An Exploratory Phase 2, Randomised, Double-blind, Placebo-controlled, and Open-label Active Comparator Study to Evaluate the Effect of MEDI0382 on Hepatic Glycogen Metabolism in Overweight and Obese Subjects with Type 2 Diabetes Mellitus

Published: 29-10-2019
Last updated: 10-04-2024

* Primary Objective:To assess the effect of MEDI0382 on hepatic glycogen levels versus placebo after 28 days (Part A) and 35 days (Part B) of treatment* Secundary Objective: - To assess the effect of MEDI0382 on hepatic glycogen levels versus...

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

Summary

ID

NL-OMON50158

Source
ToetsingOnline

Brief title
D5670C00022

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 2 Diabetes Melitus

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: MEDI0382, T2DM

Outcome measures

Primary outcome

* Change in hepatic glycogen concentration adjusted for liver volume as measured by magnetic resonance spectroscopy (MRS) at Time (T) = 4 hours post standardised morning meal from baseline (Day 1) to the end of 28 days of treatment (Part A)

* Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by magnetic resonance spectroscopy (MRS) at Time (T) = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36) (Part B)

Secondary outcome

* Percentage change in fasting hepatic glycogen concentration adjusted for liver volume as measured by MRS at T = 24 hours post standardised morning meal from baseline (Day 1) to the end of 35 days of treatment (Day 36) (Part B only)

* Change in hepatic fat fraction from baseline as measured by magnetic resonance imaging (Day 1) to the end of 35 days of treatment (Part B only)

* Measures of safety and tolerability (vital signs, electrocardiograms [ECGs], laboratory test results, adverse events [AEs])

* Development of anti drug antibodies (ADA) and titre (if confirmed positive)

Study description

Background summary

* Disease background
The rising prevalence of type 2 diabetes mellitus (T2DM) and obesity is a cause of substantial health and economic burden worldwide. In many cases of T2DM, significant weight loss (typically 5% of body weight or more) can promote improvements in glycaemic control, cardiovascular risk, and mortality rates, and may even slow or reverse disease progression (Petersen et al, 2005). Many existing therapies for T2DM focus upon lowering blood glucose; however, there is a major unmet need for treatments that both improve glycaemic control and achieve disease-modifying weight loss.

* MEDI0382 background
MEDI0382 is a synthetic peptide with both glucagon-like peptide-1 (GLP-1) and glucagon receptor agonist activity which is under development for the treatment of T2DM and non-alcoholic steatohepatitis (NASH). GLP-1 receptor agonists are established treatments for T2DM that improve glycaemic control, delay gastric emptying, and depress appetite leading to modest, but often non-sustained weight loss (typically 3% versus baseline at one year). Glucagon has similar effects to GLP-1 on gastric emptying and appetite, and has also been shown to promote increased energy expenditure (Lynch et al, 2014; Habegger et al, 2013). Oxyntomodulin, a naturally occurring peptide with GLP-1 and glucagon receptor co-agonist activity, has been shown to promote weight loss through effects on appetite and energy expenditure (Wynne et al, 2006) and co-infusion of GLP-1 and glucagon has synergistic effects on reducing food intake and promoting weight loss in human subjects (Bagger et al, 2015).

Study objective

* Primary Objective:
To assess the effect of MEDI0382 on hepatic glycogen levels versus placebo after 28 days (Part A) and 35 days (Part B) of treatment

* Secundary Objective:
- To assess the effect of MEDI0382 on hepatic glycogen levels versus liraglutide after 35 days of treatment (Part B only)
- To assess the effect of MEDI0382 on hepatic fat fraction versus placebo after 35 days of treatment (Part B only)
- To evaluate the safety and tolerability of MEDI0382 titrated up to a dose level of 300 *g

- To characterise the immunogenicity profile of MEDI0382 exposure titrated up to a dose level of 300 *g

