A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL DOSE ESCALATION STUDY OF THE SAFETY, TOLERABILITY, PHARMACODYNAMICS AND PHARMACOKINETICS OF SINGLE SUBCUTANEOUS DOSES OF HM11260C IN ADULT PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Primary:To evaluate the safety and tolerability profile of single escalating subcutaneous (sc) dose levels of HM11260C in adult patients with type 2 diabetes mellitusSecondary:To evaluate the dose response relationship of single escalating sc dose...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON34301

Source
ToetsingOnline

Brief title
HM11260C SAD study in patients with type 2 diabetes mellitus

Condition

- Diabetic complications

Synonym
diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Hanmi Pharmaceutical Company Ltd
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: HM11260C, Pharmacodynamic, Pharmacokinetic, Type 2 diabetes mellitus

Outcome measures

Primary outcome

Pharmacokinetics

Pharmacodynamics

Safety

Tolerability

Secondary outcome

N/A

Study description

Background summary

Exenatide is a GLP-1R agonist derived from the saliva of the Gila monster lizard and resistant to dipeptyl peptidase-4 (DPP-IV). Exenatide slows stomach emptying, increase in satiety and release of insulin. Exenatide was approved by FDA for type 2 diabetes due to favourable effect on diabetes. However, exenatide requires bid (bis in die [twice daily]) administration due to the

short half-life in vivo although it has resistancy against DPP-IV. The frequent administration causes inconvenience to patients and can not elicit maximal therapeutic efficacy due to fluctuation of the glucose level. The development of long-acting exenatide given at once a week or once a month would offer advantage of convenient dosing and may enhance both compliance and clinical efficacy compared with bid administered exenatide.

HM11260C is being developed by conjugating the CA Exendin-4 (Exendin-4 analog) and the constant region of human immunoglobulin G4 fragment (named as HMC001) via a non-peptidyl 3.4 KDa polyethyleneglycol (PEG) linker which is based on a novel strategy for developing long-acting proteins. Human immunoglobulin G4 fragment (HMC001) was chosen as the stabilizing agent, because it is the most prevalent blood protein and has an in vivo half-life of several weeks without effector function such as complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC).

HM11260C and exenatide belong to the therapeutic class of insulinotropic factors. HM11260C is a sustained duration form of CA Exendin-4 through decreased renal and vascular endothelium clearance. HM11260C and exenatide have shown to have identical modes of actions by sharing human GLP-1 receptor. And HM11260C showed marked increase of potency as well as sustained duration of action.

HM11260C is expected to be administered once a week to once a month by adjusting dosages and to be compatible with conventional prefilled syringe which has a fine needle due to the high solubility of HM11260C. In addition, the pharmacodynamic (PD) study of HM11260C showed that it has superior therapeutic profile compared with exenatide. In conclusion, HM11260C is expected to have a favourable therapeutic profile as well as convenience in dosing regimen when it is applied to clinic.

Study objective

Primary:
To evaluate the safety and tolerability profile of single escalating subcutaneous (sc) dose levels of HM11260C in adult patients with type 2 diabetes mellitus

Secondary:
To evaluate the dose response relationship of single escalating sc dose levels of HM11260C on pharmacodynamic (PD) parameters including 24-h glucose profiles (including fasting and post-prandial blood glucose), fasting fructosamine, C-peptide, fasting insulin, glucagon, lipids, gastric emptying, body weight, waist circumference, and a battery of safety laboratory parameters, incl. amylase, lipase, liver enzymes and hematologic parameters

To evaluate the pharmacokinetic (PK) profiles of single dose levels of HM11260C

To determine the pharmacologically active dose (PAD) of HM11260C (based on fasting glucose) as defined by the dose that results in a mean reduction in fasting glucose of more than 30 mg/dL (1.66 mmol/L) or 20% reduction from baseline, whichever is greater

To assess the immunogenicity (anti-HM11260C antibodies and anti-HM11260C neutralizing antibodies) of a single sc dose of HM11260C

Study design

Study design:
eligibility screening period
a wash-out period for anti-diabetes drug(s)
Treatment period,
involving administration of a single sc dose of HM11260C according to a randomized, double-blind, placebo-controlled, sequential dose escalation design,
3 in clinic periods of 3 days (2 nights) per period,
5 ambulatory visits
follow-up visit.

Screening period:
Medical history, physical examination, vital signs, ECG, serology (including hepatitis B surface antigen [HBsAg]), anti-hepatitis C virus [anti-HCV], and anti human immunodeficiency virus 1/2 (anti-HIV 1/2), drug and alcohol screen, pregnancy test (females only).
A blood and a urine sample will be taken for routine haematology and clinical chemistry tests (including fasting glucose and FSH (FSH for women only)). In addition, HbA1c will be measured (at screening only).

