Protocol

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

Protocol No.	HM-GCG-102
Version No. (Date)	ver. 6.0 (29 OCT 2020)
Investigational product	Test product: HM15136 Comparator: Placebo
Indication	obese or overweight subjects with comorbidities
Study Phase	Phase 1
Sponsor	Hanmi Pharm.Co., Ltd.

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[REVISION HISTORY]

No	Version No.	Version Date	Revision comments
1	Version 1.0	23/JULY/2019	Initial development
2	Version 2.0	28/AUGUST/2019	1. **Change of Stopping Criteria for Dose Escalation / Establishing a Data Monitoring Committee (DMC)** An independent DMC will be established to make dosing and cohort escalation assessments and recommendations. *Section Study Summary, section Abbreviations and Definitions, section 5.1 Number of Subjects, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 6.5 Blinding and Unblinding, section 7.3 Dose Escalation Study Stopping Criteria, section 9.2 Dosage, Method, Period of Investigational Product* 2. **Addition of a Protocol Version to the Protocol Agreement Pages** *Section Sponsor Signature page and Investigator signature page* 3. **Correction of language around the study drug and other compounds** Specification that the study drug is a long-acting glucagon analogue and correction of terminology, as the term glucagon analogue and GLP-1 RA are used interchangeably in the introductory sections of the protocol. *Section 3.1 Background, section 3.2 Background of Currently Used Treatments* **4. Incorporation of Administrative Letter #1 from 01Aug2019** Clarifying that FPG laboratory assessment is not included in clinical chemistry, subject birth date can be obtained in full and age will only be assessed at Screening, no drug or alcohol testing at Day 8, study drug will be destroyed at end of study, and SMBG procedure will be extended to Day 5 (and is not performed via YSI). *Section Study Flow, section 10.2.2 Assessment Variable, section 10.2.1 Assessment items per visit, Synopsis, section 5.2 Inclusion Criteria, section 8.5.3 Inventory Management and Record* **5. Correction of Typographical and Grammatical Errors/ Formatting** Errors will be adjusted throughout the protocol for better clarity. *Throughout various sections of the protocol* **6. Clarification around assessment of ECG** ECG readings may be assessed by 'qualified Investigator' instead of 'qualified physician'. *Section 10.2.2 Assessment Variable* **7. Allowing the Retesting of Screening Laboratory Parameter** Laboratory parameters that are out of range during screening, may be retested per Investigator discretion.

			Section 10.1.1 Scheduled Visit ***8.*** **Distribution of Diet Diaries on Study Day 8** Diet diaries will be distributed on the last day of hospitalization period 1/ in-house period 1 to document diet at home. *Section Study Flow, section 10.2.1 Assessment Items per Visit* ***9.*** **Clarification around SAE/AESI reporting** Details on SAE/AESI report preparation will be stated in the Safety Monitoring Plan (SMP). *Section 10.4.7 SAE and AESI Reporting* ***10.*** **Adjustment of Language for Hospitalization and In-house Periods** Clarification of wording in order to differentiate between hospitalization due to an adverse event and in-house periods of the study. *Throughout various sections of the protocol* 11. **Clarification of Metformin use for Subjects with T2DM in Part 2 of the Study** Per inclusion criterion # 4, subjects with T2DM on stable treatment for 3 months with metformin are allowed. In order to avoid confusion with the exclusion criteria # 5 and # 7, metformin will be added as allowed. *Section Study Summary, section 5.3 Exclusion Criteria* 12. **Clarification around Medical History** The term "reproductive history" will be taken out, as the term medical history covers the also the reproductive system. *Section 10.2.2 Assessment Variable*
3	Version 3.0	17/DECEMBER/2019	**1. Data Monitoring Committee (DMC) Meeting for Cohort 3** An independent DMC will meet after the 9th subject's visit on Day 29 in Cohort 3. The next dose level for the subsequent cohort (Cohort 4 in Part 2) will be based on the safety, tolerability, available PD, and available PK data obtained. *Section Study Summary, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, 7.3 Dose Escalation Study Stopping Criteria, section 9 Clinical Trial Methods and Adminsitration Plan* **2. Adjustment of Cohorts in Part 2** Part 2 will be adjusted and will be combined as Cohort 4, only enrolling subjects with T2DM. *Section Study Summary, Section 3.6. Rationale of Clinical Trial, section 5.1 Number of Subjects, section 5.2 Inclusion Criteria, section 5.4.2 Subject's Withdrawal, Replacement and Discontinuation, section 6.2 Study Design, section 6.3.1 Selection of Subjects in Test Group, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 9 Clinical Trial Methods and*

			Adminsitration Plan, section 9.2 Dosage, Method, Period of Investigational Product **3. Adjustment of Number for Subjects in Part 2** Thirty (30) subjects instead of 18 subjects for cohort 4 and 18 subjects for cohort 5 will be included in one combined cohort. Randomization will still be performed as planned, in a ratio of 1:1 for IP and placebo. *Section Study Summary, section 5.1 Number of Subjects, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 9.2 Dosage, Method, Period of Investigational Product, section 11.3.2 Confirmation of sample size* **4. Change of Principal Investigator (PI)** The PI for this study will change to Dr Bridgette Franey. *Section Protocol Agreement, section 2.2 Principal Investigator* **5. Reduce the Collection Frequency of Blood Samples for Part 2 of the Study** The number of blood sampling timepoints for the assessment of the safety laboratory parameters will be reduced during the In-house periods for Part 2 of the study, in order to reduce the overall blood volume for the subjects. Samples will be taken on Days 1 (pre-dose), 3 and 8 and Days 78 (pre-dose), 80 and 82. *Section Study Flow, section 10.2 Enrollment and Clinical Evaluations* **6. Incorporation of Administrative Letter #2 from 06Sep2019** Clarifying that the assessment of MRI/MRI-PDFF stated for Day -1, may be performed while the Screening Calcitonin result is still pending. All other eligibility criteria for the subject, including lab results must be approved by the Investigator. *Section Study Flow, section* Assessment variable*10.2.2 Assessment Variable* **7. Adjustment of Timepoints for the 7-Point Glucose Profiles** Time point of 15 minutes before the sleep (± 30 minutes) has been changed to 15 minutes before the evening snack (± 10 minutes), to capture glucose prior to the snack and to have an adequate assessment window prior to the snack. *Section Study Flow, section 10.2 Assessment Variable* **8. Adjustment of Contraception** a) Male subjects with a pregnant female partner at signing of informed consent, may be included in the study, as semen cannot lead to conception. b) Adjustment of language for acceptable contraceptive methods for consistency between female subjects, participating in the study and female partners of male subjects. *Section 10.2.3 Restrictions*

			9. Clarification of Inconsistency for Liver Fat Threshold Threshold for liver fat on Day -1 is stated as greater than 10% and as equal to / greater than 10% throughout the protocol. Adjustments are made to consistently state equal to / greater than 10% (≥10 %). Section Study Flow, *section 10.2.1 Assessment items per visit, section 10.2.2 Assessment Variable* **10. Reduction of Measurement Timepoints for the Assessment of Subject's Height** The height of a subjects will only be assessed once at screening, as a change in the adult population is not expected during the study. *Section Study Flow, section 10.2.2 Assessment Variable* **11. Adjustment of parameters for medical review** Amino acid labs will not undergo a medical review as these are not needed for safety evaluation of the subjects. *Section 11.2.7 Endpoints* **12. Clarification of Wording** The word "enrollment" will be replaced with the word "screening" in section 6.4.1, as enrollment is suggestive of inclusion after randomization. *Section 6.4.1 Screening No.* **13. Clarification around the term "prescription"** The Investigator will determine the final eligibility for receiving IP and will not literally write out a prescription for investigational products. Section 8.5.2 Prescription will be renamed to Release of IP. *Section 8.5.2 Release of IP* **14. Adjustment of Language for Recording of AEs and SAEs** Per section 10.4.2, concomitant conditions that exist prior to signing the informed consent form (ICF) are not considered adverse events unless they worsen during the study. The pre-existing conditions are recorded as part of the subject's medical history. Therefore, sentence in section 10.2.2 (9) will be adjusted for consistency. *Section 10.2.2 Assessment Variable, section 10.4.2 Definition of AE* **15. Clarification of Time Window for Assessment of Injection Site Reactions** A window of 30 minutes is stated for all assessment time points, but the hospitalization visits have been omitted. A window of 30 minutes has been added for consistency. *Section 10.2.2 Assessment Variable* **16. Correction of Wording for Consistency** The term "Hospitalization Visit" wil be exchanged with the term "In-house Period" for consistency throughout the protocol. *Section 10.2.2 Assessment Variable* **17. Dose Escalation Stopping Criteria**

			As stopping criteria are assessed under blinded conditions, criterion #7 is Changed from HM 15136 to IP. *Section 7.3 Dose Escalation and Stopping Criteria* **18. Clarification around number of Visits** Subjects will participate in 2 in-house periods and 16 outpatient visits, including follow-up visits. *Section 10.1 Visit Schedule* **19. Title/Function of sponsor signatory person adjusted** *Sponsor signature page* **20. Correction of Unblinding Process** Only the Principal Investigator can perform unblinding via IWRS. *Section 6.5 Blinding and Unblinding* **21. Correction of Typographical Errors/ Formatting** Errors will be adjusted throughout the protocol for better clarity. *Throughout various sections of the protocol*
4	Version 4.0	20/FEBRUARY/2020	**1. Conduct of an Interim Analysis** An interim analysis will be performed, after Part 1 of the study has been completed. For this analysis, unblinding will occur after database lock for Part 1, and data from all healthy subjects (i.e. data from completed cohorts 1-3) will be analyzed to have data for the healthy subjects available in a timely manner. The study will proceed as planned with diabetic subjects in Part 2 in a blinded fashion. Validity or integrity of data will not be compromised through the interim analysis, as the study will be performed as planned and no changes will be made upon the results /outcome of the interim analysis. *Section Study Summary, section 6.5 Blinding and Unblinding, section 11.3.1 Interim Analysis* **2. Clarification around Timepoint for Statistical Analysis Plan (SAP)** SAP will be provided prior to the first database lock, prior to the interim analysis. *Section 11.1 General Considerations* **3. Change and Clarification of Language around Contraception** a) Male subjects are required to use a valid contraceptive method, female partner of male subjects should be encouraged to use a valid method of contraception. b) The word “contraception“ was inadvertently used instead of the word “conception“, when the section about contraception for male subjects with a pregnant female partner was adjusted in the last amendment. *Section Study Summary, section 5.2 Inclusion Criteria, section 10.2.3 Restrictions, Section Revision History for Protocol Version 3.0 (Change No 8: Adjustment of Contraception)*

			4. **Clarification of Language around Confirmation of Eligibility** After the screening visit has been performed and all laboratory values are available, eligibility of subjects will be determined via in/exclusion criteria prior to the first in-house period. This is stated under section 3) already. For better clarity and to avoid redundancy, language in section 2) has been deleted or moved to section 3). *Section 10.1.1 Scheduled Visit* **5. Rescheduling of In-house Period** At check-in for the In-house Period 1, subjects will not be allowed to check in if they meet any of the criteria/variables, but the in-house period may be rescheduled per Investigator discretion. *Section Study Flow, Section 10.1.1 Scheduled Visit* **6. Optional Consulting with Medical Monitor added** The investigator may consult with the Medical Monitor about retesting of abnormal laboratory results at Screening and medical conditions that could interfere with the study results at check-in. *Section 10.1.1 Scheduled Visit* **7. Clarification on exclusion criterion #2** Use of anticoagulants are excluded. The use of acetylsalicylic acid (e.g., Bayer® Aspirin) in a low dose of 81 mg/day taken prophylactically is not considered anticoagulation therapy for the purposes of this protocol. *Section Study Summary, section 5.3 Exclusion Criteria, section 9.3 Past Medication and Concomitant Medication* 8. **Correction of Typographical Errors** Errors will be adjusted throughout the protocol for better clarity. *Throughout various sections of the protocol*
5	Version 5.0	20/MAY/2020	**A - PROTOCOL AMENDMENT - COVID-19** Modifications to this study are made due to the COVID-19 outbreak, in order to follow public health orders and the FDA guidance on "Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic". The amendment will provide an option to continue the use of the investigational product and the monitoring of subjects throughout this period and the completion of the study. Modifications may affect Part 1 of the study, and may apply to subjects that are enrolled in Cohort 3. Modifications may affect all subjects in Part 2 of the study All modification stated under this section may only be used as long as needed under COVID restrictions. As soon as restrictions are terminated or widened, the original protocol language will be followed. In case additional adjustments need to be made, they will be stated in the Operations Manual. The following modifications will be made:

			1. **In-house Periods 1 and 2 will be modified to Outpatient Day Visits (OPD).** Specific OPD visits may be performed as telephone (phone) visits to generate information/assessments in order to reduce the in-person visits. Depending on start of enrollment and according to actual visit day, a site visit may be combined with a phone visit to keep the schedule for the following visits. On combined visit days, specific data might be collected only once at that visit (e.g., assessment of 7-point profile is stated for Day 3 and Day 4, but if Visit is combined on one day, only one 7-point profile might be available). *Section Study Flow, section 9.3 Past Medication and Concomitant Medication, section 10.1 Visit Schedule, 10.1.1 Scheduled Visit, section 10.2.1 Assessment Items per Visit* 2. **Visit windows will be added/allowed** This will accommodate for limited site access and to continue the assessments as stated per protocol. *Section Study Flow, section PK Sampling Schedule, section 10.2.1 Assessment Items per Visit* 3. **Randomization may be performed on Day -2** Due to change in visit schedule, randomization may be performed on site on Day -2. *Section Study Flow, section 6.4.2 Randomization No.* 4. **ABPM and Holter monitoring modifications** ABPM and Holter monitoring will be continued as stated in the protocol for the safety of the subjects but will be moved to an outpatient setting. Subjects will therefore be provided with personal instructions on site and instructions to take home for use and care of the devices. *Section 10.1.1 Scheduled Visit, section 10.2.1 Assessment Items per Visit* 5. **Body temperature measurement will be replaced by vital sign assessment** Measurements of tympanic temperature assessment may be decreased to 1x/day during the visit at the site in order to shorten the in-person visit and therefore, it will be assessed during the assessment of vital signs. *Section Study Flow, section 10.2.1 Assessment Items per Visit, section 10.2.2 Assessment Variable* 6. **Seven (7)-point glucose profiles may be performed by subjects** Subjects will be instructed on site and will be provided with instructions to take home and a diary to record their results. This will ensure glucose results can be recorded, in case data can't be retrieved from the glucometer at the site visit. Additionally, as visits (OPV and phone visits on the next day) may be combined into one visit, only one 7-point profiles will be available per combined visit.

			Section Study Flow, section 10.2.1 Assessment Items per Visit **7. Fasting glucose assessments may be performed by subjects** Subjects may perform fasting glucose at home with glucometer in case the visit at the site was modified to a phone visit. Therefore, fasting glucose may be assessed by fasting capillary blood glucose (FBG) instead of fasting plasma glucose (FPG) as stated in the protocol. *Section Study Flow, section 10.2.1 Assessment Items per Visit* **8. Assessment of Injection Site** Subjects may perform the assessment of the injection site at home in case the visit at the site was modified to a phone visit. *Section 10.2.2 Assessment Variable* **9. 12-lead ECG timepoints may be modified** Time points may be reduced or moved to the modified visits schedule. *Section Study Flow, section 10.2.1 Assessment Items per Visit* **10. Abbreviated Physical Examination** Time points of assessment may be reduced, as some visits are modified to phone visits. *Section Study Flow, section 10.2.1 Assessment Items per Visit* **11. Vital Signs** Time points of assessment may be reduced, as some visits are modified to phone visits. *Section Study Flow, section 10.2.1 Assessment Items per Visit* **12. Diet Education and Diary Distribution and Review Modifications** As subjects will not be in-house and will not receive standardized meals for this period, the diet education as well as diet diary distribution and review will be started with the first OPV day. *Section Study Flow, section 10.2.1 Assessment Items per Visit, section 10.2.2 Assessment Variable* **13. Fasting insulin, Fasting C-peptide assessment timepoints may be reduced** Due to the modified visits schedule, some samples may not be collected on phone visit days. *Section Study Flow, section 10.2.1 Assessment Items per Visit* **14. PK Sampling Schedule may be modified** Number and timepoints of PK assessments may be adjusted and/or reduced to accommodate the modified visit schedule. The modified PK sampling schedule will not affect the primary endpoints of this study.

			Section Study Flow, section PK Sampling Schedule, section 10.2.1 Assessment Items per Visit **15. MRI/MRI-PDFF assessment** MRI/MRI-PDFF assessment will depend on the restrictions of the MRI center due to the COVID-19 restrictions. If MRI/MRI-PDFF assessment is not possible during the stated time period, due to COVID- restrictions, MRI/MRI-PDFF may be performed later than Day 85, but prior to the last Visit on Day 113. If assessment is not possible, the missing assessment will be documented in the CRFs (specific information will be captured that explains the basis of the missing data due to COVID-19). *Section Study Flow, section 10.2.1 Assessment Items per Visit, section 10.2.2 Assessment Variable* **16. Pregnancy Test in Urine** Pregnancy test in urine is adjusted to modified visit schedule and will take place on Day 78. *Section Study Flow, section 10.2.3 Restrictions* **17. Clinical Study Monitoring** In case on-site monitoring visits might no longer be possible, the use of central and remote monitoring programs to maintain oversight of clinical sites may be considered. *Section 13.7 Monitoring and Auditing* **18. Availability of Standardized Meals** Standardized meals and/or catering may be limited or not be available and may be skipped or exchanged with snack bags. *Section 9.2 Dosage, Method, Period of Investigational Product, section 10.2.3 Restrictions* B- **General Changes and Adjustments** **1. Adjustment of Cohorts in Part 2** Part 2 will be adjusted, and 3 additional cohorts may be added with already approved dose levels. Dose levels were already tested in Part 1 (conducted in healthy subjects) and approved by the iDMC for Part 2. The additional cohorts (Cohorts 5-7) will enroll subjects with T2DM. *Section Study Summary, section 5.1 Number of Subjects, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 9 Clinical Trial Methods and Administration Plan, section 9.2 Dosage, Method, Period of Investigational Product* **2. Dose Levels for Cohorts 5-7** The maximum dose level for Cohorts 5-7 will not exceed 0.06 mg/kg (tentative dose for Cohort 5 may be 0.02 mg/kg, tentative dose may be 0.04 mg/kg for Cohort 6). This dose level has been previously approved for subjects with T2DM.

Therefore, the decision to proceed to the next cohort/dose level will be made per review of safety data by Sponsor, Investigator and Medical Monitor during a Data Review Meeting (DRM), after the 9th subject's visit on Day 43 (6 weeks after dosing), and additional DMC meetings will not take place.

Section Study Summary, section 5.1 Number of Subjects, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 9 Clinical Trial Methods and Administration Plan, section 9.2 Dosage, Method, Period of Investigational Product

3. **Dose Escalation for Cohorts 5-7 and DMC Meetings for Cohorts 5-7**

   A dose level of 0.06 mg/kg has been previously approved for subjects with T2DM by the DMC. Therefore, the decision to proceed to the next cohort/dose level for Cohorts 5-7 will be made per DRM of Sponsor, Investigator and Medical Monitor, and additional meetings with independent DMC will not take place.

   After the 9th subject's visit on day 43 of each cohort (Cohorts 5 and 6), a DRM will assess the safety and will make dosing and cohort escalation assessments.

   Section Study Summary, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation

4. **Adjustment of Number for Subjects in Part 2**

   Up to 36 additional subjects may be added to Part 2 of the study, 12 subjects for each additional cohort (Cohorts 5-7). Randomization will be performed as planned, in a ratio of 3:1 for IP and placebo (n=9 active, n=3 placebo).

   Section Study Summary, section 5.1 Number of Subjects, section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 6.4.2 Randomization No., section 9.2 Dosage, Method, Period of Investigational Product

5. **Adjustments to Cohort 4**

   Enrollment of new subjects into Cohort 4 will be postponed and the cohort may be terminated with a lower number of subjects than planned. Therefore, the maximum allowed number of subjects in Cohort 4 will not be reached, and the number will include already enrolled and dosed subjects. Subjects who are currently active in Cohort 4 will continue with the study as planned.

   After additional cohorts with a lower dose level have been performed, the dose level from the current Cohort 4 may be continued. This dose level will then be further evaluated in a new Cohort (Cohort 7).

   Section Study Summary, section 6.2 Study Design

6. **Interim Analysis/Unblinding and Data Base Lock**

			Adjustment of analyses. The analyses for each part will be performed separately, once each part is complete and the data base for each part has been locked. Due to COVID-19 outbreak, an interim analysis based on partially validated data for Part 1 will be performed for administrative purpose prior to database lock of Part 1. *Section Study Summary, section 6.5 Blinding and Unblinding, 11.3.1 Interim Analysis* **7. Adjustment of Exclusion Criterion #27** History of any active infection, including any active COVID-19 infection even if mild, will be excluded. *Section Study Summary/Exclusion Criteria, section 5.3 Exclusion Criteria* **8. Clarification of PK Sample Analysis** Adjustment made in order to be consistent with the actual analysis as stated in the PK Lab Manual, samples are analyzed using serum and not plasma. *Section Study Summary, section 10.3.1 Primary Endpoints* **9. Missing HbA1c added** HbA1c added to list of assessments as stated in SOE for consistency throughout the protocol. *Section 10.2.1 Assessment items per visit, Day -2* **10. Discontinuation of Subjects** Subjects may be withdrawn from the study, in case compliance of IP dosing is <70%. *Section 5.4.2 Subject's Withdrawal, Replacement and Discontinuation* **11. Clarification of Wording** As the informed consent form (ICF) is not included in the protocol as an Appendix, the reference to it will be deleted. *Section 13.2 Informed Consent*
6	Version 6.0	29/OCT/2020	**1. Change of Timepoint for Dose Escalation from Cohort 5 to Cohort 6/Addition of another Data Review meeting (DRM)** The decision to proceed to the next cohort/dose level for Cohorts 5 will be made per DRM. Per DRM for Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5) a dose escalation to Cohort 6 will not proceed at this timepoint and another DRM will be held after all of the 12 subjects in Cohort 5 have completed the final study visit (F/U Visit) on Day 113, to assess the safety data and to make a decision to escalate to Cohort 6 or not. The conduct of cohorts 6 and 7 are optional. *Section Study Summary, section 5.1 Number of Subjects, Section 6.2 Study Design, section 6.3.4 Confirmation of Dosage and Escalation, section 7.3 Dose Escalation and Study Stopping Criteria, section 9 Clinical Trial Methods and Administration Plan, section 9.2 Dosage, Method, Period of Investigational Product, section 11.3.2 Confirmation of Sample Size*

			2. Clarification on hCG assessment for women of childbearing potential at Screening Women of childbearing potential do not need to have a serum hCG test at Screening, as urine hCG test will be assessed at Screening. A serum hCG test will only be performed for women are either sterile but do not have medical records or for women who are postmenopaual, but postmenopausal status can't be confirmed by FSH test. *Section 10.2.3 Restrictions/Contraception* **3. Clarification of End of Treatment (EOT) Visit** Language adjusted to clarify that EOT visit is not mandatory. *Section 10.1 Visit Schedule* **4. Clarification on timepoint of Injection Site Reaction (ISR) Assessment** ISRs should be evaluated in the morning, at the time of last IP administration within a window of ±30 minutes of dosing time. *Section 10.2.2 Assessment Variable*

Sponsor Signature pag

Protocol Agreement

Study Title	A Phase 1, study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with comorbidities
Protocol No.	HM-GCG-102
Version	6.0

Declaration by the sponsor or responsible medical professional

This clinical trial protocol has been critically reviewed. The information contained herein is consistent with the latest knowledge of the risks and benefits of investigational medicinal products, as well as consistent with the moral and ethical and scientific aspects of clinical studies described in the GCP Guidelines applicable to these trials.

Sponsor/Responsible medical professional:

Investigator signature page

Protocol Agreement

Study Title	A Phase 1, study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with comorbidities
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Declaration by the Principal investigator

This clinical trial protocol has been reviewed and published by the sponsor. The information contained herein is consistent with the latest knowledge of the risks and benefits of IMP, as well as consistent with the moral and ethical and scientific aspects of clinical studies described in the GCP Guidelines applicable to these trials.

Principal investigator:

[STUDY SUMMARY]

Title	A Phase 1, study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with comorbidities
Protocol No.	HM-GCG-102
Study Phase	Phase 1
Sponsor	Hanmi Pharmaceutical Co., Ltd.
Study site and investigator	Single site study at [redacted]
Study duration	The planned period of each cohort is 22 weeks including subject screening, treatments for 12 weeks, and follow-up period.
Target subjects	Obese subjects or overweight subjects with comorbidities
No of target subjects	Overall, approximately 102 subjects will participate in this study. In Part 1, approximately 36 subjects, divided into 3 cohorts with 12 subjects (HM15136 group 9 subjects, placebo group 3 subjects) per cohort. In Part 2, approximately 66 subjects, in up to 4 cohort with 30 subjects for cohort 4 (HM15136 group 15 subjects, placebo group 15 subjects) and 12 subjects per cohorts 5-7 (HM15136 group 9 subjects, placebo group 3 subjects). Cohorts 6 and 7 are optional.
Primary Clinical Trial Objectives and Endpoints	To assess safety and tolerability of HM15136 after multiple subcutaneous (SC) doses for 12 weeks. • To evaluate the incidence of adverse events (AEs): cardiovascular (CV) events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal (GI) events, and gallstone formation (cholelithiasis) will be managed following separate AE guidance document of HM15136 [Appendix]. • To evaluate the incidence of clinical lab abnormalities: including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin. Only for females, LH (Luteinizing hormone) and FSH (follicle stimulating hormone) are additionally included. • To evaluate the immunogenicity: Anti-drug antibodies (ADAbs), neutralizing antibodies (nAbs), anti-polyethylene glycol antibodies (anti-PEG) • Evaluation of clinically significant findings and incidence in physical examination • Change from baseline in vital signs: Supine position blood pressure (BP), heart rate (HR), respiratory rate, and tympanic temperature • Changes of blood pressure (BP) and heart rate: BP assessed by 24-hour ambulatory blood pressure monitoring (ABPM); HR assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG; central reader) • Change from baseline in 12-lead ECG parameters:

	the primary ECG endpoint will be QTcF • Injection site reactions To assess the pharmacokinetic (PK) profile of HM15136 after administration of multiple subcutaneous (SC) doses in obese subjects by, but not limited to: • C_{max}: Maximum concentration • T_{max}: Time to reach Cmax • C_{trough}: Trough serum concentration • AUC: Area under the concentration-time curve Ex.) AUC_{0-t}: AUC at steady state during the period of injection (AUC_{0-t} at steady state) • K_{el}: Terminal elimination rate constant • $t_{1/2}$: Terminal half-life • CL/F: Apparent clearance • Vz/F: Apparent volume of distribution
Exploratory Objectives and Endpoints	To evaluate the pharmacodynamics (PD) properties of HM15136 after multiple subcutaneous (SC) doses • Incretins / metabolic hormones 1) Glucagon-like peptide-1 (GLP-1) 2) Gastric inhibitory polypeptide (GIP) 3) Glucagon 4) Fibroblast growth factor 21 (FGF 21) 5) Leptin • Serum lipid profiles 1) Total cholesterol 2) Low-density lipoprotein (LDL) 3) High-density lipoprotein (HDL) 4) Very low-density lipoprotein (VLDL) 5) Triglycerides 6) Free fatty acids (FFAs) • Amino-acid profile • Glucose metabolism parameter 1) Fasting plasma glucose (FPG) 2) Fasting insulin, Fasting C-peptide 3) 7-point Self-monitoring of blood glucose (SMBG) 4) HbA1c 5) Fructosamine 6) Glycated albumin • Insulin resistance - Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) • Insulin secretion function - Homeostatic Model Assessment for β Cell Function (HOMA-β) • Assessment of absolute and percent (%) changes of liver fat via MRI-PDFF (Magnetic resonance imaging-estimated proton density

	fat fraction) (However, assessment of liver fat via MRI-PDFF will only be performed on day 85, if the liver fat on MRI PDFF prior to dosing ≥ 10%) • Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI • Body weight • Body mass index (BMI) • Waist circumference • Hip circumference • Waist-to-hip ratio (WHR) • Temperature (tympanic) • Inflammatory markers 1) High-sensitive C-reactive protein (hs-CRP) 2) Adiponectin • Ketone body - β-hydroxybutyrate
Study Design	This is a double-blind, randomized, placebo controlled, multiple ascending dose (MAD) study to investigate the safety, tolerability, PD, and PK of the subcutaneous (SC) administration of HM15136 in obese subjects or overweight subjects with co-morbidities. This study will be conducted in Part 1 and 2. In part 1, enrolling 12 subjects per cohort (HM15136 group 9 subjects, placebo group 3 subjects) will participate, and 3 cohorts will proceed sequentially, but may overlap during the conduct. In part 2, enrolling 30 subjects in cohort 4 (HM15136 group 15 subjects, placebo group 15 subjects) will participate, and up to 3 additional cohorts may proceed with 12 subjects per cohorts 5-7 (HM15136 group 9 subjects, placebo group 3 subjects). 12 subjects per cohort assigned to Part 1 and Part 2 will be randomized to HM15136 and placebo in a ratio of 3:1, and 30 subjects per cohort 4 assigned to Part 2 will be randomized to HM15136 and placebo in a ratio of 1:1. The final analysis for each part will be performed separately once each part is complete. Due to COVID-19 outbreak, an interim analysis based on partially validated data for Part 1 will be performed for administrative purpose prior to database lock of Part 1. After Cohort 1 randomization is completed, the DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations to decide whether subjects can be randomized into Cohort 2. Details will be defined in the DMC charter. Dose escalation from cohort 2 to next dose level for the subsequent Cohort 3 will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1 and through the 9th subject's visit on Day 29 in cohort 2. An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations.

	The next dose level for the subsequent cohort (Cohort 4 in Part 2) will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1, 2 and through the 9th subject's visit on Day 29 in cohort 3. An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations. If dose escalation is stopped, dose de-escalation may occur in subsequent cohorts, to further refine clinically relevant dose levels. The dose of cohorts 3 and 4 can be adjusted, but may not be over the planned dose of 0.08 mg/kg. The escalated dose should not be more than 2 times over the dose of the previous cohort. In part 2, after the review of the safety data, obtained by the 9th subject's visit on Day 29 of Cohort 3 (in Part 1), cohort 4 can proceed with a dose of ≤ 0.08 mg/kg dose, which is the planned maximum dose. A DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations for the study progress of Part 2. After the review of the safety data in Part 1, Part 2 may or may not proceed. Cohort 4 may be conducted with a lower number of subjects. Cohort 5 may start immediately and may overlap with the conduct of subjects in Cohort 4. In Part 2, dose escalation from cohort 5 to the subsequent Cohort 6 will be made after Data Review Meetings (DRM), held by Sponsor, Investigator and Medical Monitor, and the safety data obtained from the 9th subject's visit on Day 43 (=after 6 weeks of dosing) have been reviewed. Additionally, a second DRM will be held and safety data from the 12th subject's final visit on Day 113 _(=F/U Visit) will be reviewed to dose escalate. Dose escalation from cohort 6 to the subsequent cohort 7 will follow the same dose escalation scheme and DRM(s) of the previous cohort. Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5. If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study.
Inclusion criteria	At the screening visit, subjects who meet all of the following criteria are considered eligible for participation in the study. 1) Male or Female subjects 2) Age ≥ 18 to ≤ 65 years at Screening visit. 3) Body Mass Index (BMI) ≥ 30 kg/m^2 or 27 kg/m^2 ≥ with presence of comorbidities (Subjects in Part 1: dyslipidemia and or hypertension except for Type 2 (T2) DM, T2DM subjects in Part 2: dyslipidemia and/or hypertension with T2DM) with/without medication treatment and have had stable weight for 3 months (weight changes less than 5%). Untreated dyslipidemia is defined as LDL ≥ 160 mg/dL,

	or Triglyceride ≥ 150 mg/dL, or HDL < 40mg/dL for male and < 50 mg/dL for female, untreated hypertension is defined as Systolic Blood Pressure ≥ 140 or Diastolic Blood Pressure ≥ 90 mmHg. 4) The criteria for HbA1c and FPG are as below; ① Subjects in Part 1: 'FPG < 5.6 mmol/L (100 mg/dL)' and '< HbA1c < 5.7%' (But, if the result is out of the reference range at the screening visit, it can be tested again on another day by laboratory analysis.) ② Subjects in Part 2 with DM: Subjects diagnosed as type 2 DM, with HbA1c ≤ 9% and stable treatment for 3 months by Metformin only. 5) Female subjects must be non-pregnant and non-lactating. Females of childbearing potential must use highly effective contraceptive methods, stable at least 2 months prior to the screening. Male subjects should be surgically sterile (at least 1 year after vasectomy) or sterilized from the screening visit to 60 days after administration of IP, or if the male subject has a sexual relationship with a female partner of childbearing potential, the male subject is required, and the female partner should be encouraged to use a valid contraceptive method (e.g., condom, spermicidal form/gel/film/cream suppository combination, etc.) during the study period. 6) Subjects who agree to participate this study voluntarily and to give written informed consent.
Exclusion Criteria	Subjects who meet at least one of the following criteria are considered not eligible for participation in 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 LAPBAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe GERD) at Screening. 2) Use of antacids, anticoagulants, or drugs that directly modify gastrointestinal (GI) motility, including antacids anticholinergics, anticonvulsants, serotonin type 3 (5HT3) antagonists, dopamine antagonists, opiates; anticoagulation within 2 weeks of screening; (But, it is not limited to the above listed drugs.) The use of acetylsalicyclic acid (e.g., Bayer® Aspirin) 81 mg/day taken prophylactically is not considered anticoagulation therapy for the purposes of this protocol. 3) Uncontrolled hypertension, defined as systolic blood pressure > 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening (independent of subjects being on antihypertensive medication or not). But, if the results are out of the reference range at the screening visit, they can be tested again on another day. Subjects with uncontrolled hypertension may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy.)

	4) Uncontrolled dyslipidemia, defined as fasting triglycerides (TG) > 500 mg/dL and/or fasting low density lipoprotein (LDL) cholesterol >200 mg/dL at Screening (independent of subjects being on lipid lowering medication or not). 5) Use of any drugs that are known to interfere with glucose or insulin metabolism, within 3 months prior to screening except for metformin for T2DM subjects in part 2: oral or parenteral corticosteroids or topiramate, monoamine oxidase (MAO) inhibitors, growth hormone (But, it is not limited to the above listed drugs.) 6) Subjects who are currently diagnosed with type 1 DM or who have such medical history 7) Subjects diagnosed with type 2 DM, who have a treatment history of relevant drugs like sulfonylurea, thiazolidinediones, GLP-1 receptor agonist, SGLT2 inhibitor, insulin and DPP-4 inhibitors within 3 months before screening visit. Stable metformin therapy is allowed. 8) Any weight control treatment, including over-the-counterdrugs, herbal medications and supplements, or any medication with a labelled indication for weight loss or weight gain within 3 months prior to screening. 9) Participation in another investigational study within 1 month prior to enrollment or 5 half-lives within the last dose of investigational product (IP), whichever is longer. 10) Serum calcitonin levels > 20 pg/mL at the screening. 11) 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. 12) Personal history of cancer diagnosis prior to screening visit, if it is likely to impact the study results as judged by the investigator. 13) 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 and bupropion for reasons other than active psychiatric indications [eg, migraine, weight loss, smoking cessation] must meet a 3-month wash out.) 14) History of significant suicidal ideation or suicidal behavior/attempts. 15) History of any major surgery within 6 months prior to screening. 16) Subjects who are unable to handle noise or isolation circumstances in testing devices or have any contraindication for MRI test (e.g., pacemaker, iron implant in body, metal pieces, clips of cerebral aneurysm as well as those things in the body that can be impacted by the magnetic field.). 17) History of any serious adverse reaction or hypersensitivity to study drugs components, or have contraindication diseases (e.g., pheochromocytoma, insulinoma, glucagonoma). 18) 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) 19) Cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening. 20) Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2). 21) Anemia findings of hemoglobin < 13 g/dL in male or < 12 g/dL in female in clinical laboratory results. 22) Abnormal laboratory results for thyroid stimulating hormone (TSH) (> 1.5 x ULN or < 0.4 mIU/L) at screening. 23) Clinically significant abnormal hepatic function tests suggestive of hepatic impairment (eg, ALT and/or AST >2 x ULN). 24) Clinically significant abnormal pancreatic function tests suggestive of pancreatic impairment (eg, amylase and/or lipase >3 x ULN). 25) 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). 26) Female who is pregnant or breast-feeding, or has a positive pregnancy test at screening or Day -2. 27) History of any active infection, including any active COVID-19 infection even if mild, within 30 days prior to dosing (except mild viral illness, such as common cold), as judged by the investigator. 28) Use of a very-low calorie (1,000 kcal/day) liquid weight loss diet within 6 months prior to screening 29) History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year. 30) 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. (Subjects must be able to abstain from smoking during the confinement period.) 31) Use of debauchery drug (e.g., marijuana) within 6 weeks prior to screening or clinically under the effect at screening, as per Investigator evaluation. 32) Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) at Screening or Day -2. 33) Known history of or positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCVAb), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody. 34) Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study. 35) 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, results or interpretation of results.

<table>
<tr><td></td><td>36) Donation of whole blood (400 mL) within 60 days, or donation of blood components (500 mL) or receiving transfusion of blood products within 14 days prior to screening.
37) Unwillingness to participate, involuntary participation or language barriers precluding adequate understanding or cooperation.
38) Is employed by Hanmi (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of Hanmi staff (defined as a spouse, parent, sibling, or child, whether biological or legally adopted.).</td></tr>
<tr><td>Investigational product</td><td>Test product: HM15136, pre-filled syringe with a clear or almost colorless transparent sterile solution. The concentration is 10 mg/mL as a protein and the total amount is 0.52 mL.
Comparator: Placebo, pre-filled syringe with clear sterile solution in place, colorless or almost colorless.</td></tr>
<tr><td>Administration and dosage</td><td>Administration group and dosage
[Part 1]
<table>
<tr><th>Cohorts</th><th>Number of Subjects</th><th>Treatment</th></tr>
<tr><td rowspan="2">Cohort 1</td><td>N=9</td><td>HM15136 0.02-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 2</td><td>N=9</td><td>HM15136 0.04-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 3*</td><td>N=9</td><td>HM15136 ≤0.08-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
</table>
* Dosage of Cohort 3 can be adjusted, but cannot be over the dosage presented in the table. The escalated dose should not be over twice the dose of the previous cohort.

[Part 2]
<table>
<tr><th>Cohorts</th><th>Number of Subjects</th><th>Treatment</th></tr>
<tr><td rowspan="2">Cohort 4
(DM)</td><td>N=15</td><td>HM15136 0.06-mg/kg</td></tr>
<tr><td>N=15</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 5
(DM)</td><td>N=9</td><td>HM15136 ≤0.02-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 6
(DM)**</td><td>N=9</td><td>HM15136 ≤0.04-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
<tr><td rowspan="2">Cohort 7
(DM)**</td><td>N=9</td><td>HM15136 ≤0.06-mg/kg</td></tr>
<tr><td>N=3</td><td>Placebo</td></tr>
</table>
* In part 2, if necessary, after the review of the safety data obtained by</td></tr>
</table>

	the 9th subject's visit on Day29 of Cohort 3 in Part 1, the cohort can proceed within the 0.08 mg/kg of dose, which is the planned maximum dose. The dose and study progress of Part 2 should be guided by the recommendation of the DMC. After the review of the safety data in Part 1, Part 2 may or may not proceed. **The conduct of cohorts 6 and 7 is optional.
Statistical Methods	• Data presentation/Descriptive statistics All demographics, safety, PK and PD data will be analyzed using appropriate descriptive and comparative statistical methods and will be summarized. PK data will also be presented as graphs. PK/PD relationship for HM15136's exposure and exploratory endpoints can also be presented as graphs. • Interim Analysis An interim analyss will be performed to aid in the planning of future studies in the development program. Due to COVID-19 outbreak, an interim analysis based on partially validated data for Part 1 will be performed for administrative purpose prior to database lock of Part 1. The final analysis for Part 1 will be performed after all healthy subjects in Part 1 (i.e., Cohorts 1-3) have been finalized. The final analysis for Part 2 will be performed after all subjects in Part 2 (i.e., Cohorts 4-7) have been finalized. • Determination of sample size This study determined the number of subjects without consideration of statistical validity. The number of subjects for the Part 1 will be 12 (HM15136: placebo = 9:3) for each cohort, and for the Part 2 will be up to 66, 30 for cohort (HM15136: placebo = 15:15) and 12 for cohorts 5-7 (HM15136: placebo = 9:3). This is consistent with the typical sample size used in the similar study to evaluate safety and PK. Therefore, no formal sample size calculation will be performed. 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.

[STUDY FLOW] Part 1

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

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

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

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

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

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

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

4 Measurement time point may be adjusted after PK assessment.

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

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

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

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

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

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

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

[STUDY FLOW] Part 2

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

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

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

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

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

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

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

4 Measurement time point may be adjusted after PK assessment.

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

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

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

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

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

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

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

[STUDY FLOW] Parts 1 and 2 – COVID-19 Modification

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

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

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

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

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

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

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

4 Measurement time point may be adjusted after PK assessment.

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

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

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

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

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

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

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

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

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

[PK SAMPLING SCHEDULE]

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

[PK SAMPLING SCHEDULE] PARTs 1 and 2 - COVID-19 Modification

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

[ABBREVIATIONS AND DEFINITIONS]

ABP	Ambulatory blood pressure
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-PEG	Anti-polyethylene glycol
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{\%extrap}$	Percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
AUC_{0-t}	Area under the concentration-time curve from predose (time 0) to the time of the last quantifiable concentration
AUC_{inf}	Area under the concentration-time curve from predose (time 0) extrapolated to infinite time ($AUC_{0-t} + C_{last}/\lambda_z$)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHI	Congenital hyperinsulinism
Cl	Chloride
CL/F	Total body clearance
C_{max}	Maximum concentration
CO_2	Carbon Dioxide
CRO	Contract Research Organization
C_{trough}	Trough plasma concentration
CVA	Cardiovascular accident
DBP	Diastolic blood pressure
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram

EDC	Electronic data capture
eGFR	Estimated Glomerular filtration rate
EMA	European Medicines Agency
FiH	First-in-human
FBS	Fasting blood sugar
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV ab	Hepatitis C antibody
HDL	High-density lipoprotein
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus type 1
HOMA-IR	Homeostatic model assessment for insulin resistance
HOMA- β	Homeostatic model assessment for β Cell Function
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine contraceptive device
IUS	Intrauterine system
K_{el}	Terminal elimination rate constant
LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MAD	Multiple ascending dose

MAO	Monoamine oxidase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet renal disease
MedDRA	Medical dictionary for regulatory activities
MID	Minimum intolerable dose
MTC	Medullary thyroid carcinoma
MTD	Maximum tolerated dose
Nab	Neutralizing antibodies
NOAEL	No observed adverse effect level
NYHA	New York heart association
OTC	Over-the-counter
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PR	Pressure rate
PT	Preferred term
PT	Prothrombin time
PTT	Activated partial thromboplastin time
PV	Pharmacovigilance
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RBC	Red blood cell
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SID	Subject identification
SMBG	Self-monitoring of blood glucose

SNRIs	Serotonin norepinephrine reuptake inhibitors
SOC	System organ class
SOP	Standard operating procedure
SSRIs	Selective serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
T_{max}	Time to maximum serum concentration
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid stimulation hormone
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
Vz/F	Apparent volume of distribution
WBC	White blood cell
WHR	Waist-Hip ratio
λ_z	Terminal elimination rate constant

Table of contents

1. Clinical Trial Title and Phase

1.1. Study Title

A Phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese subjects or overweight subjects with co-morbidities.

1.2. Phase

Phase 1

2. Information of Investigators, Sponsor

2.1. Name and Address of the Institutions

2.2. Principal Investigator

2.3. Sponsor

3. Introduction

3.1. Background

Obesity emerged as an issue of priority in public health in the 21st century. According to a survey conducted in the United States in 2000, approximately 30% of the adult population was obese with the body mass index (BMI) ≥30 kg/m^2 and 35% was overweight with BMI 25-29.9 kg/m^2, indicating a 50-60% or higher increase compared to 20 years ago. In Korea, a 2005 National Health and Nutrition Examination Survey showed that 34.9% of the adult population was obese with ≥BMI 25 kg/m^2, suggesting a persistent increase from 32.7% in 2001 [(2)].

In addition, according to a recent report of the Korean Society for the Study of Obesity, while the percentage of obesity patients in Korea between 2009 and 2013 was 31.8%, decreasing from 2001, the percentage of obese or overweight patients with BMI ≥25-30 kg/m^2 in men rose greatly 35.8% in 2009 to 37.6% 2013 [(8)].

Such persistent increase in obesity is attributed to primary causes such as excessive caloric intake, reduced physical activities and lack of sleep, as well as endocrine disorders, genetic diseases (e.g.: Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Alstrom syndrome and Cohen syndrome) and effects of a drug [(8)].

Being obese is not merely a problem of gaining weight but it leads to cardiovascular diseases such as type 2 diabetes, dyslipidemia and hypertension, as well as musculoskeletal diseases such as osteoarthritis, and gastrointestinal, respiratory, endocrine and metabolic disorders and blood tumor, threatening health of mankind and also posing a continuously growing economic loss to society [(1, 2, 8)].

For such reasons, research on obesity treatment in ongoing. Initially, non-drug therapy such as diet, exercise, behavioral therapy is attempted to treat obesity and when such efforts are not effective after 3~6 months, drug treatment or even surgery is considered [(3, 8)].

Drug treatment is roughly categorized into fat absorption inhibitors, appetite suppressants, and unapproved medications with reported weight reduction effects even though they have not been approved for weight loss or maintenance. Orlistat, an active ingredient of a fat absorption inhibitor was approved by the United States Food and Drug Administration (US FDA) in 1999 and a low dose formulation was approved as an over-the-counter medication in 2007. In Korea, 120 mg and 60 mg are approved and commercially available as prescription medication. Appetite suppressants reduce appetite by stimulating the central nervous system and promoting norepinephrine secretion, and Phentermine or Mazindol are contained as an active ingredient. While drug combination represents another treatment option, it is not used frequently for safety reasons arising from concurrent use [(3)].

In addition, with reports on weight loss effects of a glucagon-like peptide receptor agonist (GLP-1 RA) subcutaneous injection used for diabetes treatment, the US FDA approved up to 3.0 mg once weekly regimen in obesity in December 2014 [(1, 3)].

Hanmi Pharmaceutical is developing HM15136, a synthetic conjugate of a glucagon analogue (called GC15136) and a G4 Fc portion of human immunoglobulin (called HMC001) linked by a [redacted] bifunctional linker molecule. This product was designed as a novel therapeutic agent for congenital hyperinsulinism(CHI) which is a rare genetic disease characterized by inappropriately elevated serum insulin. Hanmi Pharmaceutical conducted an efficacy study in target animals for the treatment of hyperinsulinism. The result showed that the drug inhibits hyperinsulinism while also promoting appetite suppression and lipolysis, suggesting its potential effects in obesity.

In vitro activity of HM15136 was evaluated using hGCGR/Chinese hamster ovary(CHO) cells. HM15136 raised the cyclical adenosine monophosphate level in cells in a dose dependent fashion and exhibited the maximum efficacy similar to natural glucagon, demonstrating its property as a complete agonist. In rat primary hepatocytes, HM15136 induced glucose production through both glycogenolysis and gluconeogenesis just like natural glucagon, suggesting that HM15136 actually has pharmacological properties similar to glucagon. In additional *in vitro* studies, HM15136 showed the minimal immune mediated effector function as it contains a non-glycosylated Fc portion derived from human IgG4. Furthermore, HM15136 has a pH dependent FcRn binding property due to a Fc portion which is essential for vascular endothelial recirculation.

In vivo efficacy of HM15136 was evaluated by measuring the glycemic profile after single and repeated doses in acute and chronic hypoglycemia rat models. *In vivo* studies demonstrated that HM15136 rapidly reverses acute hypoglycemia as well as sustainably increasing the blood sugar level in rats that mimicked human CHI.
Congenital hyperinsulinism is one of the most common diseases that cause serious and persistent hypoglycemia in newborns and infants. Insulin is a hormone that controls blood sugar levels in body and lowers the glycemic level when it is elevated after eating food. In patients with congenital hyperinsulinism, insulin does not play such a role and is secreted from the pancreas irrespective of the glycemic level. Consequently, patients experience hypoglycemia. HM15136, developed with an indication of congenital hyperinsulinism based on such mechanism, has hyperglycemic effects, an general action of glucagon, as well as appetite suppression and anti-obesity effects by activating hormone-sensitive lipase in adipocytes and promoting lipolysis as found in animal studies. Pharmacodynamic assessment in a hypoglycemic rat model observed a concentration dependent effect of HM15136 on weight loss which was estimated to be similar to the action of glucagon. Besides, different from previous technology, HM15136 overcame a short half-life, a shortcoming of previous biopharmaceuticals. Consequently, the duration of action in blood is extended and an equivalent or greater efficacy and effects are anticipated with a lower dose than previous doses applied to insulin products.

3.2. Background of Currently Used Treatments

Korean Society for the Study of Obesity recommends diet, exercise and behavioral therapy as initial treatment of obesity, and drug therapy when these approaches are not effective [3, 8]. As drug treatment, fat absorption inhibitors, appetite suppressants and drug combination therapy, etc. were developed. Recently, application of a glucagon analogue used for diabetes treatment in obesity was approved, first in the United States and also in Korea in 2017.
It is known that the lowered incretin response in type 2 diabetes can explain up to 60% of the change in the post-prandial insulin response. GLP-1 RA is a therapeutic agent to prevent degradation of glucagon like peptide-1, a key incretin in human, by dipeptidyl peptidase-4(DPP-4) [6]. It was reported that a GLP-1 RA is effective for weight loss by maintaining the incretin level in body [4].
As of 2015, there are 5 clinical trials in the United States reporting on the use of a GLP_1 RA (liraglutide) for obesity, and clinical trials at various phases were performed to investigate its effects in obesity [7].
Currently approved GLP-1 RAs include Exenatide, Liraglutide, Exenatide LAR, Lixisenatide, Albiglutide and Dulaglutide. Such GLP-1 RAs are designed to stimulate GLP-1 receptors, thereby increasing insulin secretion in response to oral and intravenous glucose to similar extents; this means the magnitude of the incretin effect should remain unchanged. [5, 6].
In this context, this clinical trial aims to investigate the effect of HM15136 after its administration in a small number of obese or overweight subjects and thereby to develop a therapeutic agent for obesity, based on a single dose clinical trial in healthy subjects (HM-GCG-101). This compound is differentiated from GLP-1 agents as it is a long-acting glucagon analogue and exhibits improved stability due to conjugation of a glucagon analogue with a Fc region of human immunoglobulin G4 by [redacted]

3.3. Investigational Product Profile

Hanmi Pharmaceutical is developing HM15136, a synthetic conjugate of a glucagon analogue (called GC15136) and a G4 Fc portion of human immunoglobulin (called HMC001) linked by a [redacted] bifunctional linker molecule.
This product was designed as a novel therapeutic agent for congenital hyperinsulinism (CHI) which is a rare genetic disease characterized by inappropriately elevated serum insulin.
When the mechanism of insulin secretion or glycemic detection is dysfunctional, the pancreatic insulin secretion is not reduced even though the glycemic level drops. If left untreated, CHI can result in a brain damage or even death secondary to hypoglycemia.
For such reasons, the effect of relieving hypoglycemia was observed in an acute and chronic hypoglycemia rat model that mimicked CHI, and it was also found that HM15136 has a concentration dependent weight loss

effect. In addition, single and repeated dose studies also noted the weight loss effect resulting from appetite suppression.
Such action is attributable to a glucagon portion of HM15136. Previous glucagon products exhibit low solubility, limited stability in physiological pH and short duration of action, resulting in limited utility. In order to overcome such shortcomings, the sponsor developed HM15136, a novel glucagon analogue with a long duration of action.

3.4. Result of Nonclinical Experiences

<*In vitro*>
In vitro activity of HM15136 was evaluated using hGCGR/Chinese hamster ovary(CHO) cells. HM15136 increased the cyclical adenosine monophosphate level in cells in a dose dependent fashion and exhibited the maximum efficacy similar to natural glucagon, demonstrating its property as a complete agonist.
In rat primary hepatocytes, HM15136 induced glucose production through both glycogenolysis and gluconeogenesis just like natural glucagon, suggesting that HM15136 actually has pharmacological properties similar to glucagon.
In additional *in vitro* studies, HM15136 exhibited the minimal immune mediated effector function as it contains a non-glycosylated Fc portion derived from human IgG4. Furthermore, HM15136 has a pH dependent FcRn binding property due to a Fc portion which is essential for vascular endothelial recirculation.

<*In vivo* efficacy study>
In vivo efficacy of HM15136 was evaluated by measuring the glycemic profile after single and repeated doses in acute and chronic hypoglycemia rat models. *In vivo* studies demonstrated that HM15136 rapidly reverses acute hypoglycemia as well as sustainably increasing blood sugar levels in rats that mimicked human CHI.
Such findings were consistent with *in vitro* study results. HM15136 exhibits endogenous activities similar to that of glucagon *in vivo* also, indicating the therapeutic potential of HM15136 in CHI treatment.

During pharmacodynamic assessment conducted in a hypoglycemia rat model, the concentration dependent effect of HM15136 in weight loss was confirmed which is estimated to be similar to a pharmacological action of glucagon. Furthermore, during a safety pharmacology study of HM15136, information on general behavioral profile, body temperature and body weight was collected for the general behavior (Irwin's test) investigation, and of these, in terms of body weight, the weight loss effect was shown at intermediate (0.583 mg/kg) and the highest concentrations (1.750 mg/kg), and a repeated dose toxicity study also found a rapid weight loss effect in both female and male.
Such findings were observed along with reduced food intake. Decreased appetite causes lipolysis and weight loss. This is estimated to be due to a pharmacological action of HM15136 in which glucagon acts directly on the liver to promote glycogenesis and glycogenolysis and thereby elevates sugar concentrations.

<Safety pharmacology study>
Effects on the cardiovascular system, respiratory system, central nervous system and *in vitro* human ether-a-go-go-related gene(hERG) channel analysis were evaluated.
No significant effect was observed in this study.

<Pharmacokinetic (PK) study>
Pharmacokinetic parameters were measured after subcutaneous administration in experimental animals. HM15136 had high bioavailability and long half-life ($t_{1/2}$) which was approximately 32.3-56.2 hours in mice, approximately 40.9-54.8 hours in rats and 26.6-34.9 hours in dogs, indicating that HM15136 is a long acting glucagon analogue.
HM15136 was found to be distributed mostly in the liver, a target organ of glucagon in gluconeogenesis.

<Toxicity study>
Up to 13 weeks of repeated dose toxicity studies in rats and monkeys and an *in vitro* genotoxicity study were conducted. Local tolerance was investigated in a repeated dose toxicity study, and a key dose limiting factor was weight loss in rats and monkeys.
In addition, no adverse event was observed in a toxicity study of HMC001.

- No Observed Adverse Effect Level (NOAEL)

The therapeutic safety margin at the no observed adverse effect level (NOAEL) was estimated as 4-fold in rats and 49-fold in monkeys, based on 0.02 mg/kg which is an expected starting clinical dose for human (NOAEL was 0.5 mg/kg in rats and 3 mg/kg in monkeys. Human equivalent dose converted from an animal dose based on the body surface area was 0.08 mg/kg in rats and 0.97 mg/kg in monkeys).

- 4 week-repeated dose toxicity study

Vulnerable target organ was not identified in a 4 week-repeated dose toxicity study. While all changes returned to normal during the recovery phase, atrophy of the thymus, spleen, pancreas, parotid salivary gland and mesenteric lymph node in monkeys persisted. Most of observed responses were related to the effect of fasting or pharmacological action of glucagon. There was no adverse finding related to the test chemical at the injection site. Anti-HM15136 antibody was detected in monkeys but not in rats. There was no difference in exposure by sex in 4 week-toxicity studies in rats and monkeys.

- 13 week-repeated dose toxicity study

In a 13 week-repeated dose toxicity study in rats, reduced body weight and food intake were observed, and the relevant findings partially returned to normal after a 4 week- recovery phase. In some dose groups, reduced RBC and atrophy of multiple organs (lymphatic organs, intestine, adrenals, ovaries and vagina) was noted; such changes were due to an excessive pharmacological action of HM15136 and did not appear to represent adverse effects. In a 13 week-repeated dose toxicity study in monkeys, erythroid disturbance and atrophy of multiple organs (thymus, spleen, pancreas, salivary gland, lymph node and bone marrow) were observed; such changes were due to an excessive pharmacological action of HM15136 and did not represent adverse effects.

- Genotoxicity study

The compound was negative in genotoxic potential.

For further details, see the Investigator Brochure (IB)[9].

3.5. Result of Clinical Trial Experiences

Safety, tolerability, pharmacokinetic and pharmacodynamic factors are under clinical evaluation in 8 subjects per cohort (investigational product : placebo = 6 : 2) with a total of 7 cohorts of healthy subjects (0.01, 0.02, 0.03, 0.05, 0.08, 0.10, 0.12 mg/kg) by HM15136 dose (HM-GCG-101). Data is not available yet, but there was no significant safety issue to date.

3.6. Rationale of Clinical Trial

This clinical trial aims to evaluate safety, pharmacokinetics and pharmacodynamics after repeated dose in volunteers with dyslipidemia and/or hypertension in part 1 subjects and dyslipidemia and/or hypertension with type 2 diabetes in part 2 diabetes subject, among

overweight volunteers with obesity or comorbidity, based on findings from a previous clinical trial in healthy volunteers (HM-GCG-101).

3.7. Risks Assessment

Pharmacologic and pre-clinical data known for individual agonists suggest that the following toxicities are expected.

- Gastrointestinal system: Nausea, vomiting, gastrointestinal hypotonia, diarrhea, indigestion, weight loss, anorexia, dehydration, gastroesophageal reflux disease
- Metabolism: Hyperglycemia, hypoglycemia, body temperature change
- Cardiovascular system: Hypertension or hypotension (increased heart rate and inotropic action)
- Immune system: Systemic allergic reaction including anaphylaxis, angioedema, urticaria, dyspnea and hypotension
- General: Injection site reaction, pyrexia, abdominal pain, abdominal distension
- Laboratory: Hepatic dysfunction (transient elevation of aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), bleeding and blood coagulation disorder, hypokalemia, elevated creatinine levels, anemia
- Nervous system: Agitation, dizziness, headache
- Skin legion: Necrolytic migratory erythema
- Changed salivation
- Diuresis

4. Study Objectives

To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of HM15136 in obese subjects or overweight subjects with co-morbidities

4.1. Primary Objectives

- To assess safety and tolerability of HM15136 after multiple subcutaneous (SC) doses.
- To assess the pharmacokinetic (PK) profile of HM15136 after administration of multiple SC doses.

4.2. Exploratory Objectives

- To assess pharmacodynamics (PD) properties of HM15136 after multiple SC doses.

5. Subject Selection

The subjects with obese or overweight with co-morbidities, should provide informed consent in writing based on the information, and should meet all of inclusion criteria and should not meet any exclusion criteria.

5.1. Number of Subjects

This study will be enrolled with 12 subjects in each cohort according to in/exclusion in Part 1, planned 3 cohorts. 9 subjects randomized to the HM15136 group will be administered IP in each cohort, 3 subjects will receive placebo. In part 2, up to 66 subjects will be enrolled. Thirty (30) subjects in cohort 4 will be randomized to HM15136 or placebo in a ratio of 15:15, 12 subjects in each of the cohorts 5-7 in a ratio of 9:3. Part 2 will only be performed, if deemed necessary, after the safety data, obtained by the 9th subject's visit on Day 29 of Cohort 3 in Part 1, have been reviewed.
An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations for the dose and study progress of Part 2. After the review of the safety data in Part 1, Part 2 may or may not proceed.

[Part 1]

Cohorts	Number of Subjects	Treatment
Cohort 1	N=9	HM15136 0.02 mg/kg
	N=3	Placebo
Cohort 2	N=9	HM15136 0.04 mg/kg
	N=3	Placebo
Cohort 3*	N=9	HM15136 ≤0.08 mg/kg
	N=3	Placebo

* Dosage of Cohort3 can be adjusted, but cannot be over the dosage presented in the table.
The escalated dose should not be over twice the dose of the previous cohort.

[Part 2]

Cohorts	Number of Subjects	Treatment
Cohort 4* (DM)	N=15	HM15136 0.06 mg/kg
	N=15	Placebo
Cohort 5 (DM)	N=9	HM15136 ≤0.02-mg/kg
	N=3	Placebo
Cohort 6** (DM)	N=9	HM15136 ≤0.04-mg/kg
	N=3	Placebo
Cohort 7** (DM)	N=9	HM15136 ≤0.06-mg/kg
	N=3	Placebo

* In part 2, enrolling 30 subjects per cohort 4, 15 subjects randomized to HM15136 group will be administered IP, (15 subjects will receive placebo).
The dose and study progress of Part 2 should be guided by the recommendation of the DMC. After the review of the safety data in Part 1, Part 2 may not proceed.

** Cohorts 6 and 7 will be optional.

5.2. Inclusion Criteria

Subjects who meet all of the following criteria are considered eligible for participation in the study.

1) Male or Female subjects
2) Age ≥ 18 to ≤ 65 years at Screening visit.
3) Body Mass Index (BMI) ≥ 30 kg/m^2 or 27 kg/m^2 ≥ with presence of comorbidities (Subjects in Part 1: dyslipidemia and or hypertension except for Type 2 (T2) DM, T2DM subjects in Part 2: dyslipidemia and/or hypertension with T2DM) with/without medication treatment and have had stable weight for 3 months (weight changes less than 5%), Untreated dyslipidemia is defined as LDL ≥ 160 mg/dL, or Triglyceride ≥ 150 mg/dL, or HDL < 40mg/dL for male and < 50 mg/dL for female, untreated hypertension is defined as Systolic Blood Pressure ≥ 140 or Diastolic Blood Pressure ≥ 90 mmHg. -
4) The criteria for HbA1c and FPG (Fasting Plasma Glucose) are as below.
   ① Subjects in Part 1: 'FPG < 5.6 mmol/L (100 mg/dL)' and 'HbA1c < 5.7%' (But, if the result is out of the reference range at the screening visit, it can be tested again on another day by laboratory analysis.)
   ② Subjects in Part 2 with DM: the subjects diagnosed as type 2 DM, and stably treated with HbA1c ≤ 9% for 3 months by Metformin only.
5) Female subjects must be non-pregnant and non-lactating. Females of childbearing potential must use highly effective contraceptive methods, stable at least 2 months prior to the screening.
   Male subjects should be surgically sterile (at least 1 year after vasectomy) or sterilized from the screening visit to 60 days after administration of IP, or if the male subject has a sexual relationship with a female partner of childbearing potential, the male subject is required, and the female partner should be encouraged to use a valid contraceptive method (e.g., condom, spermicidal form/gel/ film/cream suppository combination, etc.) during the study period.
6) Subjects who agree to participate this study voluntarily and to give written informed consent.

5.3. Exclusion Criteria

Subjects who meet at least one of the following criteria are considered not eligible for participation in 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 LAPBAND®), as well as clinically significant gastrointestinal disorders (e.g. peptic ulcers, severe GERD) at Screening.
2) Use of antacids, anticoagulants, or drugs that directly modify gastrointestinal (GI) motility, including antacids anticholinergics, anticonvulsants, serotonin type 3 (5HT3) antagonists, dopamine antagonists, opiates; anticoagulation within 2 weeks of screening;(But, it is not limited to the above listed drugs.) The use of acetylsalicyclic acid (e.g., Bayer® Aspirin) 81 mg/day taken prophylactically is not considered anticoagulation therapy for the purposes of this protocol.
3) Uncontrolled hypertension, defined as systolic blood pressure > 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening
   (Independent of subjects being on antihypertensive medication or not, But, if the results are out of the reference range at the screening visit, they can be tested again on another day. Subjects with uncontrolled hypertension may be rescreened after 3 months, following initiation or adjustment of antihypertensive therapy.)
4) Uncontrolled dyslipidemia, defined as fasting triglycerides (TG) > 500 mg/dL and/or fasting low density lipoprotein (LDL) cholesterol >200 mg/dL at Screening (independent of subjects being on lipid lowering medication or not).

5) Use of any drugs that are known to interfere with glucose or insulin metabolism, within 3 months prior to screening except for metformin for T2DM subjects in part 2: oral or parenteral corticosteroids or topiramate, monoamine oxidase (MAO) inhibitors, growth hormone
(But, it is not limited to the above listed drugs.)
6) Subjects who are currently diagnosed with type 1 DM or who have such medical history
7) Subjects diagnosed with type 2 DM, who have a treatment history of relevant drugs like sulfonylurea, thiazolidinediones, GLP-1 receptor agonist, SGLT2 inhibitor, insulin and DPP-4 inhibitors within 3months before screening visit. Stable metformin therapy is allowed.
8) Any weight control treatment, including over-the-counter drugs and herbal medications and supplements, or any medication with a labelled indication for weight loss or weight gain within 3 months prior to screening.
9) Participation in another investigational study within 1 month prior to enrollment or 5 times of half-lives within the last dose of investigational product, whichever is longer.
10) Serum calcitonin levels > 20 pg/mL at the screening.
11) 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.
12) Personal history of cancer diagnosis prior to screening visit, if it is likely to impact the study results as judged by the investigator.
13) 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 and bupropion for reasons other than active psychiatric indications [eg, migraine, weight loss, smoking cessation] must meet a 3-month wash out.)
14) History of significant suicidal ideation or suicidal behavior/attempts.
15) History of any major surgery within 6 months prior to screening.
16) Subjects who cannot cope with noise or isolation circumstances in testing devices or have any contraindication for MRI test (e.g., pacemaker, iron implant in body, metal pieces, clips of cerebral aneurysm as well as those things in the body that can be impacted by the magnetic field.).
17) History of any serious adverse reaction or hypersensitivity to study drugs components, or have contraindication diseases (e.g., pheochromocytoma, insulinoma, glucagonoma).
18) 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)
19) Cardiac arrhythmia requiring medical or surgical treatment within 6 months prior to screening.
20) Personal or family history of medullary thyroid carcinoma (MTC) or a genetic condition that predispose to MTC (ie, multiple endocrine neoplasia type 2).
21) Anemia findings of hemoglobin < 13 g/dL in male or < 12 g/dL in female in clinical laboratory results.
22) Abnormal laboratory results for thyroid stimulating hormone (TSH) (> 1.5 x ULN or < 0.4 mIU/L) at screening.
23) Clinically significant abnormal hepatic function tests suggestive of hepatic impairment (eg, ALT and/or AST >2 x ULN).
24) Clinically significant abnormal pancreatic function tests suggestive of pancreatic impairment (eg, amylase and/or lipase >3 x ULN).
25) 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).
26) Female who is pregnant or breast-feeding, or has a positive pregnancy test at screening or Day -2.
27) History of any active infection, including any active COVID-19 infection even if mild, within 30 days prior to dosing (except mild viral illness, such as common cold), as judged by the investigator.
28) Use of a very-low calorie (1,000 kcal/day) liquid weight loss diet within 6 months prior to screening

29) History of alcohol or illicit drug abuse as judged by the Investigator within approximately 1 year.
30) 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. (Subjects must be able to abstain from smoking during the confinement period.)
31) Use of debauchery drug (e.g., marijuana) within 6 weeks prior to screening or clinically under the effect at screening, as per Investigator evaluation.
32) Subject has positive urine drug test (e.g., cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids) at Screening or Day -2.
33) Known history of or positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCVAb), or human immunodeficiency virus type 1 (HIV-1) or type 2 (HIV-2) antibody.
34) Any anticipated procedures (eg, surgery), that might interfere with the compliance or completion of the study.
35) 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, results or interpretation of results.
36) Donation of whole blood (400 mL) or blood components (500 mL) within 60 days, or received transfusion of blood products within 14 days prior to screening.
37) Unwillingness to participate, involuntary participation or language barriers precluding adequate understanding or cooperation.
38) Is employed by Hanmi (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of Hanmi staff (defined as a spouse, parent, sibling, or child, whether biological or legally adopted).

5.4. Withdrawal and Discontinuation Criteria

5.4.1. Violation of Protocol

The investigator should report to Hanmi Pharm. Co., Ltd. as soon as possible if a subject violation has occurred, and determine whether the subject should continue to participate in the clinical trial or not. When a subject withdraws due to a violation of protocol, it has to be written in the CRF. Serious violations of the protocol include, but are not limited to:

1) Violation of inclusion and exclusion criteria that may affect efficacy, safety, exploratory evaluation.
2) Administration of prohibited medications or using prohibited therapies.
3) Any other violation considered as a serious protocol violation

5.4.2. Subject's Withdrawal, Replacement and Discontinuation

The subject may withdraw his/her consent to participate in the clinical trial at any time for any reason without any disadvantage or impact on future medical care. Although the subject is not required to state the reasons for withdrawing consent to participate in the clinical trial, the reasons for withdrawal must be recorded in all cases. If the randomization code for the subject is broken, the date, time and reason must be recorded. Subject's participation may be terminated before completion of the study.
Subjects who have received IP but for whatever reason cannot participate in the entire study period are classified as 'withdrawals'.
If the subject requests the study discontinuation or consent withdrawal or the investigator judges that the subject should be discontinued, the subject may be withdrawn at any time. If the study would be discontinued or withdrawn, the results of the study obtained prior to that point in time may be reviewed for final evaluation if assessible.

The reasons for the withdrawals or discontinuation of individual subjects are as follows.

1) If the subject who is healthy in Part 1 has a FPG exceeding 10 mmol/L (180 mg/dL). Subjects FPG should be re-tested and FPG must be confirmed by a morning plasma glucose level (after 10 hours of fasting) that is ≥ 180 mg/dL (10.0 mmol/L), verified by a standard laboratory analysis (ie, YSI glucose analyzer at the site). Subjects who have confirmed FPG values that have reached the threshold limits will be counseled first. They will then have their FPG re-assessed, per PI discretion. If the FPG is still above the threshold they will be dropped from the study and may be replaced.
2) If the subject who has type 2 DM in Part 2 has an FPG exceeding 15 mmol/L (270 mg/dL). Subjects FPG should be re-tested and confirmed by a morning fasting plasma glucose level (after 10 hours of fasting) that is ≥ 270 mg/dL (15.0 mmol/L), verified by a standard laboratory analysis (ie, YSI glucose analyzer at the site). Subjects who have confirmed FPG values that have reached the threshold limits will be counseled first. They will then have their FPG re-assessed, per PI discretion. If the FPG is still above the threshold they will be dropped from the study and may be replaced.
3) Difficult to keep taking part in the clinical trial due to any adverse events (AE).
4) Violation of protocol
5) Impossible to follow up on a subject.
6) Withdrawal of consent by subject or legally acceptable representative.
7) In case of discontinuation by the sponsor
8) If the investigator judged that it is difficult to continue this study.
9) If the subject is pregnant.
10) Participation of subject who is not acceptable per inclusion and exclusion criteria.
11) Administration of prohibited medications, or necessary to administer it.
12) Treatment of prohibited therapies, or necessary to treat with them.
13) Poor medication compliance.
14) Others
15) If missing dosing and/or visits occurs for many times (due to COVID-19 or any other inevitable reasons), The study investigator may withdraw or discontinue a subject from participation in the study, if the subject missed a specific numbers of dosing/dosing visits. Missed doses <70% may lead to discontinuation of subject, based on decision of investigator and sponsor. If a subject must miss dosing due to COVID-19 or any other unavoidable reasons, the willingness and safety of the subject will be taken into consideration.

If for any reason during the study period the subject is withdrawn from participation or dropped the study prior to completion, the investigator should make every effort to conduct the planned evaluation in the follow-up visit. If possible, early termination visit is planned within 1 - 3 days after discontinuation of IP. Last IP administration date, withdrawal reason and all of information until the termination point should be recorded in source documents (SD) and Case Report Form. In order to prevent omissions of any adverse events, the investigator should contact the withdrawn subject via phone calls, letters (or e-mail), direct visits, etc., and leave relevant records. Also, even if tracking is not possible, try to contact as much as possible to minimize follow up failure and leave relevant record. In case of withdrawal caused by AE, should be followed until recovered (or the investigator judges normalization) or until the subject's last visit completion, or until further follow up is judged to be meaningless. Particularly, in case of withdrawal caused by elevation of FPG corresponding to the reason 1) and 2), IP should be stopped and follow up occur until FPG recovered or judged to be normal with the subject's consent. If the investigator made the subject withdraw participation, that subjects cannot re-participate in this study.

If the subject is withdrawn from the study prior to administration of IP, the subject may be replaced by a candidate subject. The subject who is withdrawn for reasons not related to safety, may be considered for replacement with the judgement of the investigator and sponsor. The results of study obtained from the subject until the withdrawal point may be reviewed for final evaluation if assessible.

6. Study Design

6.1. Duration of Clinical Trial

The planned period of each cohort is 22 weeks including subject screening, treatments for 12 weeks, and follow-up period.

6.2. Study Design

This is a double-blind, randomized, placebo controlled, multiple ascending dose (MAD) study to investigate the safety, tolerability, PD, and PK of the subcutaneous (SC) administration of HM15136 in obese subjects or overweight subjects with comorbidities.

This study will be conducted in Part 1 and 2. In part 1, 12 subjects per cohort (HM15136 group 9 subjects, placebo group 3 subjects) will participate, and 3 cohorts will proceed sequentially, but may overlap during the execution. In part 2, enrolling 30 subjects in cohort 4 (HM15136 group 15 subjects, placebo group 15 subjects) will participate, and up to 12 subjects each in cohorts 5-7 (HM15136 group 9 subjects, placebo group 3 subjects). 12 subjects per cohorts assigned to Part 1 and Part 2 will be randomized to HM15136 and placebo in a ratio of 9:3, and 30 subjects per cohort 4 assigned to Part 2 will be randomized to HM15136 and placebo in a ratio of 15:15.

After Cohort 1 randomization is completed, the DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations to decide whether subjects can be randomized into Cohort 2.

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

Dose escalation from cohort 3 to next dose level for the subsequent cohort (Cohort 4 in Part 2) will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1, 2 and through the 9th subject's visit on Day 29 in cohort 3. An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations.

If dose escalation is stopped, dose de-escalation may occur in subsequent cohorts, to further refine clinically relevant dose levels.

The dose of cohorts 3 and 4 can be adjusted, but may not be over the planned dose of 0.08 mg/kg. The escalated dose should not be more than 2 times over the dose of the previous cohort.
In part 2, after the review of the safety data, obtained by the 9th subject's visit on Day 29 of Cohort 3 (in Part 1), Cohort 4 can be processed, if within the 0.08 mg/kg of dose, which is the planned maximum dose.
The DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations for the progress of Part 2. After the review of the safety data in Part 1, Part 2 may or may not proceed.

Cohort 4 may be conducted with a lower number of subjects to adopt escalation design as previously performed in Part 1 for the safety assessment of the T2DM subjects.
The maximum dose level for Part 2 will not exceed 0.06 mg/kg (tentative dose for Cohort 5 may be 0.02 mg/kg, tentative dose may be 0.04 mg/kg for Cohort 6). This dose level has been previously approved for subjects with T2DM by the independent DMC. Therefore, the decision to proceed to the next cohort/dose level from cohorts 5-7 will be made per review of safety data by Sponsor, Investigator and Medical Monitor during a Data Review Meeting (DRM), which will take place after the 9th subject has comleted Visit Day 43 (which is after 6 weeks of dosing).
Per DRM of Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed at this timepoint and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit), to assess the safety data and to make a decision to escalate to Cohort 6 or not.

Dose escalation from cohort 6 to the subsequent cohort 7 will follow the same dose escalation scheme and DRM(s) of the previous cohort.
Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5.
If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study.
The conduct of cohorts 6 and 7 is optional.

6.3. Rationale of Trial Design

6.3.1. Selection of subjects in test group

Part 1 in this study is to administer HM15136 once a week for a total of 12 weeks to subjects who are obese or overweight with comorbidities. All cohorts in Part 2 will receive HM15136 once a week for a total 12 weeks for subjects who have type 2 DM among the obese or overweight with comorbidities.

6.3.2. Selection of controlled Group

The control group of each group of this study recruits the subjects on the same criteria as the test group.

6.3.3. Rationale of initiation and maximum dosage adjustments

A dose of 0.01, 0.02, 0.03, 0.05, 0.08, 0.10, or 0.12 mg/kg was given to HM-GCG-101, a single-dose study of HM15136 in healthy volunteers. In general, assuming that the clearance rate is the same for each dose, the AUC (AUC168ss) value for 1 week in the steady state after repeated administration is equal to the AUC_{inf} value when the same dose is administered once.
The planned maximum dose for this study is 0.08 mg/kg. The maximum AUC_{inf} observed in the single dose study (HM-GCG-101) administered at this dose was 60,772 ng·h/mL. In addition, when the NOAEL of 0.5 mg/kg (human equivalent dose 0.08 mg/kg) in the rat 13-week toxicity evaluation (2018-0265) was repeatedly administered, the most conservative AUC0-168h value was 98,300 ng·h/mL at the 13th week. The safety margin of the maximum therapeutic dose of 0.08 mg / kg is approximately 1.6 times the most conservative value of the 13-week AUC0-168h (98,300 / 60,772) in the NOAEL of the rat toxicity assessment at the 13th week.

The planned starting dose for this study is 0.02 mg/kg. This was calculated in reverse order to achieve the maximum planned capacity (0.08 mg/kg) assuming a maximum two-fold of the three planned cohorts, and was also selected by considering the minimum effective capacity (ED10) value in the weight loss potency test (Dv-8088, E2018242) conducted in rats and mice (In the weight loss efficacy test of rats and mice, ED10 was 0.012 and 0.014 mg/kg respectively converted to equivalent human dose).

6.3.4. Confirmation of dosage and escalation

1) Part 1

After Cohort 1 randomization is completed, the DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations to decide whether subjects can be randomized into Cohort 2.
Details will be defined in the DMC charter. Dose escalation from cohort 2 to next dose level for the subsequent Cohort 3 will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1 and from the 9th subject's visit on Day 29 in cohort 2.
The DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations.

Dose escalation from cohort 3 to next dose level for the subsequent cohort (Cohorts 4 in Part 2) will be based on

the safety, tolerability, available PD, and available PK data obtained from cohort 1, 2 and through the 9th subject's visit on Day 29 in cohort 3. An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations.

If dose escalation is stopped, dose de-escalation may occur in subsequent cohorts, to further refine clinically relevant dose levels.

The dose of cohorts 3 and 4 can be adjusted, but may not be over the planned dose of 0.08 mg/kg. The escalated dose should not be more than 2 times over the dose of the previous cohort.
In part 2, after the review of the safety data, obtained by the 9th subject's visit on Day 29 of Cohort 3 (in Part 1), Cohort 4 can proceed if within the 0.08 mg/kg dose, which is the planned maximum dose.

Based on the above, the dose per cohort of this study was planned as the below table.

Cohorts	Number of Subjects	Treatment
Cohort 1	N=9	HM15136 0.02 mg/kg
	N=3	Placebo
Cohort 2	N=9	HM15136 0.04 mg/kg
	N=3	Placebo
Cohort 3*	N=9	HM15136 ≤0.08 mg/kg
	N=3	Placebo

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

2) Part 2

If necessary, after the review of the safety data obtained by the 9th subject's visit on Day29 of Cohort 3 in Part 1, the cohort can proceed within the 0.08 mg/kg dose, which is the planned maximum dose.

The DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations for the study progress of Part 2.
The maximum dose level for Part 2, Cohorts 5-7 will not exceed 0.06 mg/kg (tentative dose for Cohort 5 may be 0.02 mg/kg, tentative dose may be 0.04 mg/kg for Cohort 6). This dose level has been previously approved for subjects with T2DM. Therefore, the decision to proceed to the next cohort/dose level will be made per review of Sponsor, Investigator and Medical Monitor during a Data Review Meeting (DRM) after the 9th subject has completed the Day 43 visit.
Per DRM for Cohort 5 (after the 9th subject's visit on day 43 of Cohorts 5), a dose escalation to Cohort 6 will not proceed at this timepoint and another DRM will be held after all 12 subjects in Cohort 5 have completed the final study visit on Day 113 (=F/U Visit), to assess the safety data and to make a decision to escalate to Cohort 6 or not.
Dose escalation from cohort 6 to the subsequent cohort 7 will follow the same dose escalation scheme and DRM(s) of the previous cohort.
Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5.
If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study.

Cohorts	Number of Subjects	Treatment
Cohort 4 (DM)	N=15	HM15136 0.06 mg/kg
	N=15	Placebo
Cohort 5 (DM)	N=9	HM15136 ≤0.02-mg/kg
	N=3	Placebo
Cohort 6** (DM)	N=9	HM15136 ≤0.04-mg/kg
	N=3	Placebo
Cohort 7** (DM)	N=9	HM15136 ≤0.06-mg/kg
	N=3	Placebo

* In part 2, if necessary, after the review of the safety data obtained by the 9th subject's visit on Day29 of Cohort 3 in Part 1, the cohort- can proceed with 0.06 mg/kg dose.
The dose and study progress of Part 2 should be guided by the recommendations of the DMC. After the review of the safety data in Part 1, Part 2 may not proceed.
** Cohorts 6 and 7 are optional.

6.4. Subjects Identification and Randomization

6.4.1. Screening No.

The unique subject identification (SID) number will be assigned to all screened subjects. The SID number consists of 4 digits and is numbered sequentially from X001 (X is institution's number.). The SID number is given in the order of subject screening (according to order consent of participation when the screening conducts in the same day.). The SID number would be managed from screening to randomization. The subject who has been withdrawn from this study prior to randomization and after screening will retain their SID number.

6.4.2. Randomization No.

The subjects enrolled in this study would be assigned randomly to each treatment group. The randomization code will be generated by biostatistics staff who are not related to this study, (independent to this study), using statistic software (SAS®, latest version) and block randomization method considering the predefined block size. Subjects in Part 1 will be assigned to HM15136 and placebo in a 3:1 ratio, in the case of Part 2, up to 66 subjects will be assigned to HM15136 and placebo. Thirty (30) subjects in Cohort 4 will be assigned in a ratio of 1:1 and 12 subjects in each Cohort 5-7 will be in a 3:1 ratio according to rules below in Table 1.

After the signing of informed consent, the investigator assigns the randomization number in the order of subjects who meet the in/exclusion criteria and are selected for participation. According to the protocol, the randomization number is given on Day -1 or Day -2, prior to administration of IP. The randomization number is kept in a limited place accessible only by pharmacy staff and can only be accessed by other personnel if the blind is broken. The randomization number includes the 3 digits of subject's number as presented in the below table.

Table 1. Randomization No. and Treatment Assignment

Part	Cohort	Randomization No.	Treatment Assignment*	
Part 1	1	101 - 112	HM15136 0.02 mg/kg (N=9)	Placebo (N=3)
	2	201 - 212	HM15136 0.04 mg/kg (N=9)	Placebo (N=3)
	3	301 - 312	HM15136 ≤0.08 mg/kg (N=9)	Placebo (N=3)
Part 2	4	401 - 430	HM15136 0.06 mg/kg (N=15)	Placebo (N=15)
	5	501 – 512	HM15136 ≤0.02 mg/kg (N=9)	Placebo (N=3)
	6	601 – 612	HM15136 ≤0.04 mg/kg (N=9)	Placebo (N=3)
	7	701 – 712	HM15136 ≤0.06 mg/kg (N=9)	Placebo (N=3)

* In Part 1, dosage of Cohort 3 can be adjusted, but not be over the dosage presented in the table. The escalated dose should not be over twice the dose of the previous cohort.
* In part 2, if necessary, after the review of the safety data obtained by the 9th subject's visit on Day29 of Cohort 3 in Part 1, the cohort can be processed within the 0.06mg/kg dose.
The dose and study progress of Part 2 should be guided by the recommendations of the DMC. After the review of the safety data in Part 1, Part 2 may not proceed.

Once a randomization number has been assigned to one subject, the number cannot be assigned to another subject. If subject participation is withdrawn early and the subject is replaced under the direction of the sponsor, an alternate randomization number is assigned when the replacement subject successfully completes the screening. The randomization number of the replaced subject is generated so that it can be assigned to the same treatment group as the discontinued subject. The randomization number is divided into a total 3 digits with a 'Cohort No. (1 digit) + Enrollment order (2 digits).' Iterated randomization numbers are made up of a total 4 digits, with '1' added to the beginning of the randomization number of the subject whose participation is to be withdrawn. For example, if replaced the subject 202, the randomization number of the alternative subject would be 1202.

6.5. Blinding and Unblinding

Although this study is conducted in a double blind, those who are responsible for preparation of IP are excluded. These staff are not involved in any other activity in this study.

On a subject level, during the conduct of the study, unblinding may be conducted only for the subject who have medical emergencies that can be a problem for the subject's safety (in the case of knowing the information of IP administered to the subject may affect the treatment of the emergency situation), or DLT (Dose limiting toxicity) occurred, or for determining whether to increase or decrease dosage as specified in the protocol and/or needed for the assessment of the DMC. Except for these reasons, unblinding should not occur on a subject level. The investigator must contact the principal investigator and Hanmi Pharm. Co., Ltd. to discuss this issue before the unblinding takes place. Emergency unblinding can be performed by the principal investigator using the IWRS. It should be ensured that no study personnel is unblinded to other subjects. Study site personnel and Sponsor personnel directly associated with the conduct of the study will not be unblinded. The investigator should record the date and reason why unblinding occurred in the CRF

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

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

Unblinding for final analysis of each part will also occur after the corresponding database locks for each Part 1 and Part 2. The final analysis for each part will be performed separately, once each part is completed.
For details please see section 11.3.1. Interim Analysis.

7. Completion and Early Discontinuation of the Clinical Trial

7.1. Study Completion

The end of entire study termination defines as the last subject's study completion or the withdrawal of consent, follow-up failure, or termination caused by death. If it is judged that each subject completed the procedure of administration/visit schedule totally 22 weeks included treatment period for 12 weeks and the follow-up period, and evaluation of clinical laboratory test at the last visit, and resolve the AE occurred or proceeding at the last visit, or no further follow up is meaningful, that subject is considered to complete the study.

7.2. Study Discontinuation

If the investigator or sponsor or medical monitor got to know any situation or events that there is a potential risk to the subject if the study was continued, they may be terminated the study after appropriate discussion. Even if the above conditions are not met, the study may be terminated according to the sponsor's judgement. If the subject's safety is threatened, the study must be stopped/terminated. The sponsor has the right to terminate this study at any time for failure to enroll a targeted number of subjects or for safety or other administrative reasons.

7.3. Dose Escalation and Study Stopping Criteria

<Dose Escalation Stopping Criteria>

The procedure for determining the dose is as follows

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

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

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

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

< Data Monitoring Committee (DMC) >

The DMC is a specific committee for the study and will function for safety review and dose escalation decisions as described above. The operations of the DMC will be defined in the DMC charter.

The DMC will review safety data (adverse events, clinical laboratory, vital signs and electrocardiograms, and other unblinded relevant data). There will be 3 dose decisions. In addition the DMC will have unplanned meetings should stopping criteria appear to have been met.

After Cohort 1 randomization is completed, the DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations to decide whether subjects can be randomized into Cohort 2.

Dose escalation from cohort 2 to next dose level for the subsequent Cohort 3 will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1 and through the 9th subject's visit on Day 29 in cohort 2. The DMC will make recommendations for the decision whether subjects can be randomized into Cohorts 3.

The next dose level for the subsequent cohort (Cohorts 4 in Part 2) will be based on the safety, tolerability, available PD, and available PK data obtained from cohort 1, 2 and through the 9th subject's visit on Day 29 in cohort 3. An independent Data Monitoring Committee (DMC) will assess the safety and will make dosing and cohort escalation assessments and recommendations.

<Data Review Meeting>

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

Additionally, a second DRM will be held and safety data from the 12th subject's final visit on Day 113 _(=F/U Visit) will be reviewed to dose escalate.

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

Cohorts 6 and Cohort 7 may be conducted at doses of 0.04 mg/kg and at 0.06 mg/kg respectively upon approval by the Investigator, Medical Monitor, and the Sponsor, if the safety is demonstrated in Cohort 5.

If sufficient safety data are collected after cohort 5 or cohort 6 have been completed, no additional cohorts will be conducted, and sponsor may choose to complete study.

< Study Stopping Criteria>

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

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

8. Information and Control of Investigational Product

8.1. Test Product

Product or Code Name:	HM15136
Manufacturer:	Hanmi Pharmaceutical Co., Ltd.
Formulation/Properties:	pre-filled syringe with a clear or almost colorless transparent sterile solution
Raw material/Quantity:	A synthetic conjugate of a glucagon analogue (GC15136) and a G4 Fc portion of human immunoglobulin (HMC001). The concentration is 10 mg/mL as a protein and the total amount is 0.52 mL.
Storage:	Shade storage at 2 - 8 ℃ refrigerated condition (Stable at room temperature for up to 12 hours)
Expiration date:	Up to 24 months from date of manufacture

8.2. Comparator

Product or Code Name:	Placebo
Manufacturer:	Hanmi Pharmaceutical Co., Ltd.
Formulation/Properties:	pre-filled syringe with a clear or almost colorless transparent sterile solution
Raw material/Quantity:	Including excipients excluding the main components of the test product
Storage:	Shade storage at 2 - 8 ℃ refrigerated condition
Expiration date:	Up to 24 months from date of manufacture

8.3. Dosage and Administration

Each administration group will receive either HM15136 or placebo by subcutaneous injection in the abdomen after at least 10 hours night fasting state via SC once a week for a total of 12 weeks. Injection sites will be rotated within the abdominal area at subsequent visits.

8.4. Drug Supply, Package, Labelling and Storage

The IP should be packaged in accordance with local legal requirement, and in accordance with FDA requirements and specific country regulatory requirements.

The sponsor should pack the IP so that it is not contaminated or deteriorated during transportation or storage, and that packages of the test product and comparator can be easily distinguished according to each batch. The packing unit should consider the number of days of each visit and visit window, and provide an extra IP in order to prevent discontinuation of IP.

All supplied IP should be stored in shade storage (ie, kept in a box until use) at 2 - 8 ℃ refrigerated condition in accordance with the manufacturer's guidance. HM15136 is stable at room temperature for up to 12 hours. Until delivery to the subject, the IP should be kept in a secure location with locks and accessible only to authorized personnel.

8.5. Manufacture, Prescription, Inventory Management and Disposal/Destruction

8.5.1. Manufacture

The IP is provided in pre-filled syringes. The dosage of the drug is based on the weight measured on the day before the administration (up to two decimal places). The volume to be injected is also determined by the dose

level. The concentration of HM15136 is 10 mg/mL. The determined injection volume is prepared into the administration syringe according to the instructions contained in the pharmacy manual.
Per COVID-19 modification, weight may be measured on day -2 intead of day -1, and this weight may be used for the calculation of the IP dose for the indiviudal subject.

8.5.2. Release of IP

Releasing of IP used for this study should be done on a subject-by-subject basis by the investigator or staff in charge of this study, after confirmation of subject eligibility

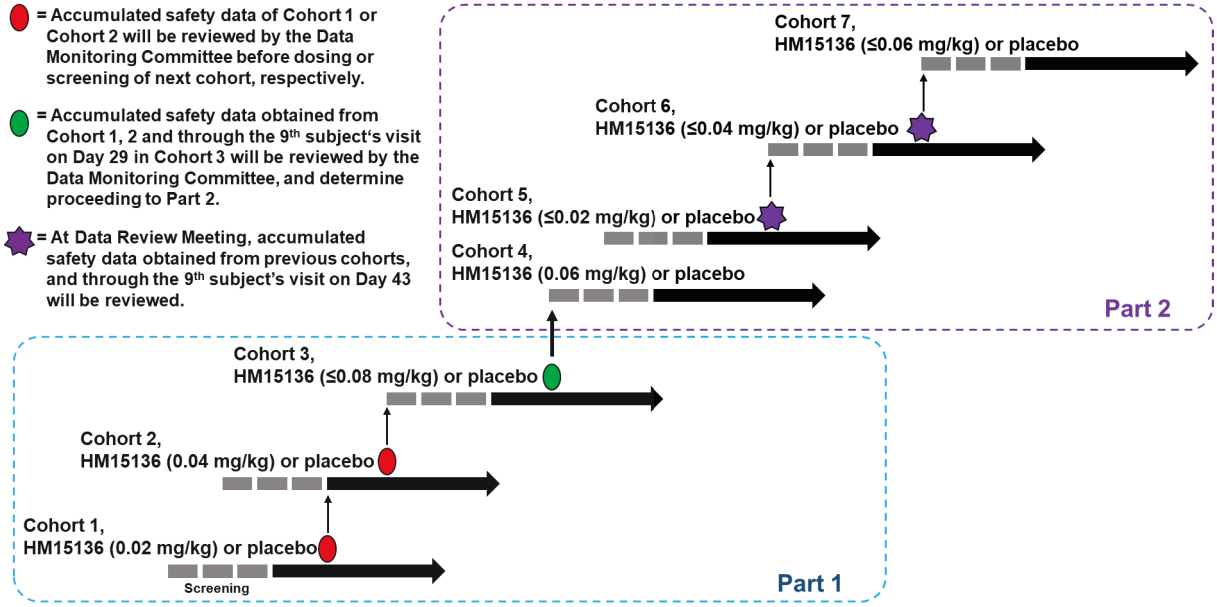
8.5.3. Inventory Management and Record

The management pharmacist should keep and manage a record of the randomization number, the date of the prescription, the number being released, etc., and check the inventory and keep a record of the receipt, storage, release, and returning of IP.
Each IP administered is also recorded.
Clinical research associate (hereinafter, CRA) for monitoring would regularly review administrative records to verify the use of all IP. The investigator is responsible for maintaining an accurate record of the IP management during the full period of study. And IP and related products should not be used for purposes other than those specified in the protocol.
The CRU will destroy all used syringes of IP and placebo at the CRU by the end of the study.

At the end of the study, all remaining IP, including unused and partially used IP will be destroyed in a documented process after confirmation by the responsible CRA.

9. Clinical Trial Methods and Administration Plan

9.1. Overall Clinical Trial Method



An additional data review meeting will be held after all of the 12 subjects in Cohort 5 have completed the final study visit (F/U Visit) on Day 113. Cohorts 6 and 7 are optional.

Dosage, Method, Period of Investigational product

The IP will be injected to the subject via SC administration in 3 dose cohorts in Part 1, and in up to 4 cohorts in part 2.
Planned cohorts are below.

Part	Cohorts	Number of Subjects	Treatment
Part 1	Cohort 1	N=9	HM15136 0.02 mg/kg
		N=3	Placebo
	Cohort 2	N=9	HM15136 0.04 mg/kg
		N=3	Placebo
	Cohort 3*	N=9	HM15136 ≤0.08 mg/kg
		N=3	Placebo
Part 2**	Cohort 4	N=15	HM15136 0.06 mg/kg
		N=15	Placebo
	Cohort 5	N=9	HM15136 ≤0.02 mg/kg
		N=3	Placebo
	Cohort 6	N=9	HM15136 ≤0.04 mg/kg
		N=3	Placebo
		N=9	HM15136 ≤0.06 mg/kg

	Cohort 7	N=3	Placebo

* Dosage of Cohort 3 can be adjusted, but not be over the dosage presented in the table. The escalated dose should not be over twice than the dose of the previous cohort.
** In part 2, if necessary, after the review of the safety data obtained by the 9th subject's visit on Day29 of Cohort 3 in Part 1, cohort can proceed within the 0.06 mg/kg dose, which is the planned maximum dose.
A DMC will assess the safety and will make dosing and cohort escalation assessments and recommendations for the study progress of Part 2.
For cohorts 5-7, after the safety data obtained by the 9th subject on day 43 are reviewed by Sponsor, investigator and medical monitor, dose escalation may proceed. An additional DRM will be held after all subjects have completed the dosing for Cohort 5.

Each subject will receive either HM15136 or placebo in the morning of Day 1 in the abdomen, after at least 10 hours night fasting state, via SC injection. The subject should maintain fasting state for 4 hours after the injection. After 4 hours, a post-administration assessment is performed, and a standardized lunch is provided to the subject. Per COVID-19 modification, if standardized lunch is not available, subjects may be provided with a snack bag.

The administration period of IP is a total of 12 weeks at once a week. Dosing windows for in-house and outpatient visits will be provided in the Operations Manual.

9.2. Past medication and Concomitant Medication

During the period from within 2 weeks before the screening visit to the follow-up visit, antacids, anticoagulants, drugs that directly modify gastrointestinal (GI) motility (Anticholinergics, anticonvulsants, serotonin type 3 (5HT3) antagonists, dopamine antagonists or opiates) are prohibited unless approved by the sponsor. The use of acetylsalicyclic acid (e.g., Bayer® Aspirin) 81 mg/day taken prophylactically is not considered anticoagulation therapy for the purposes of this protocol. During the period from within 3 months before the screening visit to the follow-up visit, drugs known to interfere with glucose or insulin metabolism (Use of any drugs regardless of oral or parenteral corticosteroids or topiramate, monoamine oxidase (MAO) inhibitors, growth hormone etc.) are prohibited unless approved by the sponsor. Any weight control treatments are prohibited, including prescription drugs, over the counter drugs, and herbal medications and supplements.
Acetaminophen/Tylenol® is prohibited 14 days before the in-house stay until a follow-up visit.
Per COVID-19 modification, Acetaminophen/Tylenol® is prohibited 14 days before the outpatient visit on Day -2 until a follow-up visit.

Concomitant medications are allowed if the investigator determines that drugs are necessary for the treatment of adverse events.

9.3. Treatment Compliance

IP administration is performed by trained and qualified person designated by the investigator. If any deviations occur from the planned dosing procedure, the description is recorded.

10. Procedure and Assessment of Clinical Trial

10.1. Visit Schedule

- Each subject should have a Screening visit up to 35 days the initial dosage.
- Each subject will be in-house 2 times and have 16 outpatient visits, including follow-up visit. Per COVID-19 modification, visit schedule may be modified to only outpatient visits and phone visits.

10.1.1. Scheduled Visit

1) Screening

Provide the subjects with sufficient information (In terms of life limitations including trial visits and diet) about their responsibilities and all the procedures anticipated in the study, the risks and benefits of HM15136 administration, and their rights during participation in the study. The subject has an opportunity to ask questions and has enough time for reflection on their study participation. If the subject wishes to participate in the study, the subject is asked to sign the informed consent form (ICF) and the date and time will be documented. Site staff must first receive written informed consent from the test subject before initiating the procedure.

Subjects who are likely to be selected for this study are required to eat and drink routinely until the screening visit. 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 (eg, laboratory assessments).

The subjects who screen fail can be re-screened once; if the lab results are out of range during the screening, they can be retested as needed at the discretion of the investigator. The investigator may also consult with the medical monitor about abnormal lab results and retesting.

2) In-house Periods

At In-house Period 1, after successful completion of the screening visit, only those subjects who meet all the inclusion criteria and none of the exclusion criteria should return to the institution on Day -2 and admit to the clinical ward. When the first admitted, the following variables are checked.

1. Alcohol exhalation test
   - Check for positive reaction
2. Drug abuse urine screening
   - Check for positive reaction
3. Pregnancy test for female of child-bearing age (Urine)
   - Check for positive reaction
4. Confirmation of the use of restricted concomitant medication/therapy within 24 hours before the admission to the unit (Day -2)
5. Any medical condition that the investigator judges may interfere with the interpretation of the study results or results. The investigator may also consult with the medical monitor.

At check-in for the in-house period, subjects will not be allowed to check in if they meet any of the criteria stated above. The in-house period may be rescheduled per Investigator discretion. Variables will be checked again.
Only subjects with T2DM, that will be eligible to participate in Part 2 of the study, will be provided with a glucometer for blood glucose control. For details please see the Operations Manual.

Per COVID-19 modification, In-house Period 1 may be performed as outpatient visits. After successful

completion of the screening visit, only those subjects who meet all the inclusion criteria and none of the exclusion criteria should return to the institution on Day -2 for the outpatient visit, where the following variables are checked.

1. Alcohol exhalation test
   - Check for positive reaction
2. Drug abuse urine screening
   - Check for positive reaction
3. Pregnancy test for female of child-bearing age (Urine)
   - Check for positive reaction
4. Confirmation of the use of restricted concomitant medication/therapy within 24 hours before the Day -2 Visit.
5. Any medical condition that the investigator judges may interfere with the interpretation of the study results or results. The investigator may also consult with the medical monitor.

Subjects will not be allowed to continue with the visit if they meet any of the criteria stated above. The visit may be rescheduled per Investigator discretion. Variables will be checked again.

3) Baseline

At baseline test (Day -2) after the admission to the unit, review the variables/criteria (only items applicable for the in-house stay and prior medication, stated as #1-5 in section above) to confirm the eligibility of the subject. The baseline evaluation is conducted from the Day -2 to Day 1, prior to the first dosing. ABP monitoring period starts on Day -2 to familiarize the subjects with the device. Measurements from Day -1 to Day 1 will be taken as baseline assessments.
Per COVID-19 modification, at baseline test (Day -2) review the variables/criteria stated as #1-5 in section above to confirm the eligibility of the subject. The baseline evaluation is conducted from the Day -2 to Day 1, prior to the first dosing. ABP monitoring period starts on Day -2 to familiarize the subjects with the device. Measurements from Day -1 to Day 1 will be taken as baseline assessments. Additionally, Holter monitoring will be initiated on Day -2 as well. Measurements from Day -1 to Day 1 will be taken as baseline assessments.

4) Treatment period

The treatment period is performed over 12 weeks, including the baseline and 2 in-house stays.

① In-house 1: The IP will be administered on Day 1, and blood sample collection will be conducted during the hospitalization assessment period (until Day 8) for the safety monitoring and PK and PD assessment.

② In-house 2: The subject will return on Day 77 and after admission, the IP will be administered on Day 78, and blood sample collection will be conducted during the hospitalization assessment period (until the Day 82) for the safety monitoring and PK and PD assessment

Per COVID-19 modification, the treatment period is performed over 12 weeks, including baseline and outpatient visits.

5) OPD visits

The OPD visits will be conducted on Day 10, 11, 15, 17, 18, 22, 29, 36, 43, 50, 57, 64, 71 with safety and PK/PD assessments.
Per COVID-19 modification, all visits may be performed as outpatient visits.

6) Follow up

The follow up visit will be conducted on Day 85, 99, 113 with safety and PK/PD assessments.

7) End of treatment (EOT) visit

Subjects who withdraw their consent or withdraw from participation in the study may have an EOT visit as soon as possible. The EOT may be performed after withdrawal of the subject's consent or withdraw from participation in the study as soon as possible. The planned evaluation and procedures for the follow-up visit on Day 113 may be conducted at the EOT. Specific assessments form the other follow-up visits may be added per request, if needed.

10.1.2. Unscheduled Visit

During the study, the subject may be required to attend additional visits separate from the planned visits in the study plan, if necessary. For example, if an AE is suspected, or follow up is needed after AE occurrence, conduct the necessary tests according to the investigator's judgment. These relevant visits should be recorded in both the CRF and source document, and the schedule of the study plan should not be changed due to unscheduled visits.

10.2. Enrollment and Clinical Evaluation

10.2.1. Assessment items per visit

1) Screening (Week -5 to -1)

(1) Informed consent
(2) In/Exclusion criteria
(3) Demographics
(4) Prior medication and medical history taking
(5) 12-lead ECG
(6) Vital signs
(7) Clinical laboratory test
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(8) Infection of HBV, HCV and Anti-body, infection of HIV
(9) Pregnancy test (Urine)
(10) Serum FSH (Only Postmenopausal female)
(11) eGFR
(12) TSH
(13) Amylase, Lipase
(14) Calcitonin
(15) HbA1c
(16) Fasting plasma glucose (FPG)
(17) Fasting insulin, Fasting C-peptide
(18) Serum lipid profiles
(19) Physical examination (PE)
(20) Concomitant medication
(21) Adverse events
(22) Drug abuse urine screening and alcohol exhalation test
(23) Body weight
(24) Height, BMI
(25) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

2) Day -2

(1) In/Exclusion criteria
(2) PD assessment
  ① FPG
  ② HbA1c
(3) 12-lead ECG
(4) ABP monitoring
(5) Vital sign
(6) Clinical laboratory test (not performed in Part 2)
  ⑤ Hematology
  ⑥ Blood chemistry
  ⑦ Blood coagulation
  ⑧ Urine analysis
(7) Pregnancy test (Urine)
(8) Abbreviated PE
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Dietary education and counseling
(13) Body weight
(14) BMI
(15) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

Per COVID-19 modification, Day -2 may include the following assessments:

(1) In/Exclusion criteria
(2) Randomization
(3) PD assessment
  ① MRI/MRI-PDFF, only if available and MRI center can perform assessment
  ② FPG
  ③ HbA1c
(4) 12-lead ECG
(5) Instructions on ABP monitoring
(6) ABP monitoring
(7) Instructions on Holter monitoring
(8) Holter monitoring
(9) Vital sign
(10) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(11) Pregnancy test (Urine)
(12) Abbreviated PE
(13) Concomitant medication
(14) Adverse events
(15) Drug abuse urine screening and alcohol exhalation test
(16) Dietary education and counseling
(17) Diet Diary Distribution

(18) Body weight
(19) BMI
(20) Tympanic temperature
(21) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(22) Instructions on 7-point SMBG at home
(23) SMBG Diary Distribution
(24) Instructions on FBG measurements at home via glucometer

Per COVID-19 modification, Day -2 has a visit window of ±1 day.

3) Day -1

(1) Randomization
(2) PD assessment
  ① MRI/MRI-PDFF
  ② FPG
(3) 7-point Self-monitoring of blood glucose (SMBG)
(4) ABP monitoring
(5) Holter monitoring
(6) Vital sign
(7) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(8) Concomitant medication
(9) Adverse events
(10) Body weight

Per COVID-19 modofication, Day -1 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) PD assessment
  ① MRI/MRI-PDFF, only if available and MRI center can perform assessment
(2) Reminder to perform and record 7-point self-monitoring of blood glucose (SMBG) and bring diary to next visit
(3) Concomitant medication
(4) Adverse events

Per COVID-19 modification, Day -1 has a visit window of ±2 day.

4) Day 1

(1) Administration IP
(2) PK assessment
(3) PD assessment
  ① Fructosamine, Glycated albumin
  ② FPG
  ③ Fasting insulin, Fasting C-peptide
  ④ HOMA-IR, HOMA-β
  ⑤ Incretins / metabolic hormones
  ⑥ Amino-acid profile

⑦ Serum lipid profiles
⑧ Inflammatory markers
⑨ β-hydroxybutyrate

(4) 7-point SMBG
(5) ABP monitoring
(6) Holter monitoring
(7) Vital signs
(8) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(9) TSH
(10) Amylase, lipase
(11) Calcitonin
(12) LH, FSH (Only female subject)
(13) Injection site reactions
(14) Immunogenicity (ADAbs, nAbs, anti-PEG)
(15) Concomitant medication
(16) Adverse events
(17) Body weight
(18) BMI
(19) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

Per COVID-19 modification, Day 1 may have additional assessments:
(20) Drug abuse urine screening and alcohol exhalation test
(21) SMBG diary review
(22) SMBG Diary Distribution
(23) ABP monitoring data may be downloaded
(24) Holter monitoring data may be downloaded
(25) Diet diary distribution
(26) Diet diary review
(27) Dietary education

Per COVID-19 modification, Day 1 has a visit window of ±1 day.

5) Day 2

(1) PK assessment
(2) PD assessment
① FPG
② Fasting insulin, Fasting C-peptide
(3) 7-point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test (not performed in Part 2)
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis

(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 2 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) Reminder to perform and record 7-point self-monitoring of blood glucose (SMBG) and bring diary to next visit
(2) Injection site reactions
(3) Concomitant medication
(4) Adverse events

6) Day 3

(1) PK assessment
(2) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
    ③ Incretins / metabolic hormones
    ④ Amino-acid profile
    ⑤ Serum lipid profiles
    ⑥ Inflammatory markers
    ⑦ β-hydroxybutyrate
(3) 7-point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test
    ① Hematology
    ② Blood chemistry
    ③ Blood coagulation
    ④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 3 (±1) may have additional assessments:

(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Dietary education
(15) Glucometer download and/or SMBG Diary Review
(16) SMBG Diary Distribution
(17) ABP monitoring data may be downloaded
(18) Holter monitoring data may be downloaded

If visit is not feasible on Day 3 (e.g., due to Day 1 being on a Friday), the visit can be moved to the next day or previous day and will therefore be combined with the phone visit on the that day (e.g., combined visit for Day 3 and Day 4) to keep the schedule for the following visits. If this visit is moved/combined, all other

visits between the first and second dosing will be performed as scheduled to ensure that weekly dosing can be performed as scheduled.

7) Day 4

(1) PK assessment
(2) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(3) 7-point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 4 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) Reminder to perform and record 7-point self-monitoring of blood glucose (SMBG) and bring diary to next visit
(2) Injection site reactions
(3) Concomitant medication
(4) Adverse events

Per COVID-19 modification, Day 4 has a visit window of ±1 day.

8) Day 5

(1) PK assessment
(2) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(3) 7-point SMBG
(4) 12-lead ECG
(5) ABP monitoring
(6) Holter monitoring
(7) Vital signs
(8) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(9) Injection site reactions
(10) Concomitant medication

(11) Adverse events

Per COVID-19 modification, Day 5 (±1) may have additional assessments:

(12) Drug abuse urine screening and alcohol exhalation test
(13) Diet diary distribution
(14) Diet diary review
(15) Dietary education
(16) Glucometer download and/or SMBG Diary Review
(17) SMBG Diary Distribution
(18) ABP monitoring data may be downloaded
(19) Holter monitoring data may be downloaded

If visit is not feasible on Day 5 (e.g., due to Day 1 being on a Wednesday), visit can be moved to the next day or previous day and will be combined with the phone visit on the next day (e.g., Day 6) to keep the schedule for the following visits. If this visit is moved/combined, all other visits between the first and second dosing will be performed as scheduled to ensure that weekly dosing can be performed as scheduled

9) Day 6~7

(1) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(2) 12-lead ECG
(3) Vital signs
(4) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(5) Injection site reactions
(6) Concomitant medication
(7) Adverse events

Per COVID-19 modification, Days 6 and 7 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) PD assessment
  ① FBG at home via glucometer
(2) Reminder to perform and record 7-point self-monitoring of blood glucose (SMBG) and bring diary to next visit
(3) Injection site reactions
(4) Concomitant medication
(5) Adverse events

Per COVID-19 modification, Days 6 and 7 have a visit window of ±1 day.

10) Day 8

(1) Administration IP
(2) PK assessment
(3) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide

③ Incretins / metabolic hormones
④ Amino-acid profile
⑤ Serum lipid profiles
⑥ Inflammatory markers
⑦ β-hydroxybutyrate

(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(7) Injection site reactions
(8) Concomitant medication
(9) Adverse events
(10) Diet diary distribution
(11) Body weight
(12) BMI
(13) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(14) Diet Diary Distribution
(15) Dietary education

Per COVID-19 modification, Day 8 may have additional assessments:
(16) Drug abuse urine screening and alcohol exhalation test
(17) Diet diary review
(18) Dietary education
(19) Glucometer download and/or SMBG Diary Review for FPG review that was performed on Day 6

11) Day 10

(1) PK assessment
(2) PD assessment
① FPG
② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital signs
(5) Clinical laboratory test
① Hematology
② Blood Chemistry
③ Blood coagulation
④ Urine analysis
(6) FPG via YSI
(7) Injection site reactions
(8) Concomitant medication
(9) Adverse events
(10) Drug abuse urine screening and alcohol exhalation test

(11) Diet diary distribution
(12) Diet diary review
(13) Dietary education

Per COVID-19 modification, Day 10 has a visit window of ±1 day.

12) Day 11

(1) PK assessment
(2) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital signs
(5) FPG via YSI
(6) Injection site reactions
(7) Concomitant medication
(8) Adverse events
(9) Drug abuse urine screening and alcohol exhalation test
(10) Diet diary distribution
(11) Diet diary review
(12) Dietary education

Per COVID-19 modification, Day 11 has a visit window of ±2 days.

13) Day 15(±1)

(1) Administration IP
(2) PK assessment
(3) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
  ③ Incretins / metabolic hormones
  ④ Amino-acid profile
  ⑤ Serum lipid profiles
  ⑥ Inflammatory markers
  ⑦ β-hydroxybutyrate
(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test
  ① Hematology
  ② Blood Chemistry
  ③ Blood coagulation
  ④ Urine analysis
(7) TSH
(8) Amylase, Lipase
(9) Calcitonin
(10) LH, FSH (Only female subject)
(11) FPG via YSI
(12) Injection site reactions

(13) Immunogenicity (ADAbs, nAbs, anti-PEG)
(14) Abbreviated PE
(15) Concomitant medication
(16) Adverse events
(17) Drug abuse urine screening and alcohol exhalation test
(18) Diet diary distribution
(19) Diet diary review
(20) Body weight
(21) BMI
(22) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(23) Dietary education

14) Day 17

(1) PK assessment
(2) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital signs
(5) FPG via YSI
(6) Injection site reactions
(7) Concomitant medication
(8) Adverse events
(9) Drug abuse urine screening and alcohol exhalation test
(10) Diet diary distribution
(11) Diet diary review
(12) Dietary education

Per COVID-19 modification, Day 17 has a visit window of ±1 day.

15) Day 18

(1) PK assessment
(2) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital sign
(5) FPG via YSI
(6) Injection site reactions
(7) Concomitant medication
(8) Adverse events
(9) Drug abuse urine screening and alcohol exhalation test
(10) Diet diary distribution
(11) Diet diary review
(12) Dietary education

Per COVID-19 modification, Day 18 has a visit window of ±2 days.

16) Day 22(±2)

(1) Administration IP

(2) PK assessment
(3) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(4) 12-lead ECG
(5) Vital sign
(6) Clinical laboratory test
    ① Hematology
    ② Blood Chemistry
    ③ Blood coagulation
    ④ Urine analysis
(7) FPG via YSI
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Body weight
(15) Dietary education

17) Day 29(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment
    ① Fructosamine, Glycated albumin
    ② FPG
    ③ Fasting insulin, Fasting C-peptide
    ④ Incretins / metabolic hormones
    ⑤ Amino-acid profile
    ⑥ Serum lipid profiles
    ⑦ Inflammatory markers
    ⑧ β-hydroxybutyrate
(4) 12-lead ECG
(5) Vital sign
(6) Clinical laboratory test
    ① Hematology
    ② Blood Chemistry
    ③ Blood coagulation
    ④ Urine analysis
(7) TSH
(8) Amylase, Lipase
(9) Calcitonin
(10) LH, FSH (Only female)
(11) FPG via YSI

(12) Injection site reactions
(13) Immunogenicity (ADAbs, nAbs, anti-PEG)
(14) Abbreviated PE
(15) Concomitant medication
(16) Adverse events
(17) Drug abuse urine screening and alcohol exhalation test
(18) Diet diary distribution
(19) Diet diary review
(20) Body weight
(21) BMI
(22) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(23) Dietary education

18) Day 36(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(4) 12-lead ECG
(5) Vital sign
(6) Clinical laboratory test
    ① Hematology
    ② Blood Chemistry
    ③ Blood coagulation
    ④ Urine analysis
(7) FPG via YSI
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Body weight
(15) Dietary education

19) Day 43(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(4) 12-lead ECG
(5) Vital sign
(6) Clinical laboratory test
    ① Hematology
    ② Blood Chemistry

③ Blood coagulation

④ Urine analysis

(7) FPG via YSI
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Body weight
(15) Dietary education

20) Day 50

(1) Administration IP
(2) PK assessment
(3) PD assessment

① FPG

② Fasting insulin, Fasting C-peptide

(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test

① Hematology

② Blood Chemistry

③ Blood coagulation

④ Urine analysis

(7) FPG via YSI
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Body weight
(15) Dietary education

21) Day 57(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment

① HbA1c

② Fructosamine, Glycated albumin

③ FPG

④ Fasting insulin, Fasting C-peptide

⑤ HOMA-IR, HOMA-β

⑥ Incretins / metabolic hormones

⑦ Amino-acid profile

⑧ Serum lipid profiles
⑨ Inflammatory markers
⑩ β-hydroxybutyrate

(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test
① Hematology
② Blood Chemistry
③ Blood coagulation
④ Urine analysis
(7) TSH
(8) Amylase, Lipase
(9) Calcitonin
(10) LH, FSH (Only female)
(11) FPG via YSI
(12) Injection site reactions
(13) Immunogenicity (ADAbs, nAbs, anti-PEG)
(14) Abbreviated PE
(15) Concomitant medication
(16) Adverse events
(17) Drug abuse urine screening and alcohol exhalation test
(18) Diet diary distribution
(19) Diet diary review
(20) Body weight
(21) BMI
(22) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(23) Dietary education

22) Day 64(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment
① FPG
② Fasting insulin, Fasting C-peptide
(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test
① Hematology
② Blood Chemistry
③ Blood coagulation
④ Urine analysis
(7) Injection site reactions
(8) Concomitant medication
(9) Adverse events
(10) Drug abuse urine screening and alcohol exhalation test
(11) Diet diary distribution

(12) Diet diary review
(13) Body weight
(14) Dietary education

23) Day 71(±2)

(1) Administration IP
(2) PK assessment
(3) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(4) 12-lead ECG
(5) Vital signs
(6) Clinical laboratory test
  ① Hematology
  ② Blood Chemistry
  ③ Blood coagulation
  ④ Urine analysis
(7) FPG via YSI
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Body weight
(15) Dietary education

24) Day 77

(1) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(2) 12-lead ECG
(3) ABP monitoring
(4) Vital sign
(5) Clinical laboratory test (not performed in Part 2)
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(6) Pregnancy test (Urine)
(7) Injection site reactions
(8) Abbreviated PE
(9) Concomitant medication
(10) Adverse events
(11) Drug abuse urine screening and alcohol exhalation test
(12) Body weight

(13) BMI
(14) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)
(15) Diet diary review

Per COVID-19 modification, Day 77 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) PD assessment
    ① FBG at home via glucometer
(2) Injection site reactions
(3) Concomitant medication
(4) Adverse events

Per COVID-19 modification, Day 77 has a visit window of ±1 day.

25) Day 78

(1) Administration IP
(2) PK assessment
(3) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
    ③ Incretins / metabolic hormones
    ④ Amino-acid profile
    ⑤ Serum lipid profiles
    ⑥ Inflammatory markers
    ⑦ β-hydroxybutyrate
(4) 7-Point SMBG
(5) ABP monitoring
(6) Holter monitoring
(7) Vital sign
(8) Clinical laboratory test
    ① Hematology
    ② Blood chemistry
    ③ Blood coagulation
    ④ Urine analysis
(9) Injection site reactions
(10) Immunogenicity (ADAbs, nAbs, anti-PEG)
(11) Concomitant medication
(12) Adverse events
(13) Body weight
(14) BMI
(15) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

Per COVID-19 modification, Day 78 may have additional assessments:

(16) 12-lead ECG
(17) Pregnancy test (Urine)
(18) Abbreviated PE
(19) 7-point SMBG may be partly performed at home

(20) Drug abuse urine screening and alcohol exhalation test
(21) SMBG Diary Distribution
(22) Diet Diary Distribution
(23) Diet Diary review
(24) Dietary education
(25) 12-lead ECG
(26) Glucometer download and/or SMBG Diary Review for FPG review that was performed on Day 77

26) Day 79

(1) PK assessment
(2) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
(3) 7-Point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test (not performed in Part 2)
    ① Hematology
    ② Blood chemistry
    ③ Blood coagulation
    ④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 79 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) Reminder to perform and record 7-point self-monitoring of blood glucose (SMBG) and bring diary to next visit
(2) Injection site reactions
(3) Concomitant medication
(4) Adverse events

Per COVID-19 modification, Day 79 has a visit window of ±1 day.

27) Day 80

(1) PK assessment
(2) PD assessment
    ① FPG
    ② Fasting insulin, Fasting C-peptide
    ③ Incretins / metabolic hormones
    ④ Amino-acid profile
    ⑤ Serum lipid profiles
    ⑥ Inflammatory markers

⑦ β-hydroxybutyrate

(3) 7-Point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 80 (±1) may have additional assessments:
(11) Drug abuse urine screening and alcohol exhalation test
(12) Diet diary distribution
(13) Diet diary review
(14) Dietary education
(15) Glucometer download and/or SMBG Diary Review for 7-point profile and FPG review
(16) SMBG Diary Distribution
(17) ABP monitoring data may be downloaded
(18) Holter monitoring data may be downloaded

If visit is not feasible on Day 80 (e.g., due to Day 1 being on a Wednesday), visit can be moved to the next day or previous day and will be combined with the phone visit on the next day (Day 81) to keep the schedule for the following visits. If this visit is moved/combined, all other visits after the last dosing will be performed as scheduled.

28) Day 81

(1) PK assessment
(2) PD assessment
① FPG
② Fasting insulin, Fasting C-peptide
(3) 7-Point SMBG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test (not performed in Part 2)
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events

Per COVID-19 modification, Day 81 may be performed as a phone visit and only the following variables may be assessed/will be recorded:

(1) Injection site reactions
(2) Concomitant medication
(3) Adverse events

Per COVID-19 modification, Day 81 has a visit window of ±1 day.

29) Day 82

(1) PK assessment
(2) PD assessment
  ① FPG
  ② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) ABP monitoring
(5) Holter monitoring
(6) Vital signs
(7) Clinical laboratory test
  ① Hematology
  ② Blood chemistry
  ③ Blood coagulation
  ④ Urine analysis
(8) Injection site reactions
(9) Concomitant medication
(10) Adverse events
(11) Diet diary distribution
(12) Dietary education

Per COVID-19 modification, Day 82 (±1) may have additional assessments:
(13) Drug abuse urine screening and alcohol exhalation test
(14) Diet diary distribution
(15) Diet diary review
(16) Dietary education
(17) Glucometer download and/or SMBG Diary Review for 7-point profile and FPG review
(18) SMBG Diary Distribution
(19) ABP monitoring data may be downloaded
(20) Holter monitoring data may be downloaded

30) Day 85(±2)

(1) PK assessment
(2) PD assessment
  ① MRI/MRI-PDFF (MRI-PDFF only if the liver fat's MRI-PDFF prior to the first dosing showed equal to or more than 10% [≥ 10%])
  ② HbA1c
  ③ Fructosamine, Glycated albumin
  ④ FPG
  ⑤ Fasting insulin, Fasting C-peptide

⑥ HOMA-IR, HOMA-β
⑦ Incretins / metabolic hormones
⑧ Amino-acid profile
⑨ Serum lipid profiles
⑩ Inflammatory markers
⑪ β-hydroxybutyrate

(3) 12-lead ECG
(4) Vital signs
(5) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(6) TSH
(7) Amylase, Lipase
(8) Calcitonin
(9) LH, FSH (Only female)
(10) Injection site reactions
(11) Immunogenicity (ADAbs, nAbs, anti-PEG)
(12) Abbreviated PE
(13) Concomitant medication
(14) Adverse events
(15) Drug abuse urine screening and alcohol exhalation test
(16) Diet diary review
(17) Body weight
(18) BMI
(19) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

Per COVID-19 modification, MRI/MRI-PDFF, only to be performed if available and MRI center can perform assessment. If MRI/MRI-PDFF assessment is not possible during the stated time period, due to COVID-restrictions, MRI/MRI-PDFF may be performed at a later timepoint, but prior to the last visit on Day 113.

31) Day 99(±2)

(1) PK assessment
(2) PD assessment
① FPG
② Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital signs
(5) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(6) Abbreviated PE
(7) Concomitant medication
(8) Adverse events

(9) Drug abuse urine screening and alcohol exhalation test
(10) Body weight
(11) BMI
(12) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

32) Day 113(±2)

(1) PK assessment
(2) PD assessment
① HbA1c
② Frutosamine, glycated albumin
③ FPG
④ Fasting insulin, Fasting C-peptide
(3) 12-lead ECG
(4) Vital signs
(5) Clinical laboratory test
① Hematology
② Blood chemistry
③ Blood coagulation
④ Urine analysis
(6) Pregnancy test (Urine)
(7) TSH
(8) Amylase, Lipase
(9) Calcitonin
(10) LH, FSH (Only female)
(11) Immunogenicity (ADAbs, nAbs, anti-PEG)
(12) Abbreviated PE
(13) Concomitant medication
(14) Adverse events
(15) Drug abuse urine screening and alcohol exhalation test
(16) Body weight
(17) BMI
(18) Waist circumference, Hip circumference, Waist-to-hip ratio (WHR)

10.2.2. Assessment variable

1) Demographics

- Birth Date
- Gender
- Childbearing
- Ethnicity (Hispanic / Latin American or non-Hispanic / non-Latin American)
- Race (Caucasian, American Indian / Alaska Native, Asian, Hawaiian Aboriginal or other Pacific Islander, Black / African American)
- Smoking history
- Caffeine use History (or other beverages with an arousal effect)
- Special meals (vegetarians)
- History of blood donation or plasma donation

2) Prior medication and medical history taking

- Medical history
- Medication history

3) Drug abuse urine screening and alcohol exhalation test

- Drug abuse history
- Alcohol abuse history

4) Physical examination (PE)

(Complete or Abbreviated) physical examination is performed at the time specified in the assessment schedule.

Complete PE (physical examination) includes that assessment of overall appearance and systemic review (i.e., skin, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph node, respiratory, cardiovascular, gastrointestinal, limb, musculoskeletal, nervous, psychological).

Abbreviated PE (Abbreviated physical examination) includes that assessment of overall appearance and skin, cardiovascular, respiratory system and abdomen. Abbreviated PE may lead to a complete PE if it is deemed necessary by the investigator. Other assessments may be conducted as the investigator deems necessary.

- Measurement of height taking off the shoes (cm)
- Measurement of weight taking off the shoes (kg) (Two decimal places to calculate IP dose for study)
- Waist circumference (cm)
- Hip circumference (cm)
- Waist-to-hip ratio (WHR)
- Body mass index (kg/m^2, BMI, To the first decimal place)

5) Vital Sign

In the case of visits including a sampling procedure for the assessment of pharmacokinetic parameters, the vital sign should be performed before PK Sampling.
Vital sign is evaluated at the specified schedule, and measures the following:

- Supine position BP: Systolic blood pressure (mmHg) and Diastolic blood pressure (mmHg)
- Heart rate (HR) (bpm)
- Respiratory rate (Breath per minute)
- Tympanic temperature (℃)

Supine position BP and HR are should be recorded after taking a rest for at least 5 minutes in supine position.

6) 12-lead ECG

The 12-lead ECG is performed at the specified schedule (In screening, single evaluation, all other evaluations are repeated 3 times.).

At the screening visit, a 12-lead ECG is conducted 1 time. All other 12-lead ECGs should be repeated 3 times. The mean value of the 3 baseline ECG measurements collected at Day -2 will serve as each subject's baseline for all post-dose comparisons.
ECG measurements are to be collected during screening, and on Day -2 and 77 before subjects are connected to the ABPM device. Additionally, ECG measurements are taken on Day 5 and Day 82, after ambulatory devices (Holter and ABPM) are removed.

The 12-lead ECG should be conducted after the subject has rested for at least 5 minutes in a supine position. 3 times repeated ECGs are each spaced at least 30 seconds apart, but all three ECG measurement times should not exceed 2 minutes. The ECG includes all 12 standard derivations and a lead Ⅱ rhythm strip at the bottom of traces. The ECG is recorded on paper at a speed of 25 mm/sec.

The following ECG parameters are collected:
Ventricular Rate, PR interval, QRS interval, RR interval, QT interval and QT interval corrected for heart rate (QTc) (The corrected QTc [QTcF] and QTcF using Fridericia's correction formula)
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.

All ECG must be assessed by a qualified investigator to determine if there is an abnormality.

7) ABP monitoring (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 the overnight period, measurements will be taken 1x per hour 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 2 x per hour during the day and then 1 x per hour during the night.
The post-dose assessment period will start in the morning of Day 1. Measurements will be taken 2 x per hour during the day and then 1 x per hour every day (for every 24-hour period), until the morning of Day 5. Additionally, subjects will be connected to the ABPM system again on Day 77. Blood pressure measurements will be started overnight on Day 77 to familiarize the subjects with the device. During this period, measurements will be taken 1 x per hour until the morning of Day 78.
The post-dose assessment period will start in the morning of Day 78. Measurements will be taken 2 x per hour during the day and then 1 x per hour every day (for every 24-hour period), until the morning of Day 82.
Time points stated in the Study Flow. Adequate cuff size will be documented for each subject, after determination of the patient's non-dominant arm circumference. Subject's bedtime and awakening will be recorded to divide the downloaded data into diurnal and nocturnal values. Depending on available PK and safety data, timepoints for measurements may be adjusted for the following cohorts.
Specifications about the ABPM model will be described in the Operations Manual, as well as detailed instructions of disconnection of subjects for personal hygiene (shower), blood pressure frequency, data management and medical review.
Per COVID-19 modification, ABPM will be provided for the safety of the subjects but will be moved to outpatient setting. Subjects will therefore be provided with personal instructions on site and instructions to take home for use and care.

8) Holter Monitoring

24-hour heart rate activity will be continuously recorded with an ambulatory Holter monitoring system (eg, Mortara surveyor). Holter electrodes (12 lead, 3-channel placement) will be placed to the subject's

chest and will be attached to a small recording monitor. The Holter monitor will be carried in a pocket or small pouch. Subject's activities or exercises will be recorded while wearing the monitor.
Specifications about the Holter model will be described in the Operations Manual/ Holter Procedure Manual, as well as detailed instructions of data management and medical review.
Time points stated in the Study Flow.
Per COVID-19 modification, Holter monitoring will be provided for the safety of the subjects but will be moved to outpatient setting. Subjects will therefore be provided with personal instructions on site and instructions to take home for use and care.

9) Clinical laboratory test

Clinical laboratory evaluations are performed per specified evaluation schedule, and clinical laboratory tests are conducted in the laboratories in accordance with the appropriate laboratory manual. Samples are collected in appropriate tubes and processed according to standard laboratory procedures.

< Clinical laboratory assessment>

Hematology	
White blood cell (WBC) count	Neutrophil: Percent and absolute count
Red blood cell (RBC) count	Lymphocyte: Percent and absolute count
Reticulocyte count	Monocyte: Percent and absolute count
Hemoglobin (Hb)	Eosinophil: Percent and absolute count
Hematocrit (HCT)	Basophil: Percent and absolute count
Mean corpuscular volume (MCV)	Platelet count
Mean corpuscular hemoglobin (MCH)	Red blood cell distribution width (RDW)
Mean corpuscular hemoglobin concentration (MCHC)	
Blood chemistry	
Alanine aminotransferase (ALT)	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Phosphorus (P)
Albumin	Potassium (K)
Alkaline phosphatase (ALP)	Sodium (Na)
Blood urea nitrogen (BUN)	Total bilirubin
Creatinine	Total protein
BUN/Creatinine Ratio	Triglyceride (TG)
Calcium (Ca)	Uric acid
Blood carbon dioxide (CO_2) concentration	Hemoglobin A1c (HbA1c)*****
Ferritin*	Fructosamine*****
Chloride (Cl)	Glycated albumin*****
Cholesterol	Thyroid stimulating hormone (TSH) *****
Gamma glutamyltransferase (GGT)	Estimated Glomerular filtration rate, eGFR)**
Follicle stimulating hormone (FSH)***	Amylase*****
Luteinizing hormone (LH)****	Lipase*****
	Calcitonin*****
Blood coagulation	
activated Partial thromboplastin time (PTT)	International normalized ratio (INR)
Prothrombin time (PT)	
Urine analysis	
pH and urine specific gravity	Urobilinogen
White blood cell (WBC)	Bilirubin
Albumin (protein)	Nitrite

Glucose	Color
Ketones	Microscopy
Virus serology	
Hepatitis B core antibody (anti-HBc)	Hepatitis C antibody (HCVab)
Hepatitis B surface antigen (HBsAg)	Human immunodeficiency virus (HIV)
Urine drug screening	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine
Cannabinoids	
Pregnancy test (urine)	
Beta human chorionic gonadotropin (beta-hCG): All of female	

* Measured on Day 1 prior to administration, Day 57, Day 85.
** Conducted only at screening visit
*** Serum FSH conducted at screening is evaluated only for postmenopausal female subjects. The FSH conducted at the specified evaluation schedule after the screening visit is evaluated only for the female subjects for safety evaluation.
**** The LH conducted at the specified evaluation schedule after the screening visit is evaluated only for the female subjects for safety evaluation.
***** Measured on indicated timepoints of the [STUDY FLOW] table.

All values outside the normal range are flagged for the attention of the investigator or subinvestigator. The investigator or subinvestigator indicates whether the value is of clinical significance.
If the results of any of the tests (or repeat tests if performed) on a sample taken during screening are found to be clinically significant, the subject will not be able to participate in the study without permission from the medical monitor. If medically necessary, additional tests may be carried out during the test. If a clinically significant abnormality is found in the sample collected from the date of signing the consent form to the follow-up visit, it should be recorded as an adverse event, and according to the judgement of the investigator or subinvestigator, the subjects should receive follow up until the test results are normalized or stabilized. Prior to recording an event as AE, it needs to be confirmed/determined that it is not a concomitant condition. Concomitant conditions that exists prior to signing the informed consent form (ICF) are not considered adverse events unless they worsen during the study. The pre-existing conditions are recorded as part of the subject's medical history

10) Fasting Plasma Glucose

FPG will be measured via YSI in addition to the FPG measure that is included in clinical laboratory assessments. The measurement of glucose via YSI should be performed for all subjects and for all outpatient visits. Values will be entered in the CRF.
Per COVID-19 modification, FBG measurements may be performed at home via glucometer by subjects. Data will be downloaded from glucometer at the next visit and/or data may be recorded in the SMBG diary. Timepoints will follow the SOE for COVID-19.

11) Concomitant medication

Concomitant medications are collected at each visit. Medications that have been initiated and terminated prior to the first dose of IP (Day 1) are collected as the prior medications.

12) Injection site reaction

Injection site reaction assessments for IP administration are assessed within 30 minutes before dosing and at 4 and 12 hours after dosing on Day 1 (time window is 30 min), by a person not involved in the dosing. It might be assessed more frequently, eg, after each new dosing, if deemed necessary by the Investigator.

Injection site reaction assessments on the day of administration of IP (other than Day 1) are conducted within at least 30 minutes after administration. During in-house periods, Injection Site Reactions should be evaluated every morning, at the time of last administration of the IP, within a window of ± 30 minutes of that administration. At OPD visits without administration of the IP, Injection Site Reactions should be evaluated in the morning, at the time of last IP administration within a window of ± 30 minutes of dosing time

The final injection site reaction assessment is conducted on Day 85.

Per COVID-19 modification, Injection Site Reactions may be evaluated by the subjects on days where a phone visit occurs.

erythema is evaluated as follows.

- 0 – None
- 1 – Very mild erythema (hardly noticeable)
- 2 – Marked erythema
- 3 – Moderate to severe erythema
- 4 – Severe erythema (red like red radish) or some necrotic scabs (deeply damaged)

edema is evaluated as follows.

- 0 – None
- 1 – Very mild edema (hardly noticeable)
- 2 – Mild edema (The edge of the area is clearly raised and the outline is distinct)
- 3 – Moderate edema (About 1mm raised)
- 4 – Severe edema (Over 1mm raised and extended beyond exposed area)

For injection site reaction assessment, all positive reactions are documented as adverse events. Measure the diameter of the affected area in centimeters (cm) using a measuring tape and record the condition of the injection site. All of the sites where injection site reaction has occurred should be recorded using digital photographs. For clinically significant injection site reactions, the subject may be referred to a dermatologist or a skin biopsy may be performed for additional histological examination. The biopsy is performed using a 4 mm punch biopsy around the injection site. Before biopsy is performed, the biopsy site is anesthetized with lidocaine. The wound is sealed with a Steristrip suture tape. If it is necessary the wound may be close with stitches, stitches will be removed after about 2 weeks. Record the time between injection and biopsy. Microscopic examination and histological examination for punch biopsy are performed in a qualified laboratory.

13) Pharmacodynamics (PD) assessment

Measure the MRI/MRI-PDFF test, blood sample collection, and tympanic temperature with pharmacodynamic variables.

① MRI-PDFF

MRI-PDFF test is used to assess absolute and % changes of liver fat. This test is performed prior to Day -1 for all eligible subjects (MRI may be performed while Screening calcitonin results are pending). This test should be conducted as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling. However, on Day 85 of the MRI-PDFF measurement, the MRI-PDFF will only be conducted if the liver fat on Day -1 was equal to or greater than 10% (≥ 10%).

Per COVID-19 modification, If MRI/MRI-PDFF assessment is not possible during the stated time period, due to COVID- restrictions, MRI/MRI-PDFF may be performed at a later timepoint, but prior to the last visit possible, on Day 113. If MRI/MRI-PDFF assessment is not possible due to restricted access of MRI center under COVID-19 restrictions, the missing assessment will be documented in the CRFs (specific information will be captured that explains the basis of the missing data due to COVID-19). The missing assessment will be documented as a protocol deviation (with reason due to COVID-19 stated).

② MRI imaging

The MRI imaging will be used to assess changes in visceral fat volume, determined by absolute and relative percent changes. This test is performed prior to Day -1 for all eligible subjects (MRI may be performed while Screening calcitonin results are pending). This test should be conducted as close as possible to the Day 85 of the 12th week before the Day 85 PK sampling.
Per COVID-19 modification, If MRI/MRI-PDFF assessment is not possible during the stated time period, due to COVID- restrictions, MRI/MRI-PDFF may be performed at a later timepoint, but prior to the last possible visit, which is on Day 113. If MRI/MRI-PDFF assessment is not possible due to restricted access of MRI center under COVID-19 restrictions, the missing assessment will be documented in the CRFs (specific information will be captured that explains the basis of the missing data due to COVID-19). The missing assessment will be documented as a protocol deviation (with reason due to COVID-19 stated).

③ Blood sample collection

- Incretins/metabolic hormones: Glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), glucagon, fibroblast growth factor 21 (FGF 21), leptin.
- Serum lipid profiles: Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), triglycerides, free fatty acids (FFAs).
- Amino-acid profile
- Glucose metabolism parameter: Fasting plasma glucose (FPG), fasting insulin, fasting C-peptide, HbA1c, fructosamine, glycated albumin.
- To confirm insulin resistance: HOMA-IR.
- To confirm insulin secretion function: HOMA- β.
- To confirm inflammatory markers: high-sensitive C-reactive protein (hs-CRP), adiponectin.
- To test the keton bodies: β-hydroxybutyrate.

Blood samples for analysis of the above items are collected at the specified schedule in the evaluation schedule and the PD sample collection schedule. When the PK sample collection time is changed, the time point of collecting the fasting blood glucose samples can be adjusted between the cohorts.
Details on the collection, handling and transport of blood samples are separately summarized in the laboratory manual. The blood for the sample is processed and the plasma and serum are analyzed using a verified assay method.

④ Temperature tympanic

The tympanic body temperature for PD assessment is measured along with the vital signs at the specified evaluation schedule. Additionally, during the in-house periods, tympanic temperature will be measured 2 x /24 hours. Exact measuring timepoints and windows will be stated in the Operations Manual.
Per COVID-19 modification, tympanic temperature will be measured only as stated under the section vital signs during the study.

⑤ 7-point profile, Self-monitoring of blood glucose (SMBG)

To be measured 15 minutes before the meal (± 10 minutes), 2 hours after the meal starts (± 15 minutes), and 15 minutes before the evening snack (± 10 minutes). For the Day 1 and Day 78 SMBG, 5 -point testing can be done (exclude tests before and after breakfast), as subjects need to be fasting for 4 hours after administration if IP. Details around the assessment of 7-point profiles will be provided in the Operations Manual.
Per COVID-19 modification, subjects will be instructed on how to perform a 7-point profile SMBG at home. They will receive instrcutions to take home. A SMBG diary will be distributed to record values.

⑥ Fasting condition

Fasting condition should be maintained about 10 hours when applicable.

⑦ Incretins / metabolic hormones, Inflammatory markers

All incretins, metabolic hormones, and inflammatory markers are collected at the same time as the PK Sampling collection.

14) Immunogenicity (ADAbs, nAbs, anti-PEG)

The sample blood for assessment of ADAbs, nAbs, anti-PEG should be collected at the specified schedule in the evaluation schedule.

15) Pharmacokinetic (PK) assessment

Blood samples for analysis of HM15136 should be collected at the specified schedule in the evaluation schedule and PK sample collection schedule. If PK data are available indicating that other time points would be more advantageous, the timing of sample collection for PK analysis may be adjusted between cohorts. Details of the collection, handling and transport of blood samples are separately summarized in the laboratory manual. The blood for the sample is processed and the serum are analyzed using a verified assay method.
Per COVID-19 modification, PK sampling scheduled may follow the modified PK sampling schedule.

16) Diet diary (distribution, review)

During the OPD visits (Day 10 through Day 71, Day 77 and 85), check the diet diary of the subject against protocol section 10.2.3. (Restrictions), subsection 1, regarding whether or not the eating habits are well maintained according to the restrictions on food and beverages.
The subject will receive diet diary during the outpatient period and will record the diet diary. The prepared diet diary will be reviewed and directed at the next outpatient visit.
Per COVID-19 modification, diet diary distribution will start earlier as study visit schedule was modified to OPV days.

17) Dietary education

Subjects will receive dietary education/nutrition counseling on Day -2, the first day of the in-house period, and standardized meals throughout the in-house periods. Weight maintaining diet instructions will be repeated after the completion of all examinations to ensure that the subject complies with food and beverage restrictions during the OPD visits. Repeat counseling will be performed as stated in Study Flow.
Per COVID-19 modification, diet education will start earlier, as study visit schedule was modified to OPV days.

10.2.3. Restrictions

1) Restriction on food and beverages

The subjects should fast without taking any food or drink (except water) for at least 10 hours before in-house periods, OPD visits, or follow-up visits.
During the in-house periods, a standardized weight maintaining diet will be served to the subjects. Subjects should maintain their normal diet after discharge and until the end of the study.
Therefore, the investigator or the staffs involved in the study should educate the subjects in relation to the above items during in-house and OPD visits and check whether the subject complied by checking the diet diaries.

Food intake is not allowed within 10 hours before the IP administration and 4 hours after IP administration on Day 1 and 78. This question should be recorded by asking the subjects before the IP administration.

During In-house periods 1 and 2, meals are served. For details please see the Operations Manual. On Day 1 and 78 (the days of IP administration), breakfast is not served to subject and lunch is served after 4 hours of evaluation/collection.
Breakfast is served after collecting fasting state samples.
Foods with grapefruit, pomelo, or seville Orange (including marmalade) or beverages are not allowed within 48 hours before, or during the in-house periods.
Products containing quinine (e.g., carbonated water) are not allowed within 7 days before, or during the in-house periods.
Per COVID-19 modification, standardized meals might not be available and subjects may therefore be provided with a snack bag.

2) Contraception

To ensure that female partners of male subjects exposed to clinical trial medications will not get pregnant, or to prevent any partner from being exposed to the semen of the male subject, a male subject who is not surgically sterile, (defined as at least 1 year after vasectomy), must use an acceptable method of contraception from screening visit until 60 days after IP administration. If the subject would prefer abstinence, Sexual abstinence must be consistent with a routine lifestyle of sexual inactivity. Periodic abstinence [e.g., calendar day, ovulation, symptom-related method or post ovulation method] and coitus interruptus is not an acceptable method of contraception). Condoms should be used with spermicidal foam/gel/film/cream/ suppository. Contraceptive methods for female partners should also be encouraged and are the same as those stated in the section below for female subjects of child-bearing potential. The contraceptive method must be used for a period of 60 days after administration of the IP. The adequacy of other contraceptive methods is assessed by the investigator on a case-by-case basis. Male subjects with a pregnant female partner at signing of informed consent, may be included in the study, as semen of male subject that will be exposed to trial medication cannot lead to conception.

Females must be non-pregnant and non-lactating, and either surgically sterile (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral ovariectomy) or postmenopausal for >12 months. If females' sterility or postmenopausal status is confirmed, no pregnancy testing is required during the study. The site will make an effort to retrieve medical records to document the sterility, however, the absence of records will not exclude the subject. In case that medical records cannot be obtained, serum pregnancy testing will be conducted at Screening, and urine pregnancy testing will be conducted throughout the study. Postmenopausal status will be confirmed through testing of FSH

levels outside the normal range (as specified by responsible lab) at screening for amenorrheic female subjects < 60 years of age.

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

Female subjects of childbearing potential do not need to have a serum hCG test at Screening, as urine hCG test will be assessed at Screening. 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 with perfect use, including hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence, or a surgically sterilized partner. If the subject would prefer abstinence, sexual abstinence must be consistent with a routine lifestyle of sexual inactivity. Periodic abstinence [e.g., calendar day, ovulation, symptom-related method or post ovulation method] and coitus interruptus is not an acceptable method of contraception). Oral hormonal contraceptives have to be taken at least 2 months prior to Screening until 30 days after the last Follow-up Visit. The adequacy of other contraceptive methods is assessed by the investigator on a case-by-case basis.

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.

3) Alcohol and Caffeine

Alcohol consumption should be avoided within 48 hours prior to any visit and during the subject's stay in the institution. The subjects should not consume more than 3 units of alcohol per days during the study period (1 unit is same as about a cup of beer [284 mL], a small cup of wine [125 mL], one standard volume of spirits [25 mL], a cup of raw rice wine (Makgeolli)[250 mL]).

Caffeinated food or beverages (e.g., chocolate, coffee, tea, cola, Red Bull) are not allowed within 24 hours prior to each visit and during the subject's stay in the institution.

4) Smoking and cigarettes

The heavy smoker (the subject who has daily use of more than 10 cigarettes/day, or 2 cigars/day, or equivalent use of any tobacco product) is excluded. The subject must not smoke during the in-house periods.

5) Activities and exercises

The subjects should not do the hard physical training (e.g., long-distance running, weight training, or any physical activity outside their usual activities) within 48 hours prior to all test visits and during their stay at the hospital. The subjects should not start any new physical training and not raise the training intensity beyond their usual amount during the period of participation in this study. However, the subject can participate light leisure activity (e.g., watching television, computer game, reading books).

6) Others

The subjects should not have donated whole blood (400 mL) within 60 days, or have donated blood components (500 mL) within 14 days prior to screening. And after the completion of this study, the subjects should not donate blood or plasma (500 mL or more) for at least 3 months.

The male subjects should not donate sperm throughout the entire study period, and at least 60 days after the administration of IP.

10.2.4. Handling of hypersensitivity

1) Anaphylaxis

Anaphylaxis is a rapidly progressing systemic severe allergy reaction that is a life-threatening acute immune response.

If symptoms suggesting anaphylactic shock (exacerbation of respiratory symptoms, oligopnea or peripheral organ dysfunction due to hypotension, allergic symptoms of skin-mucosal tissues, etc.) are detected within a few minutes of the administration of the IP, the IP administration should be stopped immediately, and the subject should be rested in supine position and with leg elevation, and avoid the issues caused by dyspnea or vomiting.

The IP administration must be stopped immediately.

If anaphylactic symptoms are evident, epinephrine IM (intramuscular) injection should be given to the median anterolateral side of the thigh. And the laboratory test required to diagnose to anaphylaxis like Tryptase etc. can be conducted according to the judgement of the investigator.

If necessary, treatment for dyspnea such as oxygen supply etc. and treatment for hypotension/shock such as intravenous infusion of fluid can be performed, and BP, pulse rate, respiration, and oxygen saturation can be monitored.

10.3. Endpoints

10.3.1. Primary endpoints

To assess safety and tolerability of HM15136 after repeated subcutaneous (SC) doses for 12 weeks.

- Incidence of adverse events (AEs):
  cardiovascular (CV) events, rash/inflammatory dermatitis and other skin disorders, gastrointestinal (GI) events, and gallstone formation (cholelithiasis) will be managed following separate AE guidance document of HM15136 [Appendix].
- Incidence of clinical lab abnormalities:
  including serum amylase, serum lipase, coagulation, thyroid stimulating hormone (TSH), serum calcitonin. Only for female, LH (Luteinizing hormone) and FSH (follicle stimulating hormone) are additionally included.
- Immunogenicity:
  Anti-drug antibodies (ADAbs), neutralizing antibodies (nAbs), anti-polyethylene glycol antibodies (anti-PEG)
- Incidence and severity of clinical findings on physical examination
- Change from baseline in vital signs:
  Supine position blood pressure (BP), heart rate (HR), respiratory rate, and tympanic temperature
- Changes of blood pressure (BP) and heart rate:
  BP assessed by 24-hour ambulatory blood pressure monitoring (ABPM);
  HR assessed by 24-hour ambulatory electrocardiography monitoring (Holter ECG; central reader)
- Change from baseline in 12-lead ECG parameters:
  the primary ECG endpoint will be QTcF
- Injection site reactions

To assess the pharmacokinetic (PK) profile of HM15136 after administration of repeated subcutaneous (SC) doses in obese subjects by, but not limited to:

- C_{max}: Maximum concentration
- T_{max}: Time to reach Cmax
- C_{trough}: Trough serum concentration
- AUC: Area under the concentration-time curve

Ex.) AUC_{0-t}: AUC at steady state during the period of injection (AUC_{0-t} at steady state)

- K_{el}: Terminal elimination rate constant
- $t_{1/2}$: Terminal half-life
- CL/F: Apparent clearance
- Vz/F: Apparent volume of distribution

10.3.2. Exploratory endpoints

To assess pharmacodynamics (PD) properties of HM15136 after repeated SC doses

- Incretins / metabolic hormones
  1) Glucagon-like peptide-1 (GLP-1)
  2) Gastric inhibitory polypeptide (GIP)
  3) Glucagon
  4) Fibroblast growth factor 21 (FGF 21)
  5) Leptin
- Serum lipid profiles
  1) Total cholesterol
  2) Low-density lipoprotein (LDL)
  3) High-density lipoprotein (HDL)
  4) Very low-density lipoprotein (VLDL)
  5) Triglycerides
  6) Free fatty acids (FFAs)
- Amino-acid profile
- Glucose metabolism parameter
  1) Fasting plasma glucose (FPG)
  2) Fasting insulin, Fasting C-peptide
  3) 7-point Self-monitoring of blood glucose (SMBG)
  4) HbA1c
  5) Fructosamine
  6) Glycated albumin
- Insulin resistance
  - Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)
- Insulin secretion function
  - Homeostatic Model Assessment for β Cell Function (HOMA-β)
- Assessment of absolute and % changes of liver fat via MRI-PDFF (Magnetic resonance imaging-estimated proton density fat fraction)
  (However, assessment of liver fat via MRI-PDFF will only be performed on day 85, if the liver fat prior to the first dosing ≥ 10%)
- Changes in visceral fat volume, determined by absolute and relative percent change assessed by MRI

- Body weight
- Body mass index (BMI)
- Waist circumference
- Hip circumference
- Waist-to-hip ratio (WHR)
- Temperature (tympanic)
- Inflammatory markers
  1) High-sensitive C-reactive protein (hs-CRP)
  2) Adiponectin
- Keton body
  - β-hydroxybutyrate

10.4. Safety assessment

10.4.1. Adverse Event (AE)

Reporting of AEs will begin from the date each subject signs an informed consent form (ICF) and will continue until the follow-up visit.

10.4.2. Definition of AE

An 'Adverse Event (AE)' is any untoward medical occurrence and unintentional sign, symptom or disease in a clinical study, and which does not necessarily have a causality with the IP. Concomitant conditions that existed prior to signing the ICF are not considered adverse events unless they worsen during the study. The pre-existing conditions are recorded as part of the subject's medical history.

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.

A 'Suspected adverse reaction' is defined as 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. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

A 'Serious AE (SAE) refers to any of the following cases.

1) Results in death, Is Life-threatening: This means that the subject was at risk of dying at the time of the event and does not mean an event based on the assumption that death could have resulted if the symptoms were more severe.
2) Requires inpatient hospitalization or prolongation of existing hospitalization
3) Results in persistent or significant disability/incapacity
4) Is a Congenital anomaly/birth defect
5) Is other important medical event that may require intervention to prevent items # 1 through #4, or may expose the subjects to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.

Although, important medical events that do not result in death, are not life-threatening, or do not require hospitalization, may be considered as SAEs when, based on appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed results.

Examples of such medical events include allergic bronchoconstriction requiring intensive treatment in an emergency room or clinic room, blood diseases or seizures not causing hospitalization, and the occurrence of drug dependence or drug abuse.

Serious AEs and severe AEs should be distinguished. Severity is a measure of intensity, while seriousness is defined by the above criteria. For example, if the subject has mild gastrointestinal bleeding and needs overnight hospitalization for monitoring, it may consider as a serious AE, but it is not necessarily severe. Likewise, severe AEs in terms of intensity are not necessarily serious AEs. For example, alopecia can be assessed as severe by intensity, but it is not considered a serious AE. Medical decisions and scientific judgments must be made when determining whether the AEs are serious and whether the AEs should be reported rapidly.

Adverse Event of Special Interest (AESI) are selected, non-serious adverse events. They will be reported to the sponsor within the same timeline of SAE, using a SAE report form.

The AESI in this study are as follows.

- Necrolytic migratory erythema
- Cholelithiasis

'Unexpected AE' refers to an AE pattern or risk outside of the investigator brochure (IB) or product information insert etc., that contains available relevant drug information.

'Treatment emergent adverse event (TEAE)' refers to any clinically significant event not present before exposure to study drug administration, or any event already present prior to study drug administration, that worsens in either intensity or frequency after exposure to the study drug.

The collection of AEs should continue through to the end of follow-up.

10.4.3. Recording of AE

AEs of each subject should be collected and recorded from the date of signing the ICF until the end of study participation (it refers to when the subject either discontinues or completes the study). AEs can be reported spontaneously by subject, as well as study staff can discover them from open and non-leading questions (like 'How did you feel about your health conditions since I last asked you these questions?') in the physical examination. All AEs and rescue actions should be recorded. The AE characteristics, start date (together with the time known), end date (together with time known), severity and action taken should be recorded with the seriousness of AE and causality with IP together with assessment of investigator or subinvestigator.

All AEs should be recorded using the language presented to the investigator (verbatim) individually. But this is not the case if the AE is already known as part of conditions, disease, or syndrome according to the opinion of the investigator. In the latter case, the name of condition or disease or syndrome should be specified rather than each individual symptom. The AE would be coded using MedDRA (Medical Dictionary for Regulatory Activities).

10.4.4. Severity of AE

The investigator assesses the intensity of all AEs in terms of severity in accordance with the following standard grade assessment criteria.

1) Mild: It is usually a temporary symptom, not affect the performance of routine daily activities of the subject. Usually, no treatment is required.
2) Moderate: Due to noticeable symptom, the subject feels uncomfortable. It might somewhat affect the

performance of the routine daily activities of the subject. Treatment may be required.

3) Severe: The symptoms induce considerable discomfort. It much affects the performance of the routine daily activities of the subject. It may be impossible to continue participating in the study and treatment may be required.

10.4.5. Causality with IP

The investigator will judge the causality between the AE and IP according to reviewing in many ways (e.g., past medical history, health conditions, administration time, administration status etc.) following below.

1) Related
   (1) There is an evidence that the drug has been administered.
   (2) Event or laboratory test abnormality, with plausible time relationship to drug intake.
   (3) The AE is most likely explained by the administration of this drug than any other reason.
   (4) The AE disappears with dechallenge of IP.
   (5) Rechallenge (if available) results are positive.
   (6) The AE is consistent with information already known for this drug or for the same class of drug.
   (7) The administration of this drug is judged to be due to an AE at the same level as other possible causes.
   (8) If more data are needed or an additional material is being reviewed for proper assessment of the relevance of this drug to AEs.
   (9) If the information on the causality between the administration of this drug and the AE is insufficient or cannot be determined as a conflict, and cannot be supplemented or confirmed.

2) Not related
   (1) The subject has not been administered the drug
   (2) Event or laboratory test abnormality, with unreasonable time relationship to drug intake
   (3) There is another obvious cause for AE (e.g., other drug use, latent disease and etc.) and a reasonable explanation for the AE is available.

10.4.6. Seriousness

Severity is a measure of intensity, while seriousness is defined by specified in section 10.4.2.

10.4.7. SAEs and AESI Reporting

Details of reporting SAEs and AESIs should be referenced in the Safety Management Plan (SMP). The investigator should report to the sponsor or qualified vendor writing a SAE report via fax or e-mail within 24 hours of recognizing all SAEs and AESIs regardless of their causality with the IP that occurred during the study period (the period from the subject's hospitalization to follow up visit).
SAEs and AESIs occurring after a follow-up visit (end of the study) should be reported to the sponsor by the investigator if the investigator determines that there is a reasonable causality with the IP.

The minimum information required for the initial report as follows.

- Report sender (name and contactable No. of investigator)
- Subject's identification (the screening/randomization No., not name of the subject)
- Protocol No.
- Information of SAE (start/end date, seriousness)
- Details of IP (IP dose, frequency, the first administration date, the last administration date)
- Assessment of causality

However, if available, the initial SAE report should include all of the available information about the SAE, and the written SAE report should be sent to sponsor via fax or e-mail.
Upon receipt of the initial SAE report, the sponsor's PV department reviews the information and if necessary, contacts to the investigator to obtain additional information for the assessment of the events. Details around SAE report preparation by Sponsor's PV department and timeline for submission to [redacted] for review and handling will be described in the SMP.

The investigator should report to the sponsor or qualified vendor a follow up report written within 24 hours of when conditions of the SAE or AESI have changed (i.e., discharge of post hospitalization, exacerbation of conditions) or additional information obtained. Details around SAE report preparation by Sponsor's PV department and timelines for submission to Medical Monitor and sponsor will be described in the SMP.

The investigator is responsible for notifying the IRB about the SAE, and the sponsor or qualified vendor is responsible for reporting the SAE to regulatory authorities in accordance with local requirements.
All serious and unexpected suspected 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.

10.4.8. Follow-up of AE

AEs experienced by the subject will be monitored regardless of their causality with the IP until the resolution of the AE, or all abnormal laboratory results are returned to baseline level, or stabilization to the level allowed by the investigator and responsible medical professional, or a satisfactory description of the observed change is made, or until follow up of the subject fails

10.4.9. SUSAR (Suspected unexpected serious adverse reaction)

The sponsor should report any SUSAR to the investigator and FDA until the deadline, according to the following categories. The investigator should report to the IRB until the deadline, according to the regulation of the IRB.

- Results in death or Life-threatening: The sponsor must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Other SUSARs: The sponsor must notify FDA of any other SUSAR as soon as possible but in no case later than 15 calendar days after the sponsor's initial receipt of the information.

10.5. Pregnancy

The investigator is responsible for reporting all pregnancy events occurring during the study period (from the signing the ICF until the follow up visits) to the sponsor and following up.
Pregnancy only is not considered to be an AE, unless it is suspected that the IP may have interfered with the effectiveness of the contraceptives. The choice of abortion should not be considered an AE unless it is purposed as treatment. The hospitalization for normal delivery of healthy newborn infants should not be considered a SAE.
If a female subject receiving the IP becomes pregnant, the investigator should submit to sponsor the Clinical Trial Pregnancy Report within 24 hours after recognizing subject's pregnancy. Even if the subject's study participation is withdrawn or the study is terminated, the investigator should follow up the pregnancy process and results, and record.
The investigator should submit to sponsor the Clinical Trial Pregnancy Report within 24 hours after recognizing the pregnancy results (i.e., normal delivery or choice of abortion etc.).
If a female partner of a male subject receiving the IP becomes pregnant, the investigator will notify the sponsor of that pregnancy event within 24 hours of recognizing via fax or e-mail.

The investigator should acquire the ICF to share the pregnancy information, and submit to sponsor a 'clinical trial pregnancy report' within 24 hours, and follow up and notify to sponsor about the process and results of pregnancy.

All related SAEs (e.g., serious complication of maternity, abortion purposed to treatment, ectopic pregnancy, stillbirth, congenital deformation, birth defect) occurred during the pregnancy should be recorded in template of SAE report, and should be reported to sponsor or qualified vendor within 24 hours following the SAE reporting process.

10.6. Safety Reporting to Institutional Review Boards (IRBs) or Independent Ethic Committees (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. Statistical analysis and statistical consideration

11.1. General Considerations

The statistical analysis plan will be provided separately before the first database lock takes place and it will describe the details of statistical methods. Violations in the planned analysis will be described in the clinical study report (CSR) and will be reviewed for justification.

11.1.1. Population

The blind meeting will be held to define populations before the random code release.

1) **Safety population**: Includes all random allocated subjects in the study who received at least one dose of study medication (HM15136 or placebo). The subject is included in the analysis depending on the cohort of IP in the study.

2) **PK (Pharmacokinetic) population**: Includes all random allocated subjects who have at least one quantifiable HM15136 concentration measurement (without major protocol deviation or violation that would have an impact on the absorption, distribution, metabolism or excretion of HM15136). The subject is included in the analysis depending on the cohort of IP in the study.

3) **PD (Pharmacodynamics) population**: Includes all random allocated subjects in the study who received at least one dose of study medication (HM15136 or placebo) with sufficient evaluable PD data appropriate for the evaluation of interest (without major protocol deviation or violation that would have an impact on the PD of HM15136). The subject is included in the analysis depending on the cohort of IP in the study.

11.1.2. Handling of Missing Data

For a missing value occurred due to withdrawal or other reasons before the end of the study after the administration of the IP, the imputation method will be defined in the SAP. The missing data pattern of data related to COVID-19 will be explored and if needed, an exploratory data analysis (EDA) will be conducted.

11.2. Statistical Analysis

11.2.1. General Principles of Statistical Analysis

Continuous data will be summarized using descriptive statistics (number, mean, standard deviation (SD), minimum, median, and maximum) for each cohort (but placebo in each cohort/dose level will be combined as one group). If applicable, there will be summarized the changes to the baseline. Categorical data will be summarized using a frequency table (number, percentage) for each cohort/dose level (but placebo in each cohort/dose level will be combined as one group).

11.2.2. Protocol Deviation/Violation

Protocol violations will be listed by subjects.

11.2.3. Subject participation status

The subjects to be excluded from the safety population, PK population, and PD population and the excluded data will be listed together with the reason for exclusion. Summarize the subject's participant status by cohort/dose

level (but placebo in each cohort/dose level will be combined as one group) but including as below: The number of group, percentage, number of subjects who received the IP after randomization, number and percentage of subjects who completed a study, number and percentage of subjects who are excluded in a study (describe reasons for exclusion). A data of all subjects who random allocated will be presented.

Discontinuation of subject's participation will be listed by the end date of participation, the period of treatment, reasons for discontinuation and the answer to prior consent.
Provide a list of randomization and include follows: Randomization number, screening number, cohort, Dose level that the subject is assigned.

11.2.4. Demographics, Physical examination and Baseline characteristics

Demographics (age, gender, ethnicity, race) and physical examination (height, weight, BMI) will be listed by each subject and summarized about safety population, using each dose level (but, placebo in each cohort/dose level will be combined as one group). The denominator of the percentage will be the number of subjects in the safety population or the number of all subjects in each cohort/dose level.
Medical history will be listed by subjects, explanation of disease (or surgery), AE classification using a MedDRA (System Organ Class (SOC), preferred term (PT), an onset date and an end date (or in progress).

11.2.5. Prior medication and concomitant medication and Administration of medication

Prior medications refer to medications that were started and terminated before administration of the IP. Concomitant medication refers to medications that were administered after administration of the IP (includes the medication that start before the IP and continue to be used together).
Prior medications and concomitant medications will be listed by each subject.
Prior medications and concomitant medications will be classified by the latest version of WHO (World Health Organization) drug dictionary.

11.2.6. IP administration status

A list of IP administration including dosing date and time will be generated.

11.2.7. Endpoints

All demographics, safety data, PK / PD data will be summarized and tabulated with descriptive statistics and/or testing statistics. PK data will be presented as graph. PK/PD relationship about IP exposure and exploratory evaluation variables will be presented as graph.

1) Adverse events (AEs)

All of AEs will be listed. The number of subjects and their percentages who meet AEs are tabulated using SOC and PT by each cohort/dose level (but, placebo is combined one dose separately). The number of subjects and their percentages who meet AEs at least one or more are listed. AEs will be classified by severity and related status with IP and will be tabulated. SAEs will be listed separately.

2) Physical examination (PE)

Abnormalities of physical examination will be listed.

3) Vital signs

Changed values of vital signs which are measured from baseline to each visit will be listed by subject. Clinically significant abnormalities of vital sign that the investigator assesses as AEs will be presented in the AE list. Changed values from baseline to each visit will be tabulated.

4) 12-lead ECG

The mean and individual values of the 3-time repeated ECG intervals will be listed in each subject and each visit, and the mean changes versus the baseline as well as the observed measurement will be presented. The observed measurement will be summarized descriptively by table form. The changes versus baseline by all of 12-lead ECG data will be summarized descriptively. Categorical QTc analysis will be also performed. The primary ECG endpoint will be QTcF.

5) ABPM and Holter ECG

The 24-hour blood pressure (day and nighttime systolic/diastolic BP) collected from ABPM, and 24-hour Holter ECG (endpoints will be defined in the SAP) will be summarized descriptively by cohort/dose level.

6) Laboratory test

A listing of laboratory values will be provided by subject. Notable values among laboratory values will be flagged and will be assessed by the investigator. Clinically significant abnormalities of laboratory values that the investigator assesses as AEs will be presented in the AE list. Changed values from baseline to each visit will be tabulated. Amino acid labs will not undergo a medical review as these are not needed for safety evaluation of the subjects.

7) Assessment of Injection site reaction

All injection site reactions will be considered as AEs and will be analyzed in the AE analysis.

8) Pharmacodynamics (PD) assessment

A descriptive summary of the PD assessment will be presented each time point by cohort/dose level (But placebo in each cohort/dose level will be combined as one group.). The PD parameters will be summarized by cohort/dose level. The association between IP exposure and PD assessment valuables will be analyzed by showing pharmacodynamic (PD) graphs or by modeling PK/PD as appropriate.

9) Immunogenicity (ADAbs, nAbs, anti-PEG)

The result of Immunogenicity (ADA, nAbs, anti-PEG) will be listed by each subject and will be presented and will be summarized by cohort/dose level (But placebo in each cohort/dose level will be combined as one group.).

10) Pharmacokinetic (PK) assessment

The concentration-time data of a subject will be listed and will be displayed as a graph from a linear and a log scale. Concentration-time data will be summarized as a table and a graph (a linear and a log scale) by cohort/dose level. Noncompartmental PK parameters will be analyzed using R, SAS or Phoenix® WinNonlin®. The PK parameter data will be listed and will be summarized by cohort/dose level.

Dose proportionality will be assessed using log-transformed PK parameters AUC_{0-t}, AUC_{inf}, C_{max} values and a linear regression approach to log-transformed dose levels. Dose proportionality will be presented by graph. Based on the results of the data review, additional analysis will be conducted if deemed necessary.

11.3. Statistical Analysis Timing and Decision for Sample Sizes

11.3.1. Interim analysis

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

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

Both analyses for Part 1 may occur, while Part 2 will continue in a blinded fashion. The study will be conducted as outlined in this protocol. Part 2 will be performed independently from the conduct/results of the Part 1 and will not lead to changes to the conduct of the protocol. After Part 2 (T2DM cohorts) has been completed, a final analysis, that only includes the results of Part 2, will be conducted after data base lock of Part 2.

For details on the interim analysis based on semi-clean data, please refer to the Interim Analysis Unblinding and Information Dissemination Plan.

11.3.2. Confirmation of sample sizes

This study determined the number of subjects without consideration of statistical validity. The number of subjects for the Part 1 will be 12 (HM15136: placebo = 3:1) for each cohort, and for the Part 2 will be 30 for the cohort 4 (HM15136: placebo = 1:1), and 12 for cohorts 5-7 (HM15136: placebo = 3:1). This is consistent with the typical sample size used in the similar study to evaluate safety and PK. Therefore, no formal sample size calculation will be performed. 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.

12. Data Management

12.1. Data Recording

Use the electronic case report form (eCRF), an electronic data collection system, to manage data collection during the clinical trials. The eCRF is a software tool designed to ensure quality assurance and facilitate data collection during clinical trials. This system complies with the Code of Federal Regulations (CRF) 21 part 11. The investigator should record all data that is collected from this study on the e-CRF which Hanmi Pharm. Co., Ltd provides. The electronic data capture (EDC) system may only use the person who is authorized and all traces of entry, modification, saving and deletion of an e-CRF through the EDC system will be recorded. The investigator guarantees that the data of the eCRF entered through electronic signature is accurate, complete, decodable and timely. The eCRF created through the EDC system will be delivered to institutions via storing on electronic storage media as the copy and stored on the same basis as the other basic documents, after the end of study.

12.2. Data Collection

All data that are required in a protocol should be collected from an e-CRF and all information are recorded on an e-CRF should be matched the Source Document (SD). The collection of data on the CRF must follow the instructions described in an e-CRF completion guideline. The investigator is ultimately responsible for collecting and reporting all clinical data entered in an e-CRF. After writing an e- CRF, the investigator signs each CRF to ensure that the information recorded in the CRF is true. The investigator is finally responsible for the accuracy and reliability of all recorded data in the CRF in all cases.

12.3. Data Access

Hanmi Pharm. Co., Ltd. should establish a security system to prevent all unauthorized access to the database. In addition, a list of authorized users needs to be prepared. The completed original CRF is the exclusive property of Hanmi Pharm. Co., Ltd., and it cannot be disclosed to a third party without written permission from the Hanmi Pharm. Co., Ltd.

12.4. Data Protection and Storage

Both the Hanmi Pharm. Co., Ltd. and the investigator have responsibilities to archive the study data, including all documents for at least 3 years even if the study completed or terminated mandatory. However, the archiving period may be extended if it is deemed necessary.
Hanmi Pharm. Co., Ltd. should notify the investigator and principal of institution as the document about the necessity and storage period of the data. If it is judged that there is no need to keep the data, Hanmi Pharma. Co., Ltd. should notify the investigator and principal of institution as the document.

13. Ethical considerations and administrative procedures

13.1. Ethical Considerations

This study will be conducted in accordance with the Protocol , the International Conference on Harmonization - Good Clinical Practice (ICH-GCP)[10]: Consolidated Guidance (E6), the Declaration of Helsinki[11] 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, in conducting and evaluating the study and recording the results of the study. This clinical trial will also be implemented in accordance with national applicable regulatory requirements.

13.2. Informed Consent

The investigator should give the subject a sufficient opportunity to explain all the details related to the clinical trial and to know all the predictable results. The contents of the subject's consent must be documented. The investigator must sign and confirm the subject's informed consent form. The investigator should not carry out any specific examination for the purpose of clinical trial only, until the consent of the subject is obtained.

13.3. IND (Investigational New Drug) Approval

Protocol and related documents must be reviewed and approved by a properly constituted IRB and the FD.

13.4. Case Report Form (CRF)

Relevant Documents (RDs) means physician's records of subjects held by the institutions. Most of RDs is a chart of the hospital or physician and all recorded information in the CRF should be matched with the RDs. The case record used in this study is eCRF, the development, maintenance and data management of the eCRF is performed by the CRO entrusted by Hanmi Pharm. Co., Ltd. The input and modification of the data would be made by the authorized subinvestigator by the principal investigator (PI) and final review and signature of the data should be done by the PI. The PI signs and ensures that the information recorded in the CRF is true, and the PI is finally responsible for the accuracy and reliability of all recorded data in the CRF in all cases. If the input data is modified, the revision history is automatically saved, and it is not possible to delete the input data. The eCRF should be submitted as a copy if necessary, and Hanmi Pharm. Co., Ltd. should keep it for 3 years from the end of the study.

13.5. Confidentiality

The names of all subjects should be kept confidential and recorded and evaluated by the number given in the clinical trial to identify the subjects. Informs the subject that all clinical trial data will be stored on the computer and treated as strictly confidential. The signed subject's ICF is kept by the PI. The PI should keep the relevant records of the subject's number and name list. The subject's ICF and the subject's list should be kept by the institution for 3 years from the end of the study. After that consult and determine with Hanmi Pharm. Co., Ltd. about storage and management. To prevent errors that may appear, the investigator will contact Hanmi Pharm. Co., Ltd. before the discarding the records.

13.6. Knowledge of Protocol

The Principal Investigator and study staffs have to understand the protocol and then conduct.

13.7. Monitoring and Auditing

Hanmi Pharm. Co., Ltd. or delegated CRO may perform a Pre-Study Visit (PSV). In order to ensure that clinical trials are conducted in accordance with the ICH-GCP, Declaration of Helsinki and other applicable regulatory requirements, and the clinical trial may be registered domestic/oversea. Hanmi Pharm. Co., Ltd. or qualified designee can conduct monitoring and audit. The principal investigator has agreed to permit the audit by signing this protocol. When monitoring this clinical trial, it is necessary to confirm that the case record is complete and clear, and can be compared with the original records (source data), and the investigator should cooperate with the Hanmi Pharm. Co., Ltd. or qualified designee at any time.
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.
Per COVID-19 modification, in case on-site monitoring visits might not be possible, the use of central and remote monitoring programs to maintain oversight of clinical sites may be considered.

13.8. Recording and Dissemination of Results

13.8.1. Recording

1) All data collected during this study should be recorded by the investigator in the eCRF provided by Hanmi Pharm. Co., Ltd. or designee.
2) Ife data are missing, the investigator should give a reasonable explanation.
3) The final, recorded CRF is signed by the principal investigator.
4) When the modification of the CRF data, original data should be remained, and the information of staff who modified the data should be remain too.

13.8.2. Dissemination

As the signing this protocol, the investigator agrees to use the results of this study for registration, publishment and offering this information for medical/pharmaceutical experts, etc. Hanmi Pharm. Co., Ltd. reserves the right to review the contents about this study results, before the publishment of this study result in academic magazine or journals.

13.9. Protocol Amendment

Neither the investigator nor Hanmi Pharm. Co., Ltd. can change the protocol during the study without the consent of the other party. Once the study has begun, it should be modified only in exceptional cases. When the protocol is needed to any modification, all parties involved must be signed and agreed in written. Depending on what has been modified, approval from the FDA and/or the IRB may be required.

14. Other considerations to conduct the clinical trial

14.1. Institution

The principal of the institution should prepare perfectly necessary laboratories, facilities, and experts in order to conduct the study properly.

14.2. Investigator

The principal investigator should be fully understood the AEs and precautions specified in this protocol, during the study or after the study, the subject should be provided with appropriate medical treatment for any AEs (including any clinical significant laboratory abnormal results) occurring in the study. If the subject's comorbidities discovered by the investigator are in need of medical treatment, it should be notified to subject. In the event of any SAE occurred during clinical trials, it should be reported to the IRB and Hanmi Pharm. Co., Ltd. immediately.

14.3. Subinvestigator

The expected AEs and precautions specified in this protocol should be fully understood in advance, if any SAE occurred during the clinical trial, it should be reported to the principal investigator and Hanmi Pharm. Co., Ltd. immediately.

15. References

1. Kim, W. J., & Lee, C. B. (2016). New drugs for obesity treatment. The Korean Journal of Medicine, 90(2), 121-126.
2. Lee, Ji Soo, et al. "Effect of weight reduction on obesity-specific quality of life (QOL) in obese subjects." *The Korean Journal of Obesity* 15.2 (2006): 106-113.
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4. Young Sil Eom and Byung-Joon Kim. " Glucagon-Like Peptide-1 (GLP-1) Agonist." *Korean Journal of Medicine* 87.1 (2014): 9-13.
5. Oh, Seungjoon. "Glucagon-like Peptide-1 Analogue and Dipeptidyl Peptidase-IV Inhibitors." *Journal of Korean Endocrine Society* 21.6 (2006): 437-447.
6. Chun, Hyun-Ji, and Hyuk-Sang Kwon. "Clinical Efficacy of Glucagon Like Peptide-1 (GLP-1) Analogues." *Journal of Korean Diabetes* 14.3 (2013).
7. Nuffer, W. A., & Trujillo, J. M. (2015). Liraglutide: a new option for the treatment of obesity. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 35(10), 926-934.
8. Korean society for the study of obesity (http://www.kosso.or.kr)
9. HM15136(LAPSGCG36: Long-Acting Glucagon Analog-HMC001 conjugate) investigator brochure (IB)
10. International Conference on Harmonization. ICH Harmonized Tripartite Guideline. Good Clinical Practice. 01-May-1990.
11. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects, 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[Appendix] Adverse Event Guidance of HM15136

<General Statement>

As any new investigational product may have unexpected adverse events, the following guidance is offered for potential, but unexpected, toxicities for HM15136. The following diagnostic work-up and procedures are suggested actions and should be tailored to the clinical presentation as assessed by the Investigator.

1. Cardiovascular Toxicity

Definitions:

Signs and symptoms may include:

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

Diagnostic Workup:

At baseline:

- Electrocardiogram
- Cardiac biomarkers (creatine kinase and troponin)

Depending on presentation:

- Inflammatory biomarkers (ESR, CRP, WBC count)
- O2 Saturation
- BNP
- Emergency room/hospital transfer
- Cardiology consultation
- Chest x-ray

Additional testing to be guided by cardiology and may include:

- Echocardiography
- Stress test
- Cardiac catheterization
- Cardiac MRI

Grading*	Management
G1: Asymptomatic abnormal cardiac biomarker testing, including abnormal ECG	All grades (G1-G4) warrant workup and intervention given potential for cardiac compromise Please consider the following: • Hold therapy and permanently discontinue after G1 • Management of cardiac symptoms according to ACC/AHA guidelines • Transfer patient to the emergency room at the hospital for further evaluation and management for any grade > G1 • Cardiology consultation
G2: Mild symptoms consistent with cardiotoxicity with or without abnormal cardiac biomarkers	
G3: Moderate symptoms consistent with cardiotoxicity and/or clinically significant abnormal cardiac biomarkers	
G4: Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions	
Qualifying Statement: Treatment recommendations are based on local standards of care and the life-threatening nature of cardiovascular complications. Holding therapy is recommended for complication grades greater than G2. The appropriateness of rechallenging remains unknown.	

* Not associated with CTCAE grading system

2. Rash/Inflammatory Dermatitis and Other Skin Disorders

Definitions:

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

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

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

Grading Grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	Management
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	• Consider continuing therapy for mild localized reaction, e.g., injection site erythema • Consider treatment with topical emollients and/or mild-moderate potency topical corticosteroids • Counsel patients to avoid skin irritants and sun • exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis.	• Dermatology consultation with possible biopsy • Consider holding therapy and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 • Consider initiating prednisone (or equivalent) at dosing 1 mg/kg tapering over at 4 weeks • In addition, treat with topical emollients, oral antihistamines and medium-to-high potency topical • corticosteroids
G3: As grade 2 but with failure to respond to indicated interventions for a grade 2 dermatitis.	• Hold therapy and consult with dermatology to determine appropriateness of resuming • Treat with topical emollients, oral antihistamines and high potency topical corticosteroids • Initiate oral prednisone or equivalent • (0.5-1 mg/kg/day) tapering over at least 4 weeks
G4: All severe rashes not manageable with prior intervention	• Immediate hold therapy and consult dermatology to determine appropriateness of resuming therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) 10mg or less. • Systemic steroids: IV (methyl)prednisolone (or equivalent) dosed at 1–2mg/kg with slow tapering when the toxicity resolves • Monitor closely for progression to Severe Cutaneous Adverse Reaction • Should admit patient immediately with an urgent • consult by dermatology

3. Gallstones (Cholelithiasis), Biliary Cholic or Cholecystitis

Definition:

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

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

When should symptomatic gallbladder stones be suspected?

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

Diagnostic Workup for Symptoms Suggestive of Gallstone-related Disorders:

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

4. Gastrointestinal Events

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

Severity of symptoms should be assessed as following:

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