Effect of SRT2104 on endotoxin-induced inflammation.

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Activation of SIRT1 (silent information regulator transcript) results in inhibition of inflammation in humans.

Ethische beoordeling	Niet van toepassing
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21773

Bron
NTR

Verkorte titel
LPS-SRT2104 study

Aandoening

Gram negative infection, Sepsis, Lipopolysaccharide, SRT21040, Sirtuins, innate immunity

Ondersteuning

Primaire sponsor: Academic Medical Center (AMC), Center of Experimental Molecular Medicine
Overige ondersteuning: Sirtris Pharmaceuticals, Inc.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:
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.

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 e.g., lipid profile, serum amyloid phospholipids, metabolic profiles and gene expression analysis etc.

Study design:
Double-blind, placebo-controlled intervention study.

Study population:
24 healthy male subjects (18-35 years).

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.

Main study parameters/endpoints:

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

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
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.

Doel van het onderzoek

Activation of SIRT1 (silent information regulator transcript) results in inhibition of inflammation in humans.

Onderzoeksopzet

1. Medication or placebo intake:
Day 1 – day 7, 7:00 AM.

2. Endotoxin (LPS, 4 ng/kg) administration:
Day 7 at 10 AM (3 hours after last medication or placebo intake).

3. Measurements (Blood, urine, ECG, physical examination):
Day 1-2 and day 6-8.

Onderzoeksproduct en/of interventie

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Known diseases;

2. A history of smoking within the last six months, or regular consumption of greater than three units of alcohol per day;

3. Administration of any investigational drug within 30 days of study initiation;

4. Donation of blood within 60 days, or loss of greater than 400 ml of blood within 12 weeks of study initiation;

5. History of enhanced bleeding tendency;

6. History of heparin-induced thrombocytopenia;

7. History of serious drug-related reactions, including hypersensitivity.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-11-2009
Aantal proefpersonen:	24
Type:	Verwachte startdatum

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1859
NTR-old	NTR1971

Register	ID
Ander register	Sirtris Pharmaceuticals, Inc. : SRT-2104-010
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A