Wash out period:
Subject will discontinue their hypoglycaemic treatment starting on Day -14. In the period from Day -14 to Day -3, these subjects will have to telephone the clinical research facility if their fasting blood glucose level reaches 11 mmol/L or higher. If in this period a patient reports a fasting blood glucose level higher than 13.3 mmol/L, he/she will be advised to restart his/her prior diabetes medication immediately and will not be dosed in the study.

Treatment period:
The subjects will arrive at the clinic in the afternoon of Day -2 (Day 1 is the day of drug administration) and will leave 168 h after drug administration on Day 8. In addition, the subjects will stay in the clinic from Days 13-15, 20-22, 27-29. There will be ambulatory visits on Days -15, 10, 35, 42 and 49. If glucose >14 mmol/L on 2 consecutive days he/she will be advised to restart their prior hypoglycaemic medication immediately.

In this first-in-patient study, safety, tolerability, PK and PD of single sc

doses of HM11260C will be studied in diabetes patients.

Four cohorts of each six patients. Based on the results of the first four groups, the study is optionally extended with a cohort of 6 patients (four verum and two placebo).

Subjects will be genotyped/phenotyped for a total of 1069 alleles that have been associated with altered drug metabolism and disposition, in case the Sponsor deems this necessary.

Follow-up
The follow up medical examination will be performed between 4 and 6 weeks after the last blood sample has been taken. Follow-up medical examination will consist of: physical examination, vital signs, ECG and clinical laboratory tests.

Treatments Administered
The following treatments will be administered (as a single dose) according to the randomisation schedule.
Group 1: a single sc injection 2 µg/kg HM11260C (n=5) or placebo (n=1) on Day 1
Group 2: a single sc injection 4 µg/kg HM11260C (n=5) or placebo (n=1) on Day 1
Group 3: a single sc injection 8 µg/kg HM11260C (n=5) or placebo (n=1) on Day 1
Group 4: a single sc injection 14 µg/kg HM11260C (n=5) or placebo (n=1) on Day 1

The study may be extended with the following cohort:
Group 5: 6 patients (4 on active and 2 on placebo who will be treated with minimally 2 µg/kg and maximally 20 µg/kg HM11260C, depending on the results of Group 1, 2, 3 or 4.

Blood sampling:
PK blood sampling: pre-dose untill 1152 h post-dose

PD blood sampling for glucose, insulin and C-peptide: 24-h profiles

PD blood sampling for glucose (without insulin and C-peptide): 24-h profiles

PD blood sampling for fructosamine and lipids (total cholesterol, HDL, LDL, VLDL, free fatty acids, triglycerides)

Other PD assessments:
PD assessments (body weight and waist circumference)

PD assessments (Hunger, Craving and Fullness Questionnaire)

On days with PD assessments standardized meals, with Ensure Plus® and a muffin

as breakfast, will be provided on Days -1, 1, 4, 7, 14, 21 and 28. On Days -1, 1 and 14, the muffin should be an Expiroger muffin containing 13C-octanoic acid.

13C-octanoic acid meal and breath test (Gastric emptying) will be assessed

Safety assessments:
Vital signs (including blood pressure, pulse rate, body temperature and ECG)

For patients taken off their hypoglycaemic medication: glucose measurements with a glucometer once a day

Clinical laboratory (including clinical chemistry, haematology and urinalysis)

Immunogenicity blood samples for determining anti drug antibodies and anti drug neutralizing antibodies

Physical examination

Intervention

Study Medication
Active substance: HM11260C
Activity: long-acting GLP-1R agonist
Indication: type 2 diabetes mellitus
Strength: unknown
Dosage form: sc injection

Study burden and risks

Procedures: pain, light bleeding, heamatoma and possibly an infection.

Possible (adverse) effects: body weight loss, decrease in food consumption, slight dehydration and a slight pallor.

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Type 2 diabetes mellitus,
18 - 75 years,
BMI 25 - 40 kg/m2
Non-smoker of light smoker (inclusive)

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/Aids. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 90 days from the start of the study. In case of donating more than 1.5 liters blood in the 10 months preceding the start of the study.
Use of insuline for diabetes in the past.

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:	Recruitment stopped
Start date (anticipated):	07-06-2010
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO Date:	27-04-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-05-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2010-019665-28-NL
CCMO	NL32335.056.10