 Dose Escalation Algorithm and section 6.1 Study Design* **Additional Revisions:** **2. Clarifications:** **a) Sentinel Dosing** Dosing will follow a sentinel approach, comprising one active- and one placebo-treated subject at the start of each cohort followed by the remainder of the cohort, after a dosing interval of at least 24 hours. Adjustment of language in section 6.1. *Section 6.1 Study Design* **b) PK/PD Sampling Time Windows** The actual time of PK sampling should not deviate from the nominal time by more than ± 5 minutes during inpatient period. The study window on outpatient visits (±1 day) and follow-up visit (± 2 days) will apply for the PK sampling at these visits. The PK sampling windows apply to all PD sampling timepoints as well. *Section9.1.16 Pharmacokinetic Assessments and Schedule and 9.1.17 Pharmacodynamic Assessments and Schedule* **c) Contraception** 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. Adjustment of language for consistency throughout the protocol. *Section 9.1.9 Contraception* **d) Clarification of Randomization Codes** Language added to describe the assignment of randomization codes for subjects that need to be replaced during the study. *Section 8.6 Randomization and Blinding* **e) Clarification of ECG Procedures** ECG's will be performed as triplicate 12-lead ECG's throughout the study, except for the Screening Visit. Language and footnote added.

		Section 9.1.11 ECG Procedure, Table 16-1 Schedule of Events **f) Clarification of Measurements for Vital Signs** Pulse rate and respiration rate: Pulse rate will be assessed in combination with both, supine and standing blood pressure measurements**.** Respiration rate will be assessed at time points of supine blood pressure measurements. The blood pressure measurement will start with the supine measurements after 5 minutes resting, but the standing blood pressure measurement will be taken within 3 minutes in upright position. *Section 9.1.6 Vital Signs, Footnote 1 to Table 16-1 Schedule of Events* **3. Addition of Amino Acids Analysis** During the course of the study, additional blood samples will be taken for the analysis of amino acid profiles. Samples will be taken at the same timepoints stated for GIP/ GLP-1 sampling. Amino acids will be analyzed to expand the PD assessment of the drug. *Table 9-3 PD Sampling Schedule, Table 16-1 Schedule of Events and section 9.1.17 Pharmacodynamic Assessments and Schedule* **4. FSH level for Postmenopausal Women** Lower limit of FSH value for postmenopausal women will be updated from > 40 to ≥ 25.8 mIU/mL according to laboratory reference. Additionally, female subjects who are postmenopausal, but have a FSH value < 25.8 mIU/mL, may still be enrolled in the study, if they have a negative serum hCG pregnancy test and agree to be on a highly contraceptive method. *Section 9.1.9 Contraception*

Investigator Approval Page

Protocol Title:	**A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HM15211 in Healthy Obese Subjects**
Protocol Number:	**HM-TRIA-101**
Protocol Version:	4.0
Date:	06-Apr-2018

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.

Principal Investigator:

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Name (printed)	**Signature**	**Date**

Sponsor Protocol Approval Page

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Approved for the Sponsor by:

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2.0 STUDY SUMMARY

Name of Study Drug	HM15211
Protocol Number	HM-TRIA-101
Protocol Title	**A First-in-Human, Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of HM15211 in Healthy Obese Subjects**
Primary Objectives and Endpoints	To assess safety and tolerability of HM15211 after single subcutaneous (SC) doses, in regard to: • Incidence of adverse events • Incidence of clinical laboratory abnormalities (including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin) • Immunogenicity (Anti-drug antibodies [ADAbs], neutralizing antibodies [nAbs], anti-polyethylene glycol antibodies [anti-PEG]) • Change from baseline in vital signs (blood pressure, respiratory rate, temperature, and heart rate) measurements • Incidence and severity of clinical findings on physical examination • Injection site reaction • Change from baseline in 12-lead ECG parameters; the primary ECG endpoint will be QTcF • Blood pressure (BP) assessed by 24-hour ambulatory blood pressure monitoring (ABPM); (Mean day- and night time systolic/diastolic BP) • Heart rate activity assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG); (Heart rate [HR] and heart rate variability [HRV], e.g. mean heart rate, difference between day and night HR, mean normal to normal [NN] intervals, standard deviation of all NN intervals [SDNN]) To assess the pharmacokinetic (PK) profile of HM15211 after single SC doses in regards, but not limited to:

	• Maximum concentration (C_{max}) • Time to reach Cmax (T_{max}) • Total area under the concentration time curve (AUC), including $AUC_{(0\text{-}inf)}$ • Apparent terminal half-life ($t_{1/2)}$ • Apparent clearance (CL/F) • Apparent volume of distribution at terminal phase (Vz/F) • Terminal elimination rate constant (k_{el})
Exploratory Objectives and Endpoints	To assess pharmacodynamics (PD) properties of HM15211 after single SC doses in comparison to placebo on: • Lipid metabolism: o Total cholesterol o Low-density lipoprotein (LDL) o High-density lipoprotein (HDL) o Very low-density lipoprotein (VLDL) o Triglycerides o Free fatty acid (FFA) • Body weight • Glucose metabolism: o Fasting plasma glucose (FPG) o Insulin o C-peptide • Incretin secretion: o Glucagon (GCG) o Leptin o Glucagon-like peptide-1 (GLP-1) o Gastric inhibitory peptide (GIP) • Inflammatory marker: o C-reactive protein (CRP)
Phase of Development	1
Number of Study Sites	1
Subjects	Healthy Obese Subjects

