A DOUBLE-BLINDED, PLACEBO-CONTROLLED, SINGLE DOSE AND MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND PROOF OF CONCEPT OF DM-199 IN HEALTHY SUBJECTS AND PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Primary:To evaluate the safety and tolerability of single and multiple subcutaneous doses of DM 199 in healthy subjects and type 2 diabetes mellitus patientsTo determine the plasma pharmacokinetic profile of DM-199 after administration of single and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON40545

Source
ToetsingOnline

Brief title
DM-199 SAD, MAD and POC study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type2 Diabetes Mellitus: bloodglucose.

Research involving
Human

Sponsors and support

Primary sponsor: DiaMedica Inc.
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: DM-199, MAD, POC, SAD

Outcome measures

Primary outcome

Safety:

Parts A, B, C and D: adverse events, vital signs (including supine and standing systolic and diastolic blood pressure, pulse, body temperature, respiratory rate), 12-lead ECG, clinical laboratory (including clinical chemistry, hematology, coagulation and urinalysis) tests, local tolerability at injection site and physical examination

Part A: fasting and non-fasting serum glucose

Parts B, C and D: fasting glucose using the glucometer (or determined by the clinical laboratory for Part D patients only when they are in the clinic)

Parts C and D: anti-drug antibodies (ADA)

Pharmacokinetics: Parts A, B, C and D: plasma concentrations of DM-199 and PK

parameters

Secondary outcome

Pharmacodynamics:

Parts B and C: glucose (fasting and non-fasting), insulin, C-peptide, glucagon and GLP-1 (active and total); in Part B these will be measured as a response to a meal tolerance test (MTT)

Parts C and D: analysis of immune cell populations (lymphocytes, B lymphocytes, T (helper/cytotoxic) lymphocytes, monocytes and natural killer cells)

Part D: adiponectin, aldosterone, renin and lipid (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], free fatty acids, triglycerides) concentrations

Proof of concept: Part D: glucose (fasting and non-fasting), insulin, C-peptide, glucagon and GLP-1 (active and total) as a response to an MTT, fasting glucose using the glucometer (or determined by the clinical laboratory for Part D patients only when they are in the clinic), fasting insulin,, fructosamine and HbA1c

Study description

Background summary

DM-199 is a new investigational compound that may eventually be used for the treatment of Diabetes Mellitus Type 2. This is the first time that this compound is being given to humans.

Study objective

Primary:
To evaluate the safety and tolerability of single and multiple subcutaneous doses of DM 199 in healthy subjects and type 2 diabetes mellitus patients

To determine the plasma pharmacokinetic profile of DM-199 after administration of single and multiple doses of DM-199

Secondary:
To determine the effect of DM-199 on glucose homeostasis (via fasting glucose, fasting insulin and HbA1C levels), standardized meal tolerance test, C-peptide, fructosamine, GLP-1 (active and total), glucagon, adiponectin, aldosterone, renin and lipids measurements, and homeostatic model assessment of insulin resistance/ beta cell function (HOMA) determination in type 2 diabetes mellitus patients

To assess the formation of antibodies to DM-199 after administration of multiple doses of DM-199 in healthy subjects and type 2 diabetes mellitus patients

To determine changes in immune cell populations by fluorescence-activated cell sorting analysis following multiple doses of DM-199 in healthy subjects and type 2 diabetes mellitus patients

Study design

A DOUBLE-BLINDED, PLACEBO-CONTROLLED, SINGLE DOSE AND MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND PROOF
OF CONCEPT OF DM-199 IN HEALTHY SUBJECTS AND PATIENTS WITH TYPE 2 DIABETES MELLITUS

The study consists of 4 parts. Each part (A, B, C and D) will consist of one or several periods. The research will be conducted in both healthy male and female volunteers (Part A and C) and in male and female diabetes mellitus type 2 patients (Part B and D).

Observation period:
Part A: Group 1 and 2: 3 periods in the clinic each being from Day -1 until 72 hours (Day 4) after drug administration
Part A: Group 7: 1 period in the clinic from Day -1 until 72 hours (Day 4) after drug administration
Part B: 1 period in the clinic from Day -1 until 72 hours (Day 11) after the last drug administration on Day 8
Part C: 1 period in the clinic from Day -1 until 72 hours (Day 19) after the last drug administration on Day 16, followed by 2 ambulant visit on Days 21 and 23.
Part D: 1 period in the clinic from Day -2 until 72 hours (Day 31) after the

last drug administration on Day 28, followed by 2 ambulant visits on Days 35 and 42

In Part B, an ambulatory visit will be scheduled on Day -15 for type 2 diabetes mellitus patients receiving anti-diabetic medication (such as metformin, sulphonylureas etc.). Subjects will be discontinued from this treatment (starting on Day -14). Subjects will receive dietary advice and explanation of the glucometer. They will perform glucose measurements with a glucometer once a day, in the morning (while fasting) from Day 14 to Day -1.

In Part D, an ambulatory visit will be scheduled on Day -29 for type 2 diabetes mellitus patients receiving anti-diabetic medication (such as metformin, sulphonylureas etc.). Subjects will be discontinued from this treatment (starting on Day -28). Subjects will receive dietary advice and explanation of the glucometer. They will perform glucose measurements with a glucometer once a day, in the morning (while fasting) from Day 28 to Day 30.

Intervention

Part A:
Group 1:
Period 1: a single sc dose of 0.015 mg/kg DM-199 (n=6) or matching placebo (n=3)
Period 2: a single sc dose of 0.15 mg/kg DM-199 (n=6) or matching placebo (n=3)
Period 3: a single sc dose of 0.015 mg/kg DM-199 (n=3), 0.15 mg/kg DM 199 (n=3) or matching placebo (n=3)

During Period 1 of Group 1, two volunteers will be dosed (one DM-199 and one placebo) first. After dosing, the safety and tolerability of study drug in these subjects will be closely monitored. If there are no concerns about the safety and tolerability, the remaining 7 subjects (5 DM-199 and 2 placebo) will be dosed the day after the first two subjects.

Group 2
Period 1: a single sc dose of 0.005 mg/kg DM-199 (n=6) or matching placebo (n=3)
Period 2: a single sc dose of 0.005 mg/kg DM-199 (n=3), 0.45 mg/kg DM 199 (n=3) or matching placebo (n=3)
Period 3: a single sc dose of 0.45 mg/kg DM-199 (n=6) or matching placebo (n=3)

Group 7a: a single sc dose of 0,0015 or 0.005 mg/kg DM-199 (n=6) (based on PK data from Group 1 and 2) or matching placebo (n=1)
Group 7b: a single sc dose of 0.015 mg /kg DM-199 (n=6) or matching placebo (n=1)

Part B:
Group 3:
Day 1: a single sc dose of placebo (n=10)

Day 2: a single sc dose of A* DM-199 (n=7) or matching placebo (n=3)
Day 5: a single sc dose of B* DM-199 (n=7) or matching placebo (n=3)
Day 8: a single sc dose of C* DM-199 (n=7) or matching placebo (n=3)

* The dose levels (A, B and C) of Part B will be decided based on the safety and tolerability data of Part A.
A total of 3 patients will receive placebo throughout the study and 7 patients will be given placebo on Day 1 and DM-199 on Days 2, 5 and 8.

Part C:
Group 4 sc doses of 0.003 mg/kg DM-199 (n=6) or matching placebo (n=3) once every 72 hours for a total of 6 doses
Group 5 sc doses of 0.015 mg/kg# DM-199 (n=6) or matching placebo (n=3) once on Days 1, 4 and 7 and sc doses of 0.025 mg/kg# DM-199 (n=6) or matching placebo (n=3) once on Days 10, 13 and 16

If issues with tolerability are noted following any of the doses in Group 5, the next DM-199 dose(s) may be adjusted downward to 0.015 mg/kg or 0.010 mg/kg DM-199. Changes in DM-199 dose levels will always be discussed between the Principal Investigator and the Sponsor.

Part D:
Group 6:
multiple sc doses of F* DM-199 (n=12), G* DM-199 (n=12) or matching placebo (n=6) once daily once every 72 hours for a total of 10 doses over 28 days (ie, Days 1, 4, 7, 10, 13, 16, 19, 22, 25 and 28).

* The dose levels (F and G) of Part D will be decided based on safety, tolerability, PK and PD data of Parts A, B and C. If the study medication is well tolerated after each third dose (thus doses of Day 7, 16 and 25), the dose may be titrated upwards.

Study burden and risks

During the investigation, various assessments can be experienced as more or less stressful.

Blood draw, indwelling canula:
During this study blood will be drawn. Each period 1 time an indwelling canula will be used and a number of blood draws
will be drawn by direct puncture of the vein. The insertion of the canula may be associated with pain, minor bleeding,
bruising, possible infection.

There will be also a subcutaneous (in the abdominal wall) injection for the administration of the study drug or placebo. The site of injection will be checked regularly during the study for local reactions, such as redness,

swelling, itching, or bruising. In addition, the severity of pain will be evaluated.

Single DM-199 doses up to 0.05 mg/kg were administered to healthy subjects in Part A of this study. Up to 0.015 mg/kg, DM-199 doses were well-tolerated whereas at higher dose levels, not all subjects tolerated DM-199 well. The following adverse events were reported mainly at the higher DM-199 dose levels: orthostatic hypotension and orthostatic hypotension related symptoms such as postural dizziness, abdominal discomfort, headache, nausea, vomiting, tingling in the fingers, warm sensation and tinnitus.
In Part B of this study, single doses up to 0.015 mg/kg DM-199 were administered to type 2 diabetes mellitus patients and well-tolerated. In Part C of this study, multiple doses up to 0.015 mg/kg DM-199 every 72 hours in healthy subjects were also well-tolerated; Part C is still ongoing at the time of writing this document and a higher dose of 0.025 mg/kg DM-199 is planned. The following adverse events were reported in Parts B and C: dizziness, tiredness, headache and skin irritation at the injection site. All reported events in Parts B and C were of mild intensity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age: Healthy subjects (Parts A and C): 18 - 65 years, inclusive
: Type 2 diabetes mellitus patients (Parts B and D): 18 - 75 years, inclusive ;Body Mass Index (BMI): Healthy subjects (Parts A and C): 18.0 - 30.0 kg/m2
: Type 2 diabetes mellitus patients (Parts B and D): 25.0 - 35.0 kg/m2 for Part B and 25.0 - 45.0 kg/m2 with a maximum body weight up to 165 kg for Part D.;Gender : Healthy males or females; for Part D females must be of non-childbearing potential (either surgically sterilized or at least 1 year post-menopausal)

Exclusion criteria

Suffering from : hepatitis B. cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of the study. In case of donating blood or significant loss of blood within 60 days of the start of drug dosing.

Study design

Design

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):	15-04-2013

Enrollment:	96
Type:	Actual

Ethics review

Approved WMO Date:	08-04-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2014

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2014
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	EUCTR2013-000225-30-NL
CCMO	NL43703.056.13