A Phase 2A, Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Efficacy of TRC150094 in Increasing Insulin Sensitivity in Male patients with increased Cardiometabolic Risk

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To determine the safety and efficacy (in increasing insulin sensitivity) of TRC 150094 once daily dosing for 4 weeks in male subjects with increased cardiometabolic risk.To evaluate the effect of TRC150094 on hepatic fat and metabolic parameters.To...

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

Summary

ID

NL-OMON36735

Source
ToetsingOnline

Brief title
The Torrent study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
cardiometabolic risk, obesity

Research involving
Human

Sponsors and support

Primary sponsor: Torrent Pharmaceuticals Limited
Source(s) of monetary or material Support: Torrent Pharmaceuticals;Gujarat;India

Intervention

Keyword: Cardiometabolic risk, Hyperinsulinemic euglycemic clamp, Insulin sensitivity, Thyroid hormone

Outcome measures

Primary outcome

Insulin Sensitivity:

* Rate of Glucose Disposal

* Suppression of Endogenous Glucose Production

* Suppression of rate of lipolysis

Secondary outcome

Early efficacy markers that will be explored include:

* Hepatic fat

* Lipid parameters

* Metabolic markers

Study description

Background summary

The incidence of visceral adiposity and the related comorbidities are increasing worldwide, leading to increased burden of cardiovascular risk in general population. Cardiometabolic risk which is the overall risk of cardiovascular disease (CVD) and diabetes resulting from the presence of the non-traditional risk factors and also of traditional risk has been described as

a plausible target for treatment. To date, pharmacological agents for the management of Cardiometabolic risk have been limited and unsatisfactory. TRC150094 is a novel thyromimetic analogous to 3.5-diiodothyronine (T2) being developed by Torrent for the treatment of Cardiometabolic risk associated with visceral adiposity.
In various preclinical studies conducted in multiple animal models of visceral adiposity, insulin resistance and metabolic syndrome, it was found that TRC150094 increases energy expenditure through increase in mitochondrial metabolic activity and attenuates visceral adiposity, atherogenic dyslipidemia, blood pressure and improved insulin sensitivity. If these effects are replicated in clinical setting, this profile will prove invaluable in the treatment of Cardiometabolic risk associated with visceral adiposity. We therefore propose to investigate the safety and efficacy of TRC150094 in increasing insulin sensitivity in male subjects with an increased cardiometabolic risk

Study objective

To determine the safety and efficacy (in increasing insulin sensitivity) of TRC 150094 once daily dosing for 4 weeks in male subjects with increased cardiometabolic risk.
To evaluate the effect of TRC150094 on hepatic fat and metabolic parameters.
To evaluate the ethnic differences for effect of TRC 150094 on Insulin sensitivity parameters

Study design

This will be a Phase 2A, two-centre, double-blind, placebo-controlled, multiple-dose study to assess the effect of multiple oral doses of TRC150094 on insulin sensitivity in 40 overweight/obese male subjects.20 Subjects will be enrolled in India and another 20 subjects at Amsterdam, the Netherlands. The maximum duration of participation in the study for each subject will be 9.5 weeks including a *4 weeks screening period, 4 weeks of treatment and a 10 days post treatment follow-up evaluation period .

At each study site 20 subjects will be enrolled. Each subject will attend the study centre in a fasting state, for a screening visit, 2 study visits (one baseline and one end of treatment), 1 intermediate safety visit and 1 post-study follow-up visit (Total 5 visits). The subjects at each site will be randomized to receive TRC150094 or placebo in a ratio of 1:1. The tentative dose level is 50 mg to be administered OD (morning) under fasting conditions. Dosing will take place daily on Days 1-*28. Subjects will arrive at the study centre for screening visit. Physical examination, vital signs, safety biochemistry and laboratory investigations for verification of inclusion/ exclusion criteria will be performed during screening visit. Subjects meeting all the inclusion criteria and none of the exclusion criteria and who have