Number of Subjects	Approximately 40 subjects, divided in 5 cohorts with 8 subjects per cohort.
Summary of Study Design	This is a double-blind, randomized, placebo controlled, SAD study to investigate the safety, tolerability, and PK of the subcutaneous (SC) administration of HM15211 in healthy obese subjects. The study will be conducted in 5 sequential dosing cohorts, enrolling 8 subjects per cohort. Cohorts may partially overlap, if dose escalation decision after the Day 10 Visit has been made. Subjects will be randomized to HM15211 or placebo in a ratio of 6:2 (6 on active, 2 on placebo). Dosing will follow a sentinel approach with dosing at least 24 hours apart. Based on available safety, tolerability, and PK data, and following a safety review and dose escalation meeting between the investigator and the sponsor, dose escalation to the next cohort may proceed. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels. Adjustments to the procedures may occur after the review of available safety and PK data: • Adjustments to the number of study cohorts may occur: Additional cohorts may be enrolled and proceed at a higher or a lower dose. If deemed appropriate by the investigator and sponsor, there may be more than one cohort investigated at the same dose level. • Adjustments to the 24-hr BP and HR monitoring: After the evaluation of the first cohort, tests may be rescheduled, or measurement periods may be focused on specific days to capture the 24-h measurement around the PK_{peak}. • Adjustments to the visit schedule: If PK data suggest, additional sampling times and/or outpatient visits may be added to the study schedule. Each subject will undergo a screening visit, up to 28 days prior to the first dosing. Each subject will undergo one in-house period of 9-day duration, two outpatient visits, and a follow-up visit. **Screening:**

	A Screening Visit will be performed up to 28 days prior to the first dosing to identify eligible subjects for the study. **In-house Period:** Subjects will check in to the clinic in the morning on Day -2 for a 9-day In-house Period. They will receive standardized meals throughout their inpatient stay. Subjects will be connected to an ABPM system, and overnight measurements will be taken to familiarize the subjects with the device. ABPM measurements will continue throughout Day 4. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation. In the morning of Day -1, subjects will get connected to a Holter ECG for 24-hour measurements and will continue these until the morning of Day 4. Only 24-hour monitoring data from Day -1 will be used for the baseline monitoring evaluation. Subjects will be randomized to a single SC injection of HM15211 or placebo. On Day 1, the active study 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, PK and laboratory parameter will be performed for safety evaluation. ABPM and Holter ECG monitoring will be continued until the morning of Day 4 for the post-dose evaluation. 24-hour monitoring evaluations will be performed together with available PK data, in order to determine the best time period for 24-h monitoring period around PK_{peak}. Subjects will continue to stay in-house for safety evaluations and PK. They will be released from the clinical research unit (CRU) in the morning of Day 7 and will return for two outpatient visits on Day 10 and 17. **Outpatient Visits:** Subjects will return to the CRU on Days 10 (± 1) and 17 (± 1) for two outpatient visits. Blood samples for PK analysis will be collected, additional safety assessments as stated in Table 16-1 will occur. **Follow-up Visit:** A follow-up visit will take place on Day 30 (± 2).

<table>
<tr><td></td><td>Time points for study procedures and sample collections for PK measurements will be specified in detail in Table 16-1 of the protocol.

Safety assessments will occur throughout the duration of the study.</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</td><td>N=6</td><td>HM15211 - 0.01 mg/kg</td></tr>
<tr><td>N=2</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 2</td><td>N=6</td><td>HM15211 ≤ 0.02 mg/kg</td></tr>
<tr><td>N=2</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 3</td><td>N=6</td><td>HM15211 ≤ 0.04 mg/kg</td></tr>
<tr><td>N=2</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 4</td><td>N=6</td><td>HM15211 ≤ 0.08 mg/kg</td></tr>
<tr><td>N=2</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 5</td><td>N=6</td><td>HM15211 ≤ 0.16 mg/kg</td></tr>
<tr><td>N=2</td><td>Placebo</td></tr>
</table>
Starting dose is determined with 0.01 mg/kg for Cohort 1. The maximum human dose is determined by the exposure seen at the NOAEL in the 4-week toxicology study in the rat which corresponds to approximately 0.16 mg/kg in a human according to PK prediction. Doses between cohorts will not exceed a 2-fold increase relative to the specified doses stated above. Dose escalation will be determined in safety review and dose escalation meeting by Sponsor and Investigator and will be based on clinical safety and available PK data.</td></tr>
<tr><td>Route of Administration</td><td>All study drugs will be administered by SC injection into the abdominal wall.</td></tr>
<tr><td>Duration of Participation</td><td>The duration of participation in this study, including Screening, Treatment and Follow-up will be approximately 9 weeks for each subject.</td></tr>
<tr><td>Inclusion Criteria</td><td>Subjects who meet all criteria at Screening will be included in the study:

1. Male and female subjects.</td></tr>
</table>

	2. Age ≥ 18 to ≤ 65 years. 3. Body mass index (BMI) ≥ 30 to ≤ 40 kg/m^2, with stable body weight by history for 3 months (defined as change < 5%). 4. HbA1c < 6.5 %. 5. 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. 6. Ability to provide written informed consent.
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from the study: 1. 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 GERD) at Screening. 2. Use of antacids, anticoagulants, drugs that directly modify gastrointestinal (GI) motility, including, but not limited to, anticholinergics, antispasmodics, 5HT3 antagonists, dopamine antagonists, or opiates within 2 weeks of screening. 3. 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). 4. Use of any drugs that are known to interfere with glucose or insulin metabolism, including but not limited to oral or parenteral corticosteroids or topiramate, monoamine oxidase (MAO) inhibitors, growth hormone, within 3 months prior to screening.

