A Phase I study to evaluate single and multiple (seven) oral doses of SRT2104 on the endotoxin induced inflammatory response in healthy male subjects

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Primary objective: To determine if (a) single or (b) 7 daily doses of SRT2104 attenuates the inflammatory response in normal healthy male subjects after exposure to low-dose endotoxin (LPS)Secondary objectives: (1) To determine PK of SRT2104 in...

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

Summary

ID

NL-OMON32755

Source
ToetsingOnline

Brief title
Effect of SRT2104 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: Een bedrijf: Sirtris Pharmaceuticals Inc

Intervention

Keyword: Endotoxin, Inflammation, SIRT1, SRT2104

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. SRT2104 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. SRT2104 may be a novel compound in the treatment of inflammatory disorders in man.

Study objective

Primary objective: To determine if (a) single or (b) 7 daily doses of SRT2104 attenuates the inflammatory response in normal healthy male subjects after

exposure to low-dose endotoxin (LPS)
Secondary objectives: (1) To determine PK of SRT2104 in normal healthy male subjects exposed to low-dose endotoxin (LPS); (2) To determine the safety profile of SRT2104 in healthy male subjects exposed to low-dose endotoxin (LPS)
Exploratory objectives: To determine the effect of SRT2104 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

Double-blind, placebo-controlled intervention study

Intervention

This study consists of three treatment arms (N = 8 per arm). Subjects in arm one will receive once daily doses of SRT2104 (2.0 g/day) for seven consecutive days. Subjects in arm two will receive once daily doses of placebo for seven consecutive days. Subjects in arm three will receive once daily doses of placebo on Days 1-6 and a single dose of SRT2104 (2.0 g/day) on Day 7. Test material administration (SRT2104 or placebo) will occur on all days during the study, i.e., from Day 1 to Day 7 inclusive. Subjects will take SRT2104 or placebo approximately 15 minutes following consumption of a standardized meal on all dosing days. Subjects must wait at least 1-2 hours after dosing before consuming additional calories. On day 7, 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 dosing.

Study burden and risks

The burden of this study involves a screening visit, two 2-nights admissions to the clinical research unit, the ingestion of SRT2104 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. SRT2104 has been well-tolerated following both the single and multiple dose periods at all dose levels investigated. In the current study the potential anti-inflammatory effects of SRT2104 will be tested in the human endotoxemia model. The risks are low, whereas the study will generate information regarding the anti-inflammatory activity of SRT2104. 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 28 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. No history of HIV 1 and 2, and hepatitis B and C
5. Normal 12 lead ECG without any clinically significant abnormality as judged by the Investigator and average QTcB or QTcF < 450 msec
6. Normal renal and liver function (normal serum creatinine and liver function tests (ALT, AST, Total bilirubin, alkaline phosphatase)

7. Subjects must agree with their partners to use double-barrier birth control or abstinence while participating in the study and for 12 weeks following the last dose of study drug

Exclusion criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study: As a result of the medical interview, physical examination or screening investigations, the Investigator or appropriately qualified designee considers the subject unfit for the study.;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 renal impairment
4. Subject has a past or current gastro-intestinal disease which may influence drug absorption
5. The subject has a known positive test for hepatitis C antibody or hepatitis B surface antigen
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
7. The subject has a known positive test for HIV antibody 1 or 2
8. 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
9. 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
10. 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
11. 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.
12. Subject has difficultly in donating blood or accessibility of a vein in left or right arm.
13. Subject has donated more than 350 mL of blood in last 3 months
14. Subject uses tobacco products
15. Any other issue that, in the opinion of the Principal Investigator, would could be harmful to the subject or compromise interpretation of the data

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:	Pending
Start date (anticipated):	01-11-2009
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	SRT2104
Generic name:	SRT2104

Ethics review

Approved WMO

Date:	13-11-2009
Application type:	First submission
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	EUCTR2009-014157-32-NL
CCMO	NL29509.018.09
Other	NTR; nummer volgt nog