* Exploratory Objectives:
- To assess the effect of MEDI0382 on hepatic glycogen levels at different time points postprandially versus placebo (Part A and B) and liraglutide (Part B only) after 28 days (Part A) or 35 days (Part B) of treatment
- To assess the effect of MEDI0382 on 24-hour hepatic glycogen levels versus placebo (Part A and B) and liraglutide (Part B only) after 28 days (Part A) or 35 days (Part B) days of treatment
- To assess the effect of MEDI0382 on glucose lowering versus placebo (Part A and B) and liraglutide (Part B only) after 28 days (Part A) or 35 days (Part B) of treatment
- To assess the effect of MEDI0382 on hepatic fat fraction versus liraglutide after 35 days of treatment (Part Bonly)
- To assess the effect of MEDI0382 on liver volume versus placebo (Part A and B) and liraglutide (Part B only) at specific time points postprandially after 28 days (Part A) or 35 days (Part B) of treatment
- To assess the effect of MEDI0382 on gluconeogenesis versus placebo (Part A and B) and liraglutide (Part B) after 28 days (Part A) or 35 days (Part B) of treatment
- To assess the effect of MEDI0382 on glycogenolysis versus placebo (Part A and B) or liraglutide (Part B) after 28 days (Part A) or 35 days (Part B) of treatment
- To assess the effect of MEDI0382 on energy-related and gluconeogenic metabolites versus placebo (Part A and B) and liraglutide (Part B) after 28 days (Part A) or 35 days (Part B)
of treatment
- To assess systemic exposure of MEDI0382 up-titrated to 300 µg

Study design

This is a 2-part (Part A and Part B) exploratory Phase 2 study.
Part A is a randomised, double-blind, placebo-controlled study to evaluate the effect of MEDI0382 administered once daily SC for 28 days on hepatic glycogen metabolism in overweight and obese subjects with T2DM. Part A is planned to randomise up to 20 subjects. Subjects will be consented, screened for suitability, and randomised within 60 days if eligible. Subjects from Part A will not be re-enrolled in Part B.
Part B is an exploratory Phase 2 randomised, double blind, placebo-controlled and an open-label active comparator study to evaluate the effect of MEDI0382 on hepatic glycogen metabolism in overweight and obese subjects with T2DM. Part B is planned to randomise approximately 30 subjects (not to exceed a maximum of 35 subjects). Subjects in Part B will be randomised to receive double-blind MEDI0382 titrated from 50 to 300 µg or placebo, or open label liraglutide titrated from 0.6 to 1.8 mg once daily for 35 days.
The study will involve measurement of hepatic glycogen content using a carbon

(C) 13 MRS based technique before and after completion of the treatment period.
In Part A, MEDI0382 will be titrated in 7 day intervals from 100 to 300 *g in comparison to placebo. In Part B MEDI0382 will be titrated in 7 day intervals from 50 to 300 *g and compared to placebo and liraglutide at a dose of 1.8 mg once daily titrated from 0.6 mg to 1.8 mg in 7 day intervals.
In Parts A and B subjects will undergo a 5 day washout period where metformin therapy will be suspended at the beginning of the study starting from Day 4 (metformin dosing to resume on Day 2). This washout is repeated at the end of the treatment period starting from Day 24 in Part A and Day 32 in Part B.
Across Part A of the study (up to 126 days in total including screening) subjects will have a total of 6 study visits, 6 nights of inpatient stay and will undergo a total of 10 MRS scans alongside additional assessments and blood sampling. In Part B, subjects will participate in the study for approximately 133 days and will have a total of 7 study visits (including 2 remote contacts), 6 nights of inpatient stay and will undergo a total of 8 MRS scans alongside additional assessments and blood sampling. The duration of MRS scans will be approximately 40 minutes with the exception of the baseline and end of treatment scans used for liver fat evaluation (Part B only) which will be prolonged and up to 1 hour 45 minutes in duration. Subjects will also be given the option to stay overnight prior to study visits if more convenient for them.
From Day 2 to Day 1 (and again on Day 8 to Day 15, Day 27 to Day 29 [Part A] and Day 34 to Day 36 [Part B] subjects will be asked to provide a stool sample for microbiome research purposes; this component of the study is optional.
On Day -3 in both parts of the study, subjects will be admitted to the clinical unit for 3 nights inpatient stay and will undergo initial safety assessments and receive training in SC injection administration. On Day 3 and Day 2, subjects will be provided with standardised solid meals (balanced with respect to nutrient content, but not calorie restricted) for breakfast, lunch, and evening meal and be expected to consume the entire meal and abstain from consumption of additional meals during this period. On the evening of Day -2, subjects will undergo a baseline blood test for 2H-glucose prior to consuming deuterated water (2H2O) divided into two aliquots and separated by a 4 hour interval. Subjects will be expected to fast for 14 hours overnight (except for drinks of deuterated water).
On Day -1 subjects will undergo a baseline MRS scan to measure liver volume and glycogen (and liver fat in part B only) and will have blood samples collected for 2H-glucose and baseline assessments prior to undergoing a standardised mixed meal tolerance test (MMTT). The MMTT will consist of a liquid meal (400 mL Ensure Plus milkshake) (at Time [T] = 0). Blood will then be collected at specified time points to measure glucose levels. In Part A, at T = 4 hours after the MMTT a repeat MRS scan will be performed to measure liver volume and glycogen. For the remainder of the day serial MRS scans will be performed and blood samples will be collected at T = 9, and 14 hours and subjects will be given standardised solid meals for lunch and evening meal. In Part B, a repeat MRS scan to measure liver volume, fat and glycogen will be taken at T= 5 hours after the MMTT. A further MRS scan will be performed, and blood samples will be collected at T = 14 and subjects will be given standardised solid meals for

