A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Doses of ISIS 325568 Administered to Healthy Volunteers

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Primary:To evaluate the safety of a single subcutaneous injection of ISIS 325568 administered at four increasing dose levels (50, 100, 200, 400 mg/week) and to evaluate the safety and tolerability of multiple doses of ISIS 325568 (three intravenous...

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

Summary

ID

NL-OMON31095

Source
ToetsingOnline

Brief title
Antisense glucagon receptor in healthy volunteers

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes mellitus, disorder with hyperglycemia

Research involving
Human

Sponsors and support

Primary sponsor: ISIS Pharmaceuticals
Source(s) of monetary or material Support: ISIS pharmaceuticals

Intervention

Keyword: diabetes, glucagon, glucose homeostasis, healthy volunteers

Outcome measures

Primary outcome

Tolerability of ISIS 325568

PK of ISIS 325568

Effects of ISIS 325568 (hepatic glucose production)

Secondary outcome

NA

Study description

Background summary

Pharmacological antagonism of glucagon action has been investigated non-clinically as a potential therapeutic approach for type 2 diabetes. Both peptide antagonists as well as monoclonal antibodies against glucagon receptor have been shown to attenuate hyperglycemia in animal models.
Development of small molecules against the glucagon receptor has been slow due to issues with pharmacokinetics, selectivity, cross species differences and lack of sustained effects after non-competitive blockade (McCormack et.al. 2001). Only a single Phase 1 study has been published that describes the acute effects of a small molecule glucagon receptor inhibitor in man (Petersen et.al. 2001).
Antisense compounds such as ISIS 325568 is a very potent antisense inhibitor of the human glucagon receptor. After systemic administration, the primary mechanism of ISIS 325568 is to reduce hepatic and adipose tissue glucagon receptor abundance. Preclinical data indicate that the antidiabetic effects of

ISIS 325568 will likely be due to a dual mechanism (i) Reduction of hepatic glucose output that is due to attenuation of glucagon action in the liver, and (ii) A secondary increase in active GLP-1, which occurs due to increased processing of preproglucagon in the pancreas.

Study objective

Primary:
To evaluate the safety of a single subcutaneous injection of ISIS 325568 administered at four increasing dose levels (50, 100, 200, 400 mg/week) and to evaluate the safety and tolerability of multiple doses of ISIS 325568 (three intravenous doses during Study Week 1, followed by once weekly subcutaneous administration for 5 weeks) at each of the four dose levels.
Secondary:
To evaluate the pharmacokinetic profile of ISIS 325568 given subcutaneously and intravenously at each of the dose levels.
To evaluate the pharmacodynamics of ISIS 325568 given for six weeks.

Study design

Double-Blind, Placebo-Controlled, Dose-Escalation Study

Intervention

ISIS 325568 or placebo

Study burden and risks

As with each first in human study there are risks associated with this study. The risk however are considered small and manageable because there is a carefull dose escaltion, regular monitoring and experience with antisense compounds of the same generation.
The burden for the volunteers depends on the phase of the study in which they participate. It ranges from participating in a part of the study in which a single dose is adminsitered and a relatively short observation period is scheduled until a demanding phase with multiple administrations, long study days (with 2 glucagon challenges and fat biopsies and a long observation period.
These experiments have been performed earlier at CHDR and are generally well tolerated by the volunteers.

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. healthy subjects of either gender aged between 18-65 years
2. Females must be non-pregnant and non-lactating, and either surgically sterile (hysterectomy, oophrectomy, or tubal ligation) or postmenopausal. Males must be surgically sterile, abstinent or if engaged in sexual relations of child-bearing potential, subject or partner must be using an acceptable contraceptive method during the trial and for 9 weeks after the last dose of study drug.
3. Give written informed consent to participate in study and availability for all study requirements
4. Fasting plasma glucose <= the upper limit of the laboratory*s reference range
5. HbA1C <= ULN
6. BMI < 30 kg/m2

Exclusion criteria

1. Clinically significant abnormalities in medical history or physical examination
2. Abnormalities on laboratory examination (ALT > ULN, AST > ULN, bilirubin > ULN, creatinine > ULN, urine protein positive by urine dipstick, platelets < lower limit of normal and any other clinically significant laboratory findings)
3. History of clinically significant abnormalities in coagulation parameters
4. Positive test result for HIV, hepatitis B virus, and/or hepatitis C virus
5. Active infection requiring antiviral or antimicrobial therapy
6. Subjects on chronic or acute prescription medication may be permitted after discussion with the Isis Medical Monitor.
7. Malignancy (with the exception of basal or squamous cell carcinoma of the skin if adequately treated and no recurrence for > 1 year)
8. Any other concurrent condition which, in the opinion of the Investigator, would preclude participation in this study or interfere with compliance
9. History of alcohol or drug abuse
10. Undergoing or have undergone treatment with another investigational drug, biologic agent or device within 90 days prior to Screening.
11. Blood donation within three months of screening

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):	20-08-2007
Enrollment:	56
Type:	Actual

Ethics review

Approved WMO Date:	14-08-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-08-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-01-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2007-000235-25-NL
CCMO	NL17359.000.07