given their informed consent for the study will be asked to come for the study on Day 0 (or day -1 if required). Baseline investigations (including baseline clamp procedure and hepatic MRS) will be done on Day 0 (or day -1). Subjects will receive properly labelled bottle containing either Active treatment or Placebo as per the randomization number of the subject. Subjects will be asked to take the dose (tentatively 50mg) OD in the morning on Days 1-28 inclusive, in fasting conditions, with a glass of water. Drug compliance of at least 90% will be ensured. Hence the allowable limit of missing the dose should not be more than 3 days in total. Discontinuation should not be of more than 2 consecutive days at any point of time. Uniformity in timing of intake of medication will be advised which should be preferably within ± 1 hr of the time of intake of study medication on Day 1. Each subject will attend the study centre on Day 14 for safety investigations. A deviation of ± 1 day will be allowed for these visits. Subjects will attend the study centre again on Day 28 for clamp procedure and hepatic MRS. After 10 days subjects will return to the study centre for a post treatment follow-up visit. It is planned that the study will take place over 6 months (including screening and follow-up periods).

Intervention

Subjects will be treated with either TRC150094 tablets of 50 mg or placebo once a day for 28 days.
Venapunction will be performed three times
All subjects will undergo a hyperinsulinemic euglycemic clamp twice.

Study burden and risks

This study does not have specific advantages for the study subjects. The results of this study may help researchers learn whether TRC150094 may be beneficial for the treatment of male subjects with increased cardiometabolic risk. [The most important adverse event of the study drug is headaeche. 6,6-2H2] glucose is glucose labeled with a stable isotope of hydrogen, which behaves as the natural substrate and has no side effects. [2H5] labelled glycerol is glycerol labeled with 5 stable isotope of hydrogen, which behaves as the natural substrate and has no side effects. Actrapid is fast acting insulin, a hormone that could induce hypoglycemia. However, it is not in the scope of this protocol to allow hypoglycemia to occur, since plasma glucose concentration will be fixed at 5 mmol/l by a variable infusion of glucose 20% guided by frequent bedside glucose measurements. An overview of the blood samples and blood volumes taken during the study is provided in Table 1. The total blood volume to be withdrawn from any individual subject will be 391 ml for subjects at Veeda Clinical Research, India and 361 ml at AMC, Netherlands. This amount is not considered to be of negative influence to the subject*s health. MR- spectroscopy of the liver will be made which takes about 30 minutes. This spectroscopy is not considered to be potentially harmful to subjects. An X-thorax will be performed during the screening visit, to exclude

TB-infection, in patients in India only. The radiation hazard of the X-thorax is 0.02 milliSievert per X-ray. For comparison: background radiation is 2 milliSievert per year for every person.

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

1. Adult male
2. Age range 30-65 years at screening
3. Caucasian or Indian Ethnicity
4. Waist circumference * 102 cm for Caucasians and * 90 cm for Indians at screening.27
5. Fasting Serum Insulin * 10 mU/ml at screening
6. Blood Pressure 130/85 mmHg at screening(or patients taking medication for hypertension)
7. Stable weight during 3 months prior to the study (assessed through medical history of the

patient)
8. Drug naïve diabetic patients* or patients with impaired fasting glucose i.e > 100 mg/dl or 5.5 mmol/l and < 200 mg/dl or 11.0 mmol/l. Diabetic patients who were taking metformin and have undergone washout for at least 4 weeks before Day 0 and are currently on life style modification as a treatment for diabetes will also be allowed in the study

Exclusion criteria

1. Medical history, physical examination, vital signs, clinical laboratory tests, 12-lead ECG and Chest X ray (in India only) with any significant abnormalities, in the opinion of the investigator.
2. Subjects with any known somatic illness
3. Subject currently using medication, which can influence glucose or FFA metabolism such as fibrates, niacin, ACE inhibitors, PPAR agonists, omega 3 fatty acids.
4. eGFR < 60 mL/min/1.73m2 at screening
5. History of angina, Myocardial Infarction (MI) or stroke since last 6 months.
6. Hypertension with SBP/DBP *160/100 mm Hg at screening.
7. ALT or AST * ULN*3 at screening
8. Heavy smokers (who are smoking >15 cigarettes or equivalent per day).

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:	Recruiting
Start date (anticipated):	01-10-2011
Enrollment:	20

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TRC 150094
Generic name:	thyromimetic analogous to 3.5-diiodothyronine (T2)

Ethics review

Approved WMO Date:	20-05-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2011
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
EudraCT	EUCTR2010-024036-42-NL
CCMO	NL34800.018.11