Open-label, randomised, 4 parallel-group, Phase I clinical trial to investigate BI 456906 occupancy of Glucagon receptors in liver and Glucagon-like Peptide 1 receptors in pancreas in comparison with semaglutide after administration of radiolabeled tracer in male and female subjects with obesity using PET and MRI

Published: 10-01-2023
Last updated: 21-12-2024

This study has been transitioned to CTIS with ID 2024-515417-17-00 check the CTIS register for the current data. The main objective of this trial is to investigate glucagon receptor occupancy of BI 456906 in the liver with PET imaging using the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56752

Source
ToetsingOnline

Brief title
1404-0047

Condition

- Other condition
- Appetite and general nutritional disorders

Synonym
being overweight, Obesity

Health condition

obesity

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Obesity, Open label, Phase I, Semaglutide

Outcome measures

Primary outcome

Primary endpoint:

· Percentage of glucagon receptors occupancy in the liver using PET imaging at

End of Treatment visit (EOT).

Secondary outcome

Secundary endpoints:

· Percentage of glucagon-like Peptide 1 receptor occupancy in the pancreas

using PET imaging at EOT visit.

Study description

Background summary

BI 456906 is a dual agonist of Glucagon-like-Peptide 1 (GLP-1) and Glucagon (GCG) receptors. GLP-1 receptor agonists lower body weight by the inhibition of food intake and by delaying gastric emptying and intestinal transit. GCG receptor agonist is expected to reduce body weight by increasing energy expenditure and might directly increase the fatty acid oxidation in the liver, potentially reducing the lipotoxicity. Simultaneous dual activation of GLP-1 receptor and GCG receptor by BI 456906 is anticipated to improve glycemic control, body weight loss as well as NASH and fibrosis. Clinical Phase I data indicate that BI 456906 is more efficacious on body weight reduction compared to a GLP-1 agonist alone suggesting that activation of the GCG receptor contributes to the efficacy of BI 456906. However, it is not known to what extent BI 456906 activates the GLP-1 receptor and in particular the GCG receptor in man.
The trial was developed to investigate occupancy of BI 456906 on the GCG and GLP-1 receptors to prove the dual receptor agonism and to compare against the GLP-1 agonist semaglutide available on the market.

Study objective

This study has been transitioned to CTIS with ID 2024-515417-17-00 check the CTIS register for the current data.

The main objective of this trial is to investigate glucagon receptor occupancy of BI 456906 in the liver with PET imaging using the radiolabeled tracer [68Ga]Ga-DO3A-VS-Cys40-Tuna-2.
The secondary objectives is to investigate the GLP-1 receptor occupancy by BI 456906 in the pancreas with PET imaging using the radiolabelled tracer [68Ga]Ga-NODAGA-Exendin-4. The comparator for both GCG and GLP-1 receptor occupancy arms will be the GLP-1 receptor agonist, semaglutide

Study design

This trial is designed as open-label, randomised, parallel-groups, phase I clinical study of BI 456906 versus semaglutide.
It is planned to include a total of 30 subjects in the trial with BMI of >=30 and <=40 kg/m2 and body weight >=70kg and <=150 kg. The subjects will be assigned to 4 groups. Groups 1 (n=12) and 3 (n=6) will receive BI 456906, and Groups 2 (n=6) and 4 (n=6) will receive semaglutide.
The four groups will be combined into two tracer arms according to which PET tracer they will receive. The first tracer arm consists of Groups 1 and 2, receiving the GCG tracer ([68Ga]Ga-DO3A-VS-Cys40-Tuna-2) and PET/CT imaging for analysis of the liver. The second tracer arm will consist of Groups 3 and 4, which will receive the GLP-1 tracer (68Ga]Ga-NODAGA-Exendin-4) and PET/CT

imaging for analysis of the pancreas and brain.

Intervention

See the study design

Study burden and risks

Participation in this clinical trial is without any (therapeutic) benefit for subjects. However, it is anticipated, that volunteers participating in this trial might have benefit in their weight management. Their participation, however, is of major importance to investigate the effect of the trial medication on GCG and GLP-1 receptors. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.
Procedure-related risks

PET/CT examinations: In connection with the PET/CT imaging examinations, the subjects will get a low dose injection of one of two different radioactive tracers. There is a connection between ionizing radiation and risk for cell damage and cancer. Exposure to a 1 millisievert (mSv) dose of radiation results in a 1 in 17,000 chance of developing cancer. The total radiation dose per subject in this trial will be under 10 mSv. This corresponds approximately to the radiation dose from naturally occurring radiation sources during a 3 to 4 year period for a person living in a country where the clinical trial will be conducted. Previous studies in rat, Cynomolgus monkey, and human have shown that both [68Ga]Ga-DO3A-VS-Cys40-Tuna-2 and [68Ga]Ga-NODAGA-Exendin-4 demonstrate a safe profile in regards to dosimetry and adverse events, when given intravenously at microdoses [R21-1576, R21-1575, R21-1574, R21-1573]. The toxicological profile of unlabelled DO3A-VS-Cys40-Tuna-2 has previously been investigated in a single dose study in rat with intravenous bolus administration of 2, 20, or 200 µg/kg in rats. Ga-DO3A-VS-Cys40-Tuna-2 was well tolerated, with no adverse findings or evidence of delayed onset toxicity. Under the conditions of this study, the NOAEL is 200 µg/kg. The toxicological profile of unlabelled NODAGA-Exendin-4 was previously investigated in a single dose study in rat with intravenous bolus administration of maximum 20 µg/kg in rats. NODAGA-Exendin-4 was well tolerated, with no adverse findings or evidence of delayed onset toxicity noted. Under the conditions of this study, the NOAEL is 20 µg/kg. Both tracers will be infused at very low, sub-pharmacological doses and will therefore fall under the legislation of a microdosing approach according to the *Approach 1* as laid down in the *Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2) (2009)*. The tracers will be administered by i.v. injection at a target dose of <0.2 µg/kg for [68Ga]Ga-DO3A-VS-Cys40-Tuna-2 and at a target dose of <0.2 µg/kg for [68Ga]Ga-NODAGA-Exendin-4. The absolute total dose of each tracer will be <100 µg and <1/100th of the NOAEL. The target activity dose will be approximately

0.5 MBq/kg [68Ga]Ga-DO3A-VS-Cys40-Tuna-2 and maximum 0.8 MBq/kg for [68Ga]Ga-NODAGA-Exendin-4. For a subject with a body weight of 100 kg, the target dose will be therefore be approximately 50 MBq for [68Ga] Ga-DO3A-VS-Cys40-Tuna-2 and 80 MBq for [68Ga]Ga-NODAGA-Exendin-4. Based on published dosimetry data the expected radiation dose of one injection of 50 MBq [68Ga]Ga-DO3A-VS-Cys40-Tuna-2 is 1.05 mSv [R21-1576] and of one injection of 80 MBq [68Ga]Ga-NODAGA-Exendin-4 1.28 mSv [R21-1574].

The maximum expected radiation dose from the low dose CT scan, which will include both upper abdomen and brain, is 2 mSv.
The subjects in Groups 1 and 2 will undergo two [68Ga]Ga-DO3A-VS-Cys40-Tuna-2 PET/CT examinations.
The subjects in Groups 3 and 4 will undergo two [68Ga]Ga-NODAGA-Exendin-4 PET/CT examinations.
Therefore, the subjects in Groups 1 and 2 will receive a total dose of 6.1 mSv (3.05 + 3.05) for a 100kg person; subjects in Groups 3 and 4 will receive a total effective dose of 6.56 mSv (3.28 + 3.28) for a 100 kg person.

MRI examination:
The MRI examination combines strong magnetic field and radiofrequency waves. No evidence for any risks has been identified in extensive research to evaluate whether the magnetic fields and radio waves used during an MRI scan pose a risk to the human body. MRI is thus considered one of the safest medical procedures currently available. The examination can be uncomfortable if the subject suffers from claustrophobia. Subjects will be screened for any contraindications to MRI prior to being included in the study. Besides factors that risk harming a subject, also factors that may make image data unevaluable will be considered, to avoid that a subject is exposed to radiation from other parts of the protocol in vain.

Blood collection: The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising and, in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Drug-related risks and safety measures: There are no important identified risks specified for BI 456906, based on the toxicology program or any clinical trials conducted for this product to date.
There are 4 important potential risks based on other GLP 1R agonists currently approved (class effect), and data from the completed Phase II trials of BI 456906. The 4 important potential risks include MTC (C-cell carcinogenicity), acute pancreatitis, pancreatic cancer, and pre-renal acute kidney injury due to

dehydration.
The risks for subjects caused by participation in the trial, including the trial procedures and exposure to the IMP, are reasonably low and do not outweigh the potential benefits. The expected side effects are known to be temporary, dose dependent, easy to monitor, and manageable in clinical trials. An overview of trial related risks is presented in Table 1.4: 2.

Contacts

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NL
Scientific
Boehringer Ingelheim

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 years (inclusive)
3. BMI of >=30 and <=40 kg/m2 and body weight >=70 kg and <=150 kg.

4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Women of childbearing potential (WOCBP) 1 must be willing and able to use two forms of effective contraception where at least one form is a highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the subject information (Section 4.2.2.3).

Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:
1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Resting heart rate >100 beats per minute (bpm) and/or systolic blood pressure >=160 mmHg and/or diastolic blood pressure >=95 mmHg at screening
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance. Subjects with the following abnormal values are not eligible for the trial participation:
- LDL >160 mg/dL (4.15 mmol/L)
- total cholesterol >240 mg/dL (6.22 mmol/L)
- triglyceride >200 mg/dL (2.26 mmol/L)
- blood glucose >126 mg/dl (7 mmol/L) fasting and/or HbA1c >6.5%
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator. Subjects with type 1 and type 2 diabetes mellitus are not eligible for the trial
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders assessed as clinically relevant by the investigator
6. Diseases of the central nervous system (including but not limited to any kind of seizures), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, manifest hypo- or hyperthyroidism at Visit 1
9. Calcitonin >=100 pg/mL (29.26 pmol/L) at screening
10. Any suicidal behaviour or history of major depressive disorder requiring inpatient treatment or escalation of care in the past 2 years before randomization, any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months prior to Visit 1
11. Chronic or relevant acute infections
12. History of chronic or acute pancreatitis or elevation of serum lipase/amylase >2x ULN
13. History of relevant allergy or hypersensitivity (including allergy to the

trial medication or its excipients) according to investigator's assessment
14. Use of prescription or over-the counter drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial including drugs known to significantly prolong the QT/QTcF interval; please refer to Section 4.2.2
15. Intake of an investigational drug in another clinical trial within 60 d of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
16. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day) and inability to refrain from smoking on specified trial days
17. Ongoing chronic alcohol use or drug abuse other than the ones described in Table 5.2.3: 2, that in the investigator*s opinion, makes the subject an unreliable trial subject or unlikely to complete the trial
18. Blood donation of more than 500 mL within 30 d of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked baseline prolongation of QT/QTc interval (such as QTcF intervals greater than 450 ms at screening) or any other abnormal or clinically significant ECG finding at screening (e.g. type 2 second-degree AV block [Type Mobitz II] or third-degree AV block)
22. History of ventricular tachycardia, type 2 second-degree AV block (Type Mobitz II) or third-degree AV block
23. A history of additional risk factors for Torsade de Pointes (such as heart failure, hypokalaemia, Lyme disease, or family history of Long QT Syndrome)
24. Heart rhythm disturbances (e.g. bradycardia with baseline heart rate <50 bpm, in the absence of heart rate lowering medications), tachycardia or tachyarrhythmia (e.g. atrial fibrillation, atrial flutter or ventricular tachycardia), considered by the Investigator indicative of relevant cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at Visit 1
25. Any of the following conditions or procedures within the last six months prior to Visit 1: myocardial infarction, unstable angina (e.g. Canadian Cardiovascular Society [CCS] grading of Angina pectoris grade III and IV), artery bypass (e.g. coronary artery bypass graft, carotid bypass, peripheral artery bypass), percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischaemic attack, cerebrovascular accident (stroke)
26. History of or currently diagnosed with congestive heart failure, New York Health Association (NYHA) class III-IV at screening
27. Treatment with medications known to cause heart block or bradycardia, such as beta-blockers, verapamil, and diltiazem, unless these drugs are indicated for hypertension treatment
28. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe

participation in the study
29. History of a major surgery including surgery of liver and pancreas (except appendectomy) within 5 years prior to screening, or history of splenectomy
30. Confirmed diagnosis of malignancy within 5 years prior to screening, except for basal- or squamous-cell carcinoma of the skin that has been treated successfully. Trial participants under evaluation for malignant disease currently are not eligible for study participation
31. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
In addition, the following trial-specific exclusion criteria apply:
32. Contraindication to magnetic resonance imaging including, but not limited to: severe claustrophobia, extensive tattoos, inner ear implant, pacemakers or other implanted cardiac rhythm management devices, intracranial aneurysm clips incompatible with MRI, any other metallic, non-MR compatible implanted devices (e.g. insulin pump, hip joint replacement), a history of intra-orbital metal fragments that have not been removed, and weight or girth that exceeds scanner capabilities
33. Previous medical PET, SPECT, abdominal or thoracic CT examination within 12 months
34. Having worked as a metal worker or welder

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	06-05-2024
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BI 456906
Generic name:	BI 456906
Product type:	Medicine
Brand name:	Wegovy
Generic name:	semaglutide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-01-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-515417-17-00
EudraCT	EUCTR2021-000363-76-NL
CCMO	NL82814.018.22