	5. Treatment with antihypertensive medication and statins, unless on stable dose for at least 3 months prior to screening. 6. Any weight control treatment, including over-the-counter and herbal medication and supplements, or any medication with a labelled indication for weight loss or weight gain within 3 months prior to screening. 7. Any prior treatment with GLP-1 receptor agonists (e.g., exenatide, liraglutide, dulaglutide), dipeptidylpeptidase-4 (DPP-4) inhibitors, oral antidiabetic drugs and insulin. 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. Calcitonin levels > 20 pg/mL at screening. 10. 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. 11. History of major depression, anxiety, 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. (Use of SSRIs and SNRIs [including bupropion] for reasons other than active psychiatric indications [eg, migraine, weight loss, smoking cessation] must meet a 3-month wash-out) 12. History of significant suicidal ideation or suicidal behavior/attempts. 13. History of any major surgery within 6 months prior to screening. 14. History of any serious adverse reaction or hypersensitivity to study drugs components. 15. 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) 16. Cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening. 17. Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2). 18. Abnormal laboratory results for TSH (> 1.5 x ULN or < 0.5 mIU/L) 19. Abnormal laboratory results for fasting triglycerides >1151 mg/dL (≥ 13.0 mmol/L). Elevated values may be repeated once on a separate day. (Subjects with fasting triglycerides ≥ 13.0 mmol/L may be included in the study if LDL < 131 mg/dL (< 3.4 mmol/L) and if they have no history of pancreatitis, CVA, transient ischemic stroke, or myocardial infarction as approved per Investigator's discretion.) 20. Abnormal laboratory results for LDL 189 mg/dL (>4.9 mmol/L) for untreated dyslipidemia or > 158 mg/dL (> 4.1 mmol/L) for treated dyslipidemia. Elevated values may be repeated once on a separate day. 21. Clinically significant abnormal hepatic function tests suggestive of hepatic impairment (eg, ALT and AST >2 x ULN). 22. Clinically significant abnormal pancreatic function tests suggestive of pancreatic impairment (eg, amylase and lipase >3 x ULN). 23. 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). 24. History of any active infection, other than mild viral illness within 30 days prior to dosing as judged by the investigator. 25. Use of a very-low calorie (1,000 kcal/day) liquid weight loss diet within 6 months prior to screening 26. History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year.

	27. 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. 28. Frequent use of marijuana within 6 weeks, or clinically under the effect at screening, as per Investigator evaluation. 29. Known history of or 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. 30. Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study. 31. Presence of clinically significant physical, laboratory, or ECG findings (eg, QTcF > 450 msec for males, QTcF > 470 msec for females, LBBB) at screening that, in the opinion of the Investigator, may interfere with any aspect of study conduct or interpretation of results. 32. Donation or loss of >500 mL of blood or blood product within 56 days of dosing. 33. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation. 34. Is employed by Hanmi or ProSciento (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of Hanmi or ProSciento, defined as a spouse, parent, sibling, or child, whether biological or legally adopted.
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
ADCC	Antibody dependent cellular toxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
Anti-PEG	Anti-polyethylene glycol antibody
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BG	Blood glucose
BMI	Body mass index
BUN	Blood urea nitrogen
BP	Blood pressure
BW	Body weight
CDC	Complement dependent cytotoxicity
CDM	Clinical data management
C.I.	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CV	Coefficient of variation
DFT	Deviation from target
DIO	Diet-induced obesity
DMP	Data management plan
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic CRF
EE	Energy expenditure
FDA	Food and Drug Administration
FFA	Free fatty acid
FPG	Fasting plasma glucose
FSFV	First subject first visit
GCG	Glucagon
GCGR	Glucagon receptor
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal

GIP	Glucose dependent insulinotropic polypeptide/ gastric inhibitory peptide
GIPR	Glucose dependent insulinotropic polypeptide/ gastric inhibitory peptide receptor
GLP-1	Glucagon-like peptide
GLP-1R	Glucagon-like peptide receptor
HbA_{1C}	Glycosylated hemoglobin
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
HRV	Heart rate variability
IB	Investigator's brochure
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent Ethics Committee
INR	International normalized ratio
ipGTT	Intra-peritoneal glucose tolerance test
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
lb	Pound
LBBB	Left brunch bundle block
LS mean	Least square mean
MAL-PEG-ALD	Maleimide-Polyethylene glycol- Aldehyde
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
nAbs	Neutralizing antibodies
NAFLD	Nonalcoholic fatty liver disease
NCA	Non-compartmental analysis
NDA	New Drug Application
Nmol	Nanomol
NN	Normal to normal
NOAEL	No-observed-adverse-effect level
NPH	Neutral Protamine Hagedorn insulin
NSAID	Non-steroid anti-inflammatory drugs
OTC	Over the counter
PD	Pharmacodynamics
PE	Physical examination
PEG	Polyethylene glycol

PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
rDNA	Recombinant deoxyribonucleic acid
RHI	Regular human insulin
RR	Respiration rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDNN	Standard deviation of all normal intervals
SDRM	Safety data review and dose escalation meeting
SOE	Schedule of event
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal half-life
TEAE	Treatment emergent adverse event
TG	Triglycerides
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
Vz/F	Apparent volume of distribution at terminal phase
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Overweight 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 worlds adult population.[1]

Obesity impacts many organ systems. One affected system is the cardiovascular system, including 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 become the leading cause of cirrhosis and hepatocellular carcinoma. 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 as TA15211) and human immunoglobulin G4 Fc fragment (named as HMC001) linked via a bifunctional Maleimide-Polyethylene glycol- Aldehyde (MAL-PEG-ALD) linker molecule.