lunch and evening meal.
On the morning of Day 1, following an overnight fast of at least 14 hours, subjects will have a final MRS scan performed (T = 24 hours) and blood sampling. On Day -1 or Day 1, eligibility criteria will be verified (the final eligibility check may occur at any time from Day -3 to Day 1) and subjects will be randomised to receive investigational product (MEDI0382 or placebo in Part A or MEDI0382, placebo, or liraglutide in Part B). Following predose safety measures, the subjects will receive their first dose of investigational product via SC injection and will be discharged from the clinical unit with a sufficient supply of investigational product to self administer once daily by SC injection at home in the morning.
In Part A subjects will return for an outpatient visit at weekly intervals (Day 8 and Day 15) for safety assessments, dose up-titration until a dose of 300 µg MEDI0382 is reached in Part A. . Subjects will receive sufficient supply of investigational product at each outpatient visit.
On Day 26 subjects will be re-admitted to the clinical unit for a further 3 nights inpatient stay and as before will receive standardised solid meals during this period. On the evening of Day 27, subjects will fast and be given 2H2O water to drink at 2 times during the overnight period. On Day 28, following an MRS scan and blood sampling, subjects will receive an SC dose of investigational product and then undergo a MMTT as before at T = 0 and serial MRS scans and blood samples will be collected at T = 4, 9, and 14 hours. On Day 29, following an overnight fast, a final MRS scan will be performed alongside a blood test at T = 24 hours.
In Part B subjects will return for an outpatient visit on Day 8 for safety assessments, dose up-titration, and will receive an adequate supply of investigational product. On Days 14/15 and 21/22 remote contacts will be performed to advise on further dose uptitration as required and to collect AE/serious adverse events (SAEs) and concomitant medication information.
On Day 33 subjects will be re-admitted to the clinical unit for a further 3 nights inpatient stay and as before will receive standardised solid meals during this period. On the evening of Day 34, subjects will fast and be given 2H2O water to drink at 2 times during the overnight period. On Day 35, following an MRS scan and blood sampling, subjects will receive an SC dose of investigational product and then undergo a MMTT as before at T = 0 and serial MRS scans and blood samples will be collected at T = 5 and 14 hours. On Day 36, following an overnight fast, a final MRS scan will be performed alongside a blood test at T = 24 hours.
A follow up visit will be performed 28 days after the last dose of investigational product for safety assessments.

Intervention

Following a screening period of up to 60 days, subjects will be randomised to receive either MEDI0382, placebo, or open label liraglutide once daily in the morning via SC injection as follows:
* MEDI0382 50 *g for 7 days, followed by 100 *g for 7 days, followed by 200 *g

for 7 days, followed by 300 *g for 14 days (N = 10)
* Placebo for 35 days (N = 10)
* Open label liraglutide 0.6 mg for 7 days, followed by 1.2 mg for 7 days, followed by 1.8 mg for 21 days (N = 10)

Study burden and risks

If a patient participate in this study it does not mean that his/her T2DM will be better but it will help MedImmune to answer the research question(s). As the treatment duration for this study is very short, it is unlikely that the patient will experience much improvement in his/her condition. He/she will contribute to more knowledge and help T2DM patients in the future.

Disadvantages of participation in the study may be
- possible side effects of the study drug;
- possible side effects/discomforts of the evaluations in the study.

Participation in the study also means:
- that patient lose additional time;
- an additional or an extended hospitalisation;
- (additional) testing;
- that the patient has appointments that he/she has to attend;

Contacts

Public
Astra Zeneca

MedImmune Limited, Milstein Building Granta Park
Cambridge CB21 6GH
GB
Scientific
Astra Zeneca

MedImmune Limited, Milstein Building Granta Park
Cambridge CB21 6GH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Written Informed Consent and willing and able to adhere to all protocol requirements
2. Male or female at least 18 years old
3. patient with body mass index of at least 27kg/m² and up to 40 kg/m²
4. patient with a diagnosis of T2DM on metformin monotherapy
5. patient with a glycated haemoglobin of maximum 8.0%
6. Female subjects must not be pregnant and lactating females will be excluded
7. Females of childbearing potential should be using appropriate contraception
For a complete list refer to page 32-33 of the protocol

Exclusion criteria

1. History / existing condition that in the opinion of the investigator would interfere with evaluation of the investigational product, put the subject at risk, influence the subject's ability to participate or affect the interpretation of the results of the study and/or any subject unable or unwilling to follow study procedures.
2. Any subject who has received another investigational product or a GLP-1 analogue-containing preparation within the last 30 days or 5half-lives of the drug
3.Any subject who has received any of the following medications within the specified time frame prior to the start of the study:
a. Herbal preparations or drugs licensed for control of body weight or appetite
b. Opiates, domperidone, metoclopramide or other drugs known to alter gastric emptying
c. Glucagon
d. Warfarin
4. concurrent participation in another study with investigational product and repear randomistion in this study is prohibited
5. Severe allergy/hypersensitivity to any of the proposed study treatments,

excipients, C-13 labelled glucose, deuterated water (2H2O), or ingredients of standardised meals
6 Any contraindication to magnetic resonance imaging/MRS scanning including claustrophobia or dislike of confined spaces
7 Symptoms of acutely decompensated blood glucose control (eg, thirst, polyuria, weight loss), a history of type 1 diabetes mellitus (T1DM) or diabetic ketoacidosis, or if the subject has been treated with daily SC insulin within 90 days prior to screening
8 Recurrent unexplained hypoglycaemic episodes (defined as glucose < 3.0 mmol/L or < 54 mg/dL on more than 2 occasions in 6 months prior to screening)
9 Significant inflammatory bowel disease, gastroparesis, or other severe disease or surgery affecting the upper GI tract (including weight-reducing surgery and procedures) which may affect gastric emptying or could affect the interpretation of safety and tolerability data
10 Acute or chronic pancreatitis
11 Significant hepatic disease (except for NASH or nonalcoholic fatty liver disease without portal hypertension or cirrhosis) and/or subjects with any of the following results at screening:
* Aspartate transaminase (AST) * 3 × upper limit of normal (ULN)
* Alanine transaminase (ALT) * 3 × ULN
* Total bilirubin * 2 × ULN
12 Impaired renal function defined as estimated glomerular filtration rate (eGFR) < 30 mL/minute/1.73m2 at screening (glomerular filtration rate estimated according to Modification of Diet in Renal Disease (MDRD) using MDRD Study Equation IDMS-traceable (International System of Units [SI] units)
13 Poorly controlled hypertension defined as:
* Systolic blood pressure (BP) > 180 mm Hg
* Diastolic BP > 105 mm Hg
14 After 10 minutes of supine rest and confirmed by repeated measurement at screening. Subjects who fail BP screening criteria may be considered for 24-hour ambulatory blood pressure monitoring at the discretion of the investigator. Subjects who maintain a mean 24-hour BP * 180/105 mm Hg with a preserved nocturnal dip of > 15% will be considered eligible.
15 Unstable angina pectoris, myocardial infarction, transient ischemic attack or stroke within 3 months prior to screening, or subjects who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 6 months or who are due to undergo these procedures at the time of screening
16 Severe congestive heart failure (New York Heart Association Class III or IV)
17 Basal calcitonin level > 50 ng/L at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia
18 History of neoplastic disease within 5 years prior to screening, except for adequately treated basal cell, squamous cell skin cancer, or in situ cervical cancer
19 Any positive results for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody and human immunodeficiency virus (HIV) antibody
20 Substance dependence or history of alcohol abuse and/or excess alcohol

intake (defined as > 21 units per week for a male subject, and >14 units per week for a female subject). Subjects must have a negative alcohol test result at screening and prior to randomisation.
21 Involvement of any AstraZeneca, MedImmune, contract research organisation, or study site employee or their close relatives

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):	11-01-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MEDIO382
Generic name:	Cotadutide

Ethics review

Approved WMO

Date:	29-10-2019
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-02-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2017-005081-22-NL
ClinicalTrials.gov	NCT03555994
CCMO	NL70315.068.19