Randomized, double-blind, placebo-controlled study of the tolerability and pharmacokinetics of ascending single (TDU6964) and 14-day repeated (TDR6966) oral doses of SAR501788 and pilot food variability evaluation (FED6965) in healthy young male subjects - Tolerability and pharmacokinetics of 14-day repeated oral doses of SAR501788 in healthy elderly male and female subjects (TDR6967)

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to assess the tolerability and safety after single oral ascending doses of SAR501788 in healthy young male subjects (Part 1)to assess the tolerability and safety after repeated oral ascending doses of SAR501788 in healthy young male subjects (Part 3...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON32736

Source
ToetsingOnline

Brief title
SAR 501788 SRD/MRD/FE/elderly study

Condition

- Peripheral neuropathies

Synonym
neuropathies nerve pain

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sanofi-Aventis

Intervention

Keyword: FIM, Food effect, Multiple rising dose, Single rising dose

Outcome measures

Primary outcome

Criteria for evaluation

Pharmacodynamics :plasma renin, AcSDKP and aldosterone and plasma pregnenolone,

pregnenolone sulfate, testosterone, DHEA, DHEA sulphate and serum prolactin

(Parts 3 and 4)

Pharmacokinetics :plasma and urine SAR501788 concentrations, urine 6-beta-OH

cortisol and cortisol concentration, pharmacokinetic parameters

Safety :adverse events, vital signs, ECG-parameters, laboratory parameters,

physical examination, telemetry, oral body temperature

Statistical methods

Pharmacodynamic parameters :descriptive statistics (Parts 3 and 4)

Pharmacokinetics parameters :descriptive statistics

Safety parameters :descriptive statistics

Secondary outcome

NA

Study description

Background summary

The drug to be given is a new, investigational compound that may eventually be used for the treatment of diabetic and anticancer drug induced-neuropathies. SAR501788 is a novel drug that selectively binds to a specific receptor in nerves; peripheral benzodiazepine receptor (PBR). In laboratory and animal studies SAR501788 has shown to help slow down the development of nerve damage caused by diabetes (diabetic peripheral neuropathy) and to protect certain nerves from damage by some particular anti-cancer drugs. SAR501788 therefore, is expected to may help treating neuropathies (damage to nerves) caused by diabetes or anti-cancer drugs.
This study consists of 4 parts. Part 1 is a single rising dose part, in Part 2 the effect of food in combination with the drug will be investigated. In Part 3 and 4 the effects of the drug when taken in 14-day repeated ascending doses will be investigