A Phase II, 12-week, double-blind, randomised, parallel group, multi-centre, international trial to assess the effect on glycaemic control of five doses of HM11260C versus placebo or open-label liraglutide in subjects with type 2 diabetes

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Primary Objectives•To assess and compare the efficacy of five doses of HM11260C (once weekly subcutaneous injections) over the 12 weeks from baseline in comparison with placebo (once weekly subcutaneous injections) on glycaemic control, as assessed...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON40381

Source
ToetsingOnline

Brief title
HM-EXC-203

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Hanmi Pharmaceutical Co., Ltd.
Source(s) of monetary or material Support: Hanmi Pharmaceutical Co.;Ltd.

Intervention

Keyword: glycaemic control, HM11260C, type 2 diabetes

Outcome measures

Primary outcome

The primary efficacy parameter (HbA1c), as well as FPG, will be assessed at every visit during the dose-finding treatment period (Weeks 1, 2, 3, 5 and 9). The assessment to address the primary objective will be performed at Week 13 (Day 85). Subjects will be instructed to assess their 7-point blood glucose profile every 4 weeks during the study, seven readings a day (before and 90 minutes after each meal [breakfast, lunch, dinner] and at bedtime). The measurements will be averaged from two non-consecutive days during the week. Baseline measurement will be conducted on two consecutive or non-consecutive days between the dispensation of the glucometer to the subject and the baseline visit (Day 1) and averaged. Other secondary efficacy assessments will be scheduled at 4-weekly intervals. Safety assessments will be performed at all visits.

Secondary outcome

NAP

Study description

Background summary

See page 16 of the protocol section 1.1 background

Study objective

Primary Objectives
•To assess and compare the efficacy of five doses of HM11260C (once weekly subcutaneous injections) over the 12 weeks from baseline in comparison with placebo (once weekly subcutaneous injections) on glycaemic control, as assessed by HbA1c in subjects with T2DM

Secondary Objectives
•To assess and compare the safety, tolerability and immunogenicity of HM11260C versus placebo in subjects with T2DM
•To assess and compare the effect on overall diabetes-related parameters (FPG, insulin, C peptide glucagon, glycated albumin and 7-point blood glucose profile) and body weight over the 12 weeks from baseline in subjects with T2DM on HM11260C versus placebo
•To assess and compare the effect on lipid profile (low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C] and triglycerides [TG]) over the 12 weeks from baseline of HM11260C versus placebo in subjects with T2DM
•To explore the effect of HM11260C versus placebo with respect to the relationship between PK and PD measurements, which will be explored graphically as appropriate. Exploratory PK/PD modelling will be undertaken.

Exploratory Objective
•To assess and compare the safety and efficacy over the 12 weeks from baseline of HM11260C versus liraglutide in subjects with T2DM

Study design

Study design:
•This double-blind, randomised, parallel group study comprises a 4-week screening period, a 12 week dose-finding treatment period, and a 6-week follow-up period. For subjects randomised to the liraglutide titration arm, the 12-week treatment period includes a forced titration period where liraglutide will be titrated from 0.6 mg (Day 1) to 1.2 mg (Day 8) to 1.8 mg (Day 15).
•The screening visits (Visits 1A and 1B) will take place between study Days -28 and -5. Eligible subjects who meet all of the inclusion criteria and none of the exclusion criteria will return to the clinic on Day 1 for baseline assessments, randomisation and the first injection of study drug. On Day 2

(Visit 2.1), the site will phone the subject to review AEs, concomitant medications and diet and exercise therapy. Subjects will self administer HM11260C or placebo every 7 days in the morning or liraglutide every morning from Day 1 to Day 84. Subjects will visit the study centre on Days 8, 15, 29 and 57 for study procedures and assessments. All subjects will return to the clinic on Day 85 and Day 127 for follow-up evaluations.

Intervention

Subjects will be randomly assigned to one of the following seven treatment arms in a ratio of 1:1:1:1:1:1:1:
• HM11260C (0.3 mg) once per week
• HM11260C (1 mg) once per week
• HM11260C (2 mg) once per week
• HM11260C (3 mg) once per week
• HM11260C (4 mg) once per week
• Placebo once per week
• Liraglutide (0.6 mg * 1.2 mg * 1.8 mg; forced titration) once per day

If the patient is assigned to one of the doses of study drug or placebo, the patient will self-administer this weekly (every 7 days) for 12 weeks, as an injection under the skin in the abdomen (belly area). The study doctor or nurse will show the patient how to do this the first time at the second screening visit, (Visit 1B) and on study visits 2, 3 and 4. On these study visit days the patient will administer the injection during the study visit in front of the study doctor or nurse. On other injection days the patient should administer the injection in the morning, 60 minutes before a meal at a regular time.
If the patient is assigned to liraglutide (Victoza®), the patient will self-administer this daily in the morning, for 12 weeks, as an injection under the skin in the stomach area, thighs or upper arm. The study doctor or nurse will show the patient how to do this the first time at the second screening visit, (Visit 1B) and on study visits 2, 3 and 4. On these study visit days the patient will administer the injection during the study visit in front of your study doctor or nurse. On other days the patient should administer the injection at a regular time in the morning. The patient will start taking liraglutide at a dose of 0.6mg every day and continue at this dose for 1 week. This will then increase to 1.2 mg every day for the next week and then 1.8mg every day for the remaining duration of the study.
The medication comes in a pre-filled syringe for injection. Patient will be provided separate written instructions on the use and proper storage of your study medication.
If the patient was receiving metformin before he/she started this research study, the patient will continue to take the metformin at the same dose and frequency as when the patieten started the study.

Study burden and risks

Very common: Occurring in more than 1 out of 10 people who take GLP-1 agonists:
Diarrhea
Nausea
Headache

Common: Occurring in more than 1 out of 100 people to less than 1 out of 10 people who take GLP-1 agonists:
Weakness (feeling like you have no body strength)
Gastroesophageal reflux disease (is a burning sensation in chest and or upper abdomen),
Chills
Injection site reactions (bruising, itchiness, swelling or redness at the place where you give your injection)
Abnormally increased sweating
Decreased appetite
Vomiting
In some cases you may experience vomiting, or nausea or diarrhoea. It is important to avoid dehydration by drinking plenty of water.
Dizziness

Uncommon: Occurring more or equal than 1 out of 10,000 to less than 1 out of 1,000)in people who take GLP-1 agonists:
Decreased kidney function
Pancreatitis (inflammation of your pancreas): this includes severe, persistent abdominal pain, vomiting.

Injection Risks
the patient may have bruising, redness or swelling at the place where the patient gives the injection. The patient should record anything related to the injection in the diary and tell the study doctor. The study doctor will check your abdomen (belly area) each study visit.

Blood Collection Risks
Blood samples will be collected during this study. Collecting blood samples may cause fainting and some pain and/or bruising at the site on your arm where the blood was taken. In rare occasions, infection may occur.

Placebo Risks
The patient may be given placebo during the study which will not treat his/hers diabetes. If the patient receives placebo, and he/she is not receiving any other medication for the diabetes such as metformin, his/hers condition may go untreated and may worsen as a result

Sometimes serious allergic reactions to medication, that can be life

threatening, can occur. Some signs and symptoms of a serious allergic reaction (anaphylaxis) are:
• a sudden rash or hives
• itching
• having a hard time breathing
• wheezing
• a sudden drop in blood pressure (making you feel dizzy or lightheaded)
• swelling around the mouth, throat, or eyes
• a fast pulse
• sweating

Contacts

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Seoul 138-724
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Scientific
Hanmi Pharmaceutical Co., Ltd.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1)Aged >= 18 and < 75 years at screening
2)Diagnosed with T2DM for at least 3 months prior to screening
3)Received diet and exercise therapy with or without metformin monotherapy for at least 3 months prior to screening; for subjects who have taken metformin monotherapy, the following minimum stable (i.e., at least 3 months on this dose) dose requirements apply:
a)>= 1500 mg/day of metformin or
b)maximum tolerated dose (the investigator must have documented the reason why up-titration to e.g., >= 1500 mg/day was not possible) or
c)maximum dose according to the country-specific label
4)HbA1c levels of between >= 7.0% and <= 10.0%, at screening
5)Body mass index (BMI) of < 40 kg/ m2 at screening
6)Females of child-bearing potential must test negative for serum pregnancy at screening and agree to use a highly effective method of birth control throughout the study and for at least 30 days after Visit 8/ET visit. Child-bearing potential is defined as women who have not been surgically sterilized 6 weeks prior to screening or are post-menopausal <= 1 year.
A highly effective method of birth control is considered to be one of the following:
-An oral or implanted hormonal method of contraception (if it has been used for >= 3 months prior to study drug administration) while also using a barrier method (i.e., a condom or a diaphragm);
-A hormone or copper intrauterine device if it has been in place for >= 3 months prior to study drug administration (subjects using a nonhormonal or copper intrauterine device should also use a barrier method [i.e., a condom or a diaphragm])
-A vasectomised partner
-Total abstinence is acceptable; however, the subject must use a highly effective method of contraception if the subject subsequently decides not to abstain.
7)Male subjects must agree to practice highly effective birth control methods during the conduct of the study and for at least 30 days after Visit 8/ET visit
8)Written informed consent must be obtained before any study-related assessment is performed

Exclusion criteria

1)Pregnant or nursing (lactating) women
2)Diagnosis of type 1 diabetes mellitus
3)Uncontrolled diabetes defined as a fasting plasma glucose level of > 240 mg/dL (13.3 mmol/L) at screening
4)A significant change in body weight (at least ± 10%) in the 3 months before screening
5)The following medication exclusions apply:
a)Use of any concomitant medications at a dose that was not stable for the 3 months prior to randomisation, except as permitted below;
b)Use of a weight control treatment 3 months before screening, including any medication with a labelled reference to weight loss or weight gain and over-the-counter medications or

herbal supplements;
c)Any antihyperglycaemic agents (including other incretin therapy such as dipeptidyl peptidase 4 inhibitors) other than metformin for > 2 weeks within the 3 months before screening or any use within 30 days of screening.;
d)Prior insulin use for a >= 3-month period at any time, use for > 2 weeks within 3 months before screening or any use within 30 days of screening;
e)Any previous treatment with a GLP-1 analogue ever including treatment in a clinical trial;
f)Any drugs that directly reduce gastrointestinal (GI) motility, including but not limited to chronic use of anticholinergics, antispasmodics, 5-hydroxytryptamine (5HT3) antagonists, dopamine antagonists or opiates within 4 weeks of screening;
g)Any daily medication with a history of causing upper GI AEs, such as bisphosphonates and high-dose acetylsalicylic acid (daily acetylsalicylic acid of 325 mg or less is allowed). Sites considering enrolling a patient on nonsteroidal anti-inflammatory drugs (NSAIDs) known to have a high incidence of GI side effects should contact the Medical Monitor before enrolling the patient;
h)Chronic anticoagulant therapy for any reason within 3 months before screening;
i)Current use of medications that prolong the QT interval/interval corrected by Fridericia formula (QTcF) (Section 13, Appendix 1)
j)Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives (of the used drug) of enrolment, whichever is longer
6)Known history of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
7)Any history of GI intolerance (prolonged nausea and vomiting, chronic diarrhoea during the previous 6 months), gastric emptying abnormality, inflammatory bowel disease, partial bypass (ileal bypass) or gastric banding
8)Any previous GI bleeding or ulceration related to the use of NSAIDs within 3 months before screening
9)Subjects with severe heart or circulatory disease within 6 months prior to screening, defined as any one of the following:
a)Current symptomatic heart failure (New York Heart Association class III or IV) (NYHA 1994; Section 14, Appendix 2);
b)A myocardial infarction, coronary artery bypass graft surgery, or angioplasty within 6 months of screening;
c)Diagnosis of unstable angina requiring medication within 6 months of screening; or
d)Any transient ischemic attack, cerebral infarct, or cerebral haemorrhage within 6 months of screening
10)Poorly controlled hypertension (a resting systolic blood pressure [BP] > 160 mm Hg and/or diastolic BP > 100 mm Hg at screening)
11)Long QT syndrome or prolongation of QTcF interval (QTcF interval > 450 ms for males and > 470 ms for females) at screening
12)A history of additional risk factors for torsade de pointes (TdP; e.g., heart failure, hypokalaemia, family history of Long QT Syndrome)
13)Liver disease, hepatitis, alanine transaminase (ALT) levels or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal, or total bilirubin > 1.5 times upper limit of normal unless the subject has a known history of Gilbert syndrome
14)Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 using the Cockcroft Gault formula, at screening

15)Calcitonin levels > 20 pg/mL (> 20 ng/L) at screening
16)Personal or family history of medullary thyroid cancer (MTC) or a genetic condition that predisposes to MTC (i.e., multiple endocrine neoplasia type 2)
17)Plan to or have had radioactive iodine test with intravenous administration of contrast material (such as intravenous pyelography, intravenous cholangiography, angiography, or computed tomography with contrast medium, etc) within 3 months of screening
18)Any planned elective hospitalisations
19)Known history of acute or chronic pancreatitis with presence of raised serum amylase and lipase (>= 3 times the upper limit of normal) at screening
20)Fasting serum TG > 400 mg/dL (> 4.52 mmol/L) at screening (Visit 1B)
21)Proliferative retinopathy or maculopathy treated within the 6 months before screening or requiring acute treatment
22)History of or positive result at screening for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) type 1 or 2 antibody
23)History of cancer, other than squamous cell or basal cell carcinoma of the skin, that has not been in full remission for at least 5 years before screening. (Any history of treated cervical intraepithelial neoplasia I or cervical intraepithelial neoplasia II is allowed)
24)Use of or a positive screen for drugs of abuse (opiates, cocaine, amphetamines, cannabinoids), barbiturates, or benzodiazepines that may potentially jeopardise a subject*s study compliance. Subjects who have been prescribed benzodiazepines, or low dose opiates for chronic conditions, may qualify for the study at the discretion of the investigator
25)Severe neuropathy, including but not limited to a) severe autonomic neuropathy (e.g., orthostatic hypotension or treated gastroparesis) or b) severe peripheral neuropathy (e.g., non healing diabetic ulcers or requires medication for neuropathic pain)
26)Is incapable of providing proper informed consent or complying with the study procedures
27)Atypical sleep patterns (e.g., those working late night or graveyard shifts)
28)A history of drug addiction, drug or alcohol abuse or heavy alcohol use in the previous 12 months. Heavy alcohol use is defined as more than 14 units per week for women or more than 21 units per week for men (a unit is 1.5 ounces [44 mL] of 80 proof distilled spirits, 4 ounces [118 mL] of wine, or 12 ounces [355 mL] of 3-5% beer)
29)Any other condition or clinically significant abnormal findings during the physical examination, assessment of medical history (including previous anaphylactic reactions or recent severe systemic illness), or clinical laboratory test results that, in the opinion of the investigator, would make the subject unsuitable for the study or would put them at additional risk during participation

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nap
Generic name:	nap
Product type:	Medicine
Brand name:	Victoza
Generic name:	liraglutide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	27-11-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	07-02-2014
Application type:	First submission
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)

Approved WMO

Date:	12-05-2014
Application type:	Amendment

Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	20-05-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	08-10-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003625-29-NL
ClinicalTrials.gov	NCT01452451
CCMO	NL46788.028.13