A Phase I study to evaluate a single oral dose of SRT2379 on the endotoxin induced inflammatory response in healthy male subjects

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Primary objective: To determine if a single dose of SRT2379 attenuates the inflammatory response in normal healthy male subjects after exposure to low-dose endotoxin (LPS)
Secondary objectives: (1) To determine PK of SRT2379 in normal healthy male...

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

Summary

ID

NL-OMON36662

Source
ToetsingOnline

Brief title
Effect of SRT2379 on endotoxin-induced inflammation

Condition

- Other condition
- Ancillary infectious topics

Synonym
Inflammation, innate immunesystem

Health condition

Door endotoxine veroorzaakte inflammatie reactie

Research involving
Human

Sponsors and support

Primary sponsor: Sirtris Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Sirtris Pharmaceuticals Inc

Intervention

Keyword: Endotoxin, Inflammation, SIRT1, SRT2379

Outcome measures

Primary outcome

Primary study endpoints include clinical signs and symptoms and laboratory parameters for inflammation (cytokines, activation of leukocytes, coagulation and vascular endothelium).

Secondary outcome

Secondary endpoints include pharmacokinetics and safety recordings.

Exploratory endpoints include lipid profiles, acute phase proteins, metabolic profiles and gene expression analysis from white blood cells.

Study description

Background summary

Activation of SIRT1 (silent information regulator transcript) results in inhibition of inflammation. SRT2379 is a potent small molecule activator of SIRT1 that has been found to inhibit systemic inflammation induced by intravenous injection of lipopolysaccharide (LPS) in mice. SRT2379 may be a novel compound in the treatment of inflammatory disorders in man.

Study objective

Primary objective: To determine if a single dose of SRT2379 attenuates the inflammatory response in normal healthy male subjects after exposure to

low-dose endotoxin (LPS) Secondary objectives: (1) To determine PK of SRT2379 in normal healthy male subjects exposed to low-dose endotoxin (LPS); (2) To determine the safety profile of SRT2379 in healthy male subjects exposed to low-dose endotoxin (LPS) Exploratory objectives: To determine the effect of SRT2379 on other parameters following low-dose endotoxin (LPS) exposure in humans i.e. lipid profile, serum amyloid phospholipids, metabolic profiles and gene expression analysis etc.

Study design

Single-blind, placebo-controlled intervention study

Intervention

This study consists of two treatment arms (N = 8 per arm). Subjects in arm one will receive one dose of SRT2379 (1.0 g). Subjects in arm two will receive one dose of placebo. Subjects will take SRT2379 or placebo approximately 15 minutes following consumption of a standardized meal. Subjects must wait 2 hours after dosing before consuming additional calories. All subjects will be given an intravenous dose of LPS (standardized LPS preparation provided by the National Institutes of Health (NIH), Bethesda, USA; 4 ng/kg body weight). LPS will be given 3 hours after SRT2379/placebo dosing.

Study burden and risks

The burden of this study involves a screening visit, two 2-nights admission to the clinical research unit, the ingestion of SRT2379 and the intravenous injection of LPS. Intravenous LPS induces a transient influenza-like/inflammatory syndrome in humans consisting of chills, fever, nausea, headache and muscle ache. SRT2379 has been well-tolerated at all dose levels investigated. In the current study the potential anti-inflammatory effects of SRT2379 will be tested in the human endotoxemia model. The risks are low, whereas the study will generate information regarding the anti-inflammatory activity of SRT2379. This knowledge may be of future benefit to patients with inflammatory diseases.

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

A subject will be eligible for inclusion in this study only if all of the following criteria apply:
1. Healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination and laboratory tests carried out within 21 days prior to day 1. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
2. Male between 18 and 35 years of age inclusive, at the time of signing the informed consent
3. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
4. Chemistry panel including renal and liver function tests without any clinically relevant abnormality as judged by the Investigator.
5. Subjects must agree to use double-barrier birth control or abstinence while participating in the study and for 7 days following the last dose of study drug

Exclusion criteria

1. Subject has had a major illness in the past three months or any significant chronic medial illness that the investigator would deem unfavourable for enrolment including inflammatory

diseases
2. Subjects with a history of any type of malignancy with the exception of successfully treated basal cell cancer of the skin
3. Subject has a past or current gastro-intestinal disease which may influence drug absorption
4. The subject has a known positive test for hepatitis C antibody or hepatitis B surface antigen or human immunodeficiency virus (HIV) antibody 1 or 2.
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. Subject has a history, within three years, of drug abuse (including benzodiazepines, opioids, amphetamine, cocaine, THC) or a positive drug results at the Screening visit
7. History of alcoholism and/or is drinking more than 3 drinks per day. Alcoholism is defined as an average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits
8. The subject has participated in a clinical trial and has received an investigational product within three months of the first dosing day in the current study
9. Use of prescription or non-prescription drugs, and herbal and dietary supplements within 7 days unless in the opinion of the Investigator and Medical Monitor the medication will not interfere with the study procedures or compromise subject safety
10. Subject has difficultly in donating blood or accessibility of a vein in left or right arm
11. Subject has donated more than 350 mL of blood in last 3 months
12. Subject uses tobacco products
13. Any clinically relevant abnormality noted on the 12-lead ECG as judged by the Investigator or an average QTcB or QTcF < 450 msec
14. Any other issue that, in the opinion of the Principal Investigator, would could be harmful to the subject or compromise interpretation of the data
15. Prior participation in a trial where the subject received intravenous endotoxin (LPS) infusion

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2011
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	SRT2379
Generic name:	SRT2379

Ethics review

Approved WMO Date:	21-12-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2011
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	EUCTR2010-023118-30-NL
CCMO	NL34753.018.10