TA15211 is produced by chemical synthesis and the quality of TA15211 is controlled by complying with in-house specification. The HMC001 moiety was derived from the constant region of human immunoglobulin G4 fragment and produced in the transformed E. coli as an inclusion body. The inclusion body was purified after successive refolding and purification steps, and the quality of HMC001 was controlled by in-house specification. Human immunoglobulin G4 Fc fragment (HMC001) was chosen as the stabilizing agent because it is the most prevalent blood protein and has an in vivo half-life of several weeks without effector functions including antibody dependent cellular toxicity (ADCC) and complement dependent cytotoxicity (CDC). The linker is a 10 kDa polyethylene glycol (PEG) with bifunctional reactive groups (maleimide aldehyde reactive groups at individual ends, MAL-PEG-ALD). The conjugation of TA15211 and HMC001 is carried out through the formation of a thioether and amine bond between hetero-bifunctional MAL-PEG-ALD, Cys40 in TA15211, and the N-terminal amino acid in HMC001.

HM15211 is a long-acting GLP-1/Glucagon/GIP triple agonist with 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 following 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 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 first-in-human, single ascending dose study is to investigate safety and tolerability of the drug as well as the PK profile in healthy obese subjects. Five cohorts of 8 subjects will investigate the drug, and will include a placebo comparison in each cohort.

Based on the pre-clinical data and existing research on the drug components/ drug class that exists in the public domain, as well as the proposed monitoring conditions of the proposed inpatient study, it is reasonable and appropriate to investigate the study drug in the intended potential target population. Healthy obese subjects will ensure that a robust and relevant set of safety and PK data can be generated to inform the design of subsequent clinical studies.

4.3 Summary of Pre-Clinical Studies

To date, no human studies have been conducted with HM15211.

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, it shows 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 and 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 as 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.

4.4 Rationale for Starting and Maximum Dose

The proposed starting dose of HM15211 is 0.01mg/kg, selected based on the results of the 28 days toxicology assessments of HM15211 in monkeys and rats, and the application of an additional safety factor, as described in Table 4-1 below.

Table 4-1 Starting Dose Calculations

Species	28-day Toxicity Study NOAEL (mg/kg)	HED (mg/kg)	Planned Starting Dose	Safety Margin vs. NOAEL HED
Rat	0.4	0.07	0.01	7
Monkey	2	0.7		70

The NOAEL was 0.4 mg/kg in rats and 2 mg/kg in monkeys. For conversion to a human equivalent dose (HED), these values were divided by 6.2 for rats and 3.1 for monkeys, resulting in a HED of 0.07 mg/kg for rats and 0.7 mg/kg for monkeys. The starting dose of 0.01 mg/kg in this clinical study is approximately $1/7^{th}$ of the NOAEL for rats and $1/70^{th}$ of the NOAEL in monkeys during the 28-day toxicity evaluation of HM15211. Additionally, the starting dose of 0.01 mg/kg is between the ED_{10} pharmacologically active dose for mice (0.013 mg/kg) and rats (0.007 mg/kg).[5,6]

The maximum human dose is determined by the exposure seen at the NOAEL in the 4-week toxicology study in the rat which corresponds to approximately 0.16 mg/kg in a human according to PK prediction. Dose escalation will be determined in safety review and dose escalation meeting by Sponsor and Investigator and will be based on clinical safety and available PK data.

4.5 Dose Escalation Algorithm

The proposed dose escalation algorithm for HM15211 may include the following steps:

Table 4-2 Sample Allocation and Dose Escalation

Cohorts	Number of Subjects	Treatment Period
Cohort 1	N=6	HM15211- 0.01 mg/kg
	N=2	Placebo
Cohort 2	N=6	HM15211 ≤ 0.02 mg/kg
	N=2	Placebo
Cohort 3	N=6	HM15211 ≤ 0.04 mg/kg
	N=2	Placebo
Cohort 4	N=6	HM15211 ≤ 0.08 mg/kg
	N=2	Placebo
Cohort 5	N=6	HM15211 ≤ 0.16 mg/kg
	N=2	Placebo

Each subject will be randomized to HM15211 or placebo according to the table above. The dose will be 0.01 mg/kg, based on the body weight measured prior to dosing. For dose calculation and rounding, please refer to the Operational Manual/Pharmacy Manual.

After at least 6 subjects ($n \geq 4$ subjects on active drug HM15211) in each cohort have completed at least Day 10, safety and available PK data will be reviewed and a dose decision/ dose escalation decision for the subsequent cohort will be made by the Sponsor and the Investigator. Doses between cohorts will not exceed a 2-fold increase relative to the specified doses stated in the Table 4-3 above. Following the dose escalation decision, the procedures for the subsequent cohorts will be identical to those described above.

Adjustments to the procedures/cohorts may occur after the review of available safety and PK data:

- Adjustments to the number of study cohorts may occur: Additional cohorts may be enrolled and proceed at a higher or a lower dose. If deemed appropriate by the investigator and sponsor, there may be more than one cohort investigated at the same dose level.
- Adjustments to the 24-hr BP and HR monitoring: After the evaluation of the first cohort, tests may be rescheduled, or measurement periods may be focused on specific days to capture the 24-h measurement around the PK_{peak}.
- Adjustments to the visit schedule: If PK data suggest, additional sampling times and/or outpatient visits may be added to the study schedule.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives and Endpoints

To assess safety and tolerability of HM15211 after single SC doses, in regard to:

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

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

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

5.2 Exploratory Objectives and Endpoints

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

- Lipid metabolism:
  - Total cholesterol
  - Low-density lipoprotein (LDL)
  - High-density lipoprotein (HDL)
  - Very low-density lipoprotein (VLDL)
  - Triglycerides
  - Free fatty acid (FFA)
- Body weight
- Glucose metabolism:
  - Fasting plasma glucose (FPG)
  - Insulin
  - C-peptide
- Incretin secretion:
  - Glucagon (GCG)
  - Leptin
  - Glucagon-like peptide-1 (GLP-1)
  - Gastric inhibitory peptide (GIP)
- Inflammatory marker:
  - C-reactive protein (CRP)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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

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

Dosing will follow a sentinel approach with the dosing between the first 2 subjects (1 on active, 1 on placebo) and the remainder of the cohort at least 24 hours apart. A minimum of 10-days between the start date of consecutive dose levels will be maintained. Based on available safety, tolerability, and PK data of each cohort, and following a safety review and dose escalation meeting between the investigator and the sponsor, dose escalation to the next cohort may proceed. If dose escalation is stopped (please see dose escalation stopping criteria in section 6.4.1), dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels.

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

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

Figure 6-1 Study Design Schematic

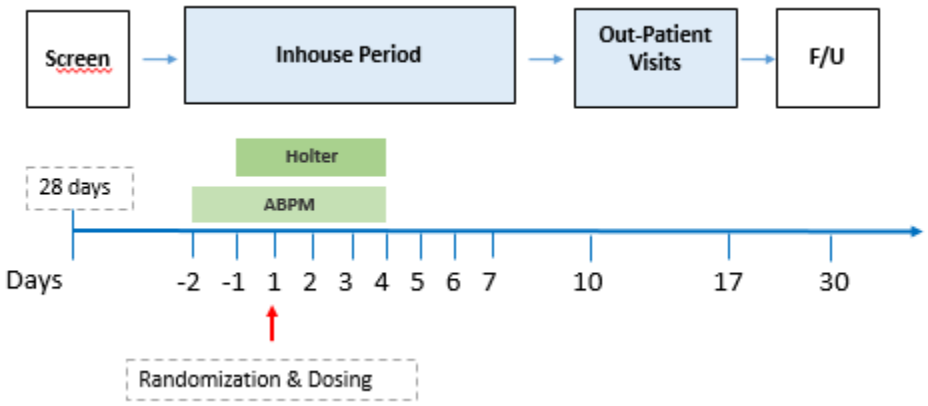
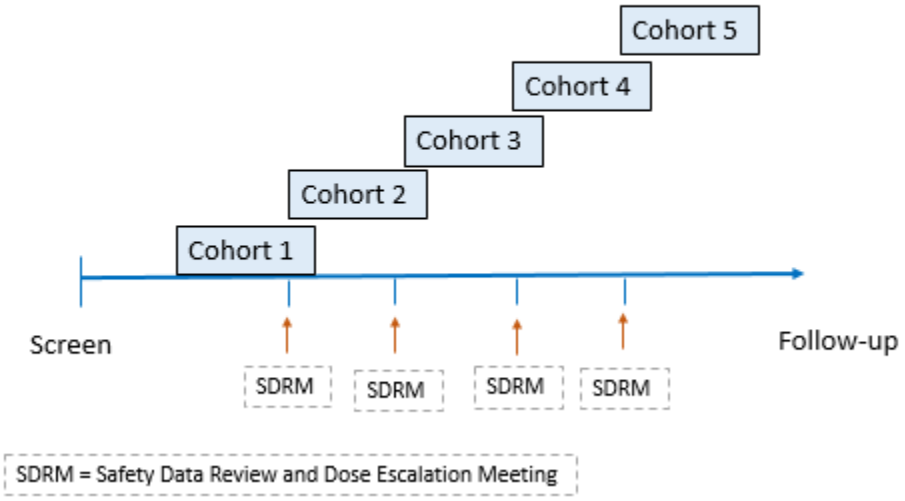


Figure 6-2 Dose Escalation Schematic



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 28 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.

In-house Period:

Subjects will check in to the clinical research unit (CRU) in the morning of Day -2 for a 9-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 4.

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 4.

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 a single SC injection of HM15211 or placebo. Randomization will take place as close to the drug administration as possible.

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, ECG, blood sampling for PK and PD analyses, local injection site evaluation, and laboratory parameter will be performed for safety evaluation, at timepoints stated in Table 16-1.

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

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

Outpatient Visits:

Subjects will return to the CRU on Days 10 (± 1) and 17 (± 1) for two outpatient visits. Blood samples for PK and PD analyses will be collected, and additional safety assessments will be performed as stated in the Table 16-1.

Follow-up Visit:

A Follow-up Visit will be performed on Day 30 (± 2) for final safety procedures. Please see Table 16-1Schedule 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 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.

Immunogenicity samples for assessment of ADAbs, nAbs and anti-PEG will be taken prior to dosing, on Day 17, and at follow-up, 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.

6.3 Rationale for Study Design and Endpoints

This SAD study will assess the safety and tolerability as well as PK of HM15211 as primary objectives.

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 double-blind design has been chosen to avoid bias and to maintain the blind between the administration of the study drug and placebo.

Healthy obese subjects 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, as body mass index will be limited to ≥ 30 to ≤ 40 kg/m^2.

After PK modeling, C_{max} is expected to be reached approximately 3 days after dosing. As this is a first-in-human study, measurements for the assessment of cardiovascular events will start right after dosing and will continue until Day 4. After evaluation of the PK values in the initial cohort(s), the monitoring period will be adjusted, to ensure that the 24-h period around the PK_{peak} is captured.

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.

The study will be conducted at a specialized early phase research centre, where the subjects will be under supervision of physicians, research nurses and additional medical staff experienced in conducting early phase clinical studies investigating new metabolic compounds.

6.4 Study Discontinuation and Stopping Criteria

6.4.1 Dose Escalation Stopping Criteria

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

- Death of a subject (AE grade 5 toxicity) in one cohort, at any time, that is considered related to the IP, judged by the Investigator

- One subject in a cohort develops an AE ≥ Grade 3 toxicity, that is considered related to the IP, judged by the Investigator
- One subject in a cohort develops an AE Grade 2 toxicity that persists for more than 7 days and is considered related to the IP, judged by the Investigator
- 2 or more of the subjects in a cohort have experienced severe adverse events, judged to be possibly or probably related to the IP, judged by the Investigator;
- 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 Investigator.

6.4.2 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.

6.4.3 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. Male and female subjects.
2. Age ≥ 18 to ≤ 65 years.
3. Body mass index (BMI) ≥ 30 to ≤ 40 kg/m^2, with stable body weight by history for 3 months (defined as change < 5%).
4. HbA1c < 6.5 %.
5. 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.
6. Ability to provide written informed consent.

7.2 Exclusion Criteria

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

1. 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 GERD) at Screening.
2. Use of antacids, anticoagulants, drugs that directly modify gastrointestinal (GI) motility, including, but not limited to, anticholinergics, antispasmodics, 5HT3 antagonists, dopamine antagonists, or opiates within 2 weeks of screening.
3. 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).
4. Use of any drugs that are known to interfere with glucose or insulin metabolism, including but not limited to oral or parenteral corticosteroids or topiramate, monoamine oxidase (MAO) inhibitors, growth hormone, oral antidiabetic drugs and insulin within 3 months prior to screening.
5. Treatment with antihypertensive medication and statins, unless on stable dose for at least 3 months prior to screening.

6. Any weight control treatment, including over-the-counter and herbal medication and supplements, or any medication with a labelled indication for weight loss or weight gain within 3 months prior to screening.
7. Any prior treatment with GLP-1 receptor agonists (e.g., exenatide, liraglutide, dulaglutide), dipeptidylpeptidase-4 (DPP-4) inhibitors, oral antidiabetic drugs and insulin.
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. Calcitonin levels > 20 pg/mL at screening.
10. 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.
11. History of major depression, anxiety, 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. (Use of SSRIs and SNRIs [including bupropion] for reason other than active psychiatric indications [eg, migraine, weight loss, smoking cessation] must meet a 3-month wash-out)
12. History of significant suicidal ideation or suicidal behavior/attempts.
13. History of any major surgery within 6 months prior to screening.
14. History of any serious adverse reaction or hypersensitivity to study drugs components.
15. 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)
16. Cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening.
17. Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2).
18. Abnormal laboratory results for TSH (> 1.5 x ULN or < 0.5 mIU/L)
19. Abnormal laboratory results for fasting triglycerides ≥ 1151 mg/dL (≥ 13.0 mmol/L). Elevated values may be repeated once on a separate day. (Subjects with fasting triglycerides ≥ 13.0 mmol/L may be included in the study if LDL< 131 mg/dL (< 3.4 mmol/L) and if they have no history of pancreatitis, CVA, transient

ischemic stroke, or myocardial infarction as approved per Investigator's discretion.)

20. Abnormal laboratory results for LDL >189 mg/dL (>4.9 mmol/L) for untreated dyslipidemia or >158 mg/dL (> 4.1 mmol/L) for treated dyslipidemia. Elevated values may be repeated once on a separate day.
21. Clinically significant abnormal hepatic function tests suggestive of hepatic impairment (eg, ALT and AST >2 x ULN).
22. Clinically significant abnormal pancreatic function tests suggestive of pancreatic impairment (eg, amylase and lipase >3 x ULN).
23. 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).
24. History of any active infection, other than mild viral illness within 30 days prior to dosing as judged by the investigator.
25. Use of a very-low calorie (1,000 kcal/day) liquid weight loss diet within 6 months prior to screening
26. History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year.
27. 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.
28. Frequent use of marijuana within 6 weeks, or clinically under the effect at screening, as per Investigator evaluation.
29. Known history of or 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.
30. Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study.
31. Presence of clinically significant physical, laboratory, or ECG findings (eg, QTcF > 450 msec for males, QTcF > 470 msec for females, LBBB) at screening that, in the opinion of the Investigator, may interfere with any aspect of study conduct or interpretation of results.
32. Donation or loss of >500 mL of blood or blood product within 56 days of dosing.
33. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
34. Is employed by Hanmi or ProSciento (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of

Hanmi or ProSciento, 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
antacids, anticoagulants, anticholinergics, antispasmodics, 5HT3 antagonists, dopamine antagonists, or opiates	Reduction/modification of GI motility	within 2 weeks of screening
oral or parenteral corticosteroids or topiramate, MAO inhibitors, growth hormone	Interference with glucose or insulin metabolism	within 3 months prior to screening.
Orlistat, lorcaserin, sibutramine	Weight control treatment, including over-the-counter and herbal medication and supplements, or any medication with a labelled indication for weight loss or gain	within 3 months prior to screening.
GLP-1 receptor agonists (e.g., exenatide, liraglutide, dulaglutide), dipeptidylpeptidase-4 (DPP-4), oral antidiabetic agents (e.g. SGLT2 inhibitors), insulin	Interference with glucose or insulin metabolism	any prior treatment
selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), antipsychotics, lithium.	Depression, anxiety, or other psychiatric disorder	within 2 years of screening
Use of SSRIs and SNRIs (including bupropion) are allowed	If taken for reason other than active psychiatric indications [eg, migraine, weight loss, smoking cessation]	must meet a 3-month wash-out

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), 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. 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 medical condition that could interfere with the study, as judged by the Investigator.
5. Any use of medicine other than any allowed concomitant medications within the last 24 hours.

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 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.

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 by SC injection into a lifted skin fold of the abdominal wall. The injection needle should be placed at a 45 to 90°degree 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.

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

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

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

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

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

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

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

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

8.7 Auxiliary Supply

ProSciento will supply laboratory material necessary for PK and PD sampling, all the safety hematology, biochemistry, and urinalyses (incl. pregnancy test), and for the immunogenicity sampling in collaboration with the laboratories.

9.0 STUDY PLAN

9.1 Study Procedures

9.1.1 Informed Consent and HIPPAA 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.

Subjects will be fully informed of their responsibilities and of all the procedures involved in the study, the possible risks, and disadvantages of being dosed with the investigational products, and their rights while participating in the study. They will have the opportunity to ask questions.

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. The Investigator will keep a Subject Screening and Enrollment Log at the investigational site. Subjects who have screen failed may be allowed to re-screen once at the discretion of the Investigator. A new screening number will be assigned.

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, avoidance of alcohol and herbal supplements, caffeinated drinks, smoking or medication and illness/infection as stated in section 7.4.

If subjects are fasting (only water for ≥10 hours), all screening 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 (e.g. laboratory assessments).

9.1.3 Demographics and Medical History

Demographic information and medical history, including smoking status, 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, and BMI

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. The measurement on Day 1 will be taken prior to dosing.

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

9.1.6 Vital Signs

Vital signs will include body temperature (*aural*), supine and standing blood pressure (supine BP after 5 minutes resting, standing BP within 3 minutes in upright position), respiration rate and pulse rate (after 5 minutes resting). Vital sign measurements will be performed at days indicated in the Table 16-1.

Body temperature: Assessments will be performed once daily, 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 measurements.

Blood pressure:
Supine and standing assessments will be performed. Measurements will be taken once at Screening and once on Day -2 and twice (morning and evening) on Day -1. The rest of the measurements will follow the following sampling schedule: On Day 1, measurements will be performed pre-dose and at 4, 8 and 12 hours post-dose. On Day 2 at 24 and 36 hours, on Day 3 at 48 hours, on Day 4 at 72 hours, on Day 5 at 96 hours, on Day 6 at 120 hours, on Day 7 at 144 hours post-dose with a sampling window of ± 15 min for each timepoint. Additional measurements will be taken on Day 10 at 216 hours (± 1 day), on Day 17 at 384 hours (± 1 day), and on Day 30 at 696 hours (± 2 days) post-dose.

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. Pulse rate will be assessed in combination with both, supine and standing blood pressure measurements. Respiratory rate will be assessed at timepoints of supine 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

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	**Hepatic function panel:** Alanine aminotransferase (ALT/SGPT) alkaline phosphatase, serum aspartate aminotransferase (AST/SGOT) bilirubin, direct bilirubin, total protein, total, serum **Renal function panel:** Albumin, serum BUN BUN: creatinine ratio	**Routine urinalysis with microscopic examination on positives**(a): Color appearance, specific gravity pH protein glucose ketones occult blood leukocyte esterase nitrite bilirubin

red cell count (RBC) white blood cell count (WBC)	calcium, serum carbon dioxide, total chloride, serum creatinine, serum glucose, 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 Lactic acid dehydrogenase (LDH) Gamma-Glutamyl Transferase Magnesium Uric Acid Free fatty acid (FFA) C-reactive protein (CRP)	urobilinogen

Diagnostic Screening

Serum/Plasma/Whole Blood	Urine	Breath
HBsAg Anti-HCV HIV 1/2 TSH(b) PTT PT INR HbA1c	**Drug Screen Profile** Amphetamines Barbiturates Benzodiazepines cocaine (as benzoylecgonine) methylenedioxymetamphetamines opiates Oxycodon phencyclidine (PCP) propoxyphene (Darvon®) tricyclic anti-depressants Urine drug screen as stated in the SOE via commercial kit at the CRU. **Female Subjects Only**	Alcohol breath test at timepoints stated in the SOE at the CRU

	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 CRU will be performed 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.	

(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 local laboratory will perform all necessary laboratory tests listed above. The results of laboratory tests will be sent to the 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. 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 ≥ 25.8 mIU/mL at screening for amenorrheic female subjects <60 years of age. Female subjects who state they are postmenopausal at the screening visit but have a FSH value < 25.8 mIU/mL, may have a serum hCG pregnancy test performed on a separate day. 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).

The Investigator will be responsible for assessing the accuracy of the electronic QTc interval recording using Fridericia correction formula

- 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.

ECG measurements are to be collected during screening and on Day -2 before subjects are connected to the ABPM device. Additionally, ECG measurements are taken on Day 4, after ambulatory devices (Holter and ABPM) are removed, and Days 5, 7, 10, 17 and 30.

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 Period. The following will be assessed:

1. Alcohol breath test.
2. Urine drug screen.
3. Urine pregnancy test.

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 4.

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 Operational 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 central system with or without a central reader). 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 Operational 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 9-2. 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. 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 ± 1 day for the Outpatient Visits and by more than Follow-up Visit ± 2 days for the Follow-up Visit. The actual time of dosing, actual sampling dates and times should be recorded.

Table 9-2 PK Sampling Schedule

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

- Date and time for dosing and PK sampling should be recorded

PK sampling times may be adjusted between the cohorts in case available PK data show that any other times would be more beneficial.

9.1.17 Pharmacodynamic Assessments and Schedule

Blood for PD analyses will be collected at the time points indicated in the Table 16-1 and follow the PD sampling schedule in Table 9-3. Sampling for insulin, C-peptide, GCG, GLP-1, GIP and amino acids will follow the PK sampling schedule, including PK sampling windows. PK sampling windows will apply for all other PD samples as well. Instructions for sample processing and shipment will be provided in the laboratory manual. Pre-dose sampling on Day 1 will be taken within 10 minutes before dosing.

Table 9-3 PD Sampling Schedule

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

- Date and time for dosing and PD sampling should be recorded, D1 blood collection time "pre-dose" should be noted as "pre-dose"

9.1.18 Immunogenicity Assessments

Blood samples will be acquired to determine ADAbs, nAbs and anti -PEG prior to the treatment, on Day 17, and at the Follow-up Visit. One 12-mL sample per scheduled time point will be collected to provide a minimum of 6 mL serum for the 3 anti-assays.

The serum will be split to provide for the following:

A minimum of 1.5 mL of serum for the ADAbs measurements and 0.5 mL of serum as a secondary back-up sample.
A minimum of 1.5 mL of serum for the nAbs measurements and 0.5 mL of serum as a secondary back-up sample.
A minimum of 1.0 mL of serum for the ant-PEG measurements and 0.5 mL of serum as a secondary back-up sample

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

9.1.19 Tolerability Assessments

After injection of the study drug, the injection site will be marked with a pen. Assessment of study drug injection site will be performed pre-dose, at 4 and 12-hour post-dose on Day 1 and then daily from Day 2 to Day 7 (a window of ±15 minutes is allowed).

The local reaction from the injection site, the insertion site, and the adhesive 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.

9.1.20 Blood Volume

Total blood sampling volume for subjects will approximately be 370 mL.
Even in case of further unexpected blood sampling, extension of blood sampling period or necessary retesting, sampling volume will increase to approximately 400 mL.

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 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.

10.1.4 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.

10.1.5 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.

10.1.6 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 or Protocol, 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.

10.1.7 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.

10.1.8 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.

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).

3= **Not Assessable/ Not Classifiable:**
The AE cannot be judged because of insufficient or contradictory information. The AE cannot be supplemented or verified.

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, 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

When an SAE occurs, 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 (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 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.

Possible anticipated, adverse effects from the study procedure are:

Risks related to repeated blood draws

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 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), including CRF data, is the responsibility of ProSciento. With permission of the Sponsor, CDM may be delegated under an agreement of transfer of responsibilities to a qualified vendor of ProSciento.

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 not be entered into the database.

Laboratory data from the central laboratory will be electronically transferred to ProSciento 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 ProSciento 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 ProSciento as to when essential documents are no longer needed to be retained.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

The Sponsor will be responsible for the statistical analysis and the statistical analysis plan (SAP). Statistical services may be delegated under an agreement of transfer of responsibilities to qualified vendors 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 (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 PD properties of HM15211 compared to placebo**
·Clinical findings on physical examination	·Injection site reaction	·Total AUC, including AUC(0-inf)	·Body weight
Clinical laboratory abnormalities (including serum amylase, lipase, coagulation, TSH, calcitonin)		·Incremental AUC	·Lipid metabolism (Total cholesterol, LDL, HDL, VLDL, Triglycerides, FFA)
·Vital signs (BP, respiratory rate, temperature, and HR) measurements		·Cmax	·Glucose metabolism (FPG, Insulin, C-peptide)
·12-lead ECG parameters (the primary ECG endpoint will be QTcF)		·Tmax	·Incretin secretion (GCG, Leptin, GLP-1, GIP)
·24-hour ABPM (Mean day- and night time systolic/diastolic BP)		·$t_{1/2}$	·Inflammatory marker (CRP)

Primary Endpoints (Safety Endpoints)	Primary Endpoints (Safety Endpoints)	Primary Endpoints	Exploratory Endpoints
·24-hour Holter ECG (HR, HRV (e.g. mean heart rate, difference between day and night HR, mean NN intervals, SDNN)		·CL/F	
·Immunogenicity (ADAbs, nAbs, anti-PEG)		·Vz/F	
·**A**dverse events		·kel	

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 with all evaluable PK data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the absorption, distribution, metabolism, or excretion of HM 15211). 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 all evaluable PD data appropriate for the evaluation of interest (without major protocol deviations or violations that would have an impact on the PD of HM 15211). 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 pharmacokinetic endpoints will be derived from the individual serum HM15211 profiles. Serum concentrations of HM15211 will be determined. Non-compartmental analysis (NCA) will be performed for PK parameters such as C_{max}, T_{max}, AUC, $t_{1/2,}$ k_{el}, CL/F and V_z/F, will be estimated for each subject. These will be summarized with descriptive statistics by dose and presented graphically if possible. The following descriptive statistics will be presented: n, geometric mean, geometric SD, geometric coefficient of variation (CV), arithmetic mean, arithmetic SD, median, minimum, and maximum. Dose proportionality may be assessed as appropriate. Log-transformation may be applied to these PK endpoints if needed to ensure data normality.

Population PK analysis will be conducted to develop a model for subsequent PK/PD analyses.

12.2.4 Analysis of the Pharmacodynamic Endpoints

Exploratory PD parameters including FPG, insulin, C-peptide, GCG, leptin, GLP-1, GIP as well as CRP, lipid profile, FFA and body weight will be summarized and analyzed.

All PD parameters will be summarized using appropriate descriptive statistics (eg, n, mean or geometric mean, CV, min, median, max) by treatment and collection day as specified in the SAP. 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.

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]) will be summarized descriptively.

AEs will be summarized using the safety analysis set. Placebo patients will be pooled across cohorts in the safety analysis.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

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

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring

The study will be monitored by ProSciento's monitor.

Monitoring visits to the CRU 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 CRU 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.

ProSciento 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, ProSciento 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 ProSciento.

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.

ProSciento or its designee will be responsible for preparing the Clinical Study Report. When all data has been fully analyzed, ProSciento 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 CRU 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

Table 16-1 Schedule of Events

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

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

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

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

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

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

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

[5]Sampling timepoints according to Table 9-2 PK Sampling Schedule.

[6]Sampling timepoints according to Table 9-3 PD Sampling Schedule.

[7]Triplicate ECG's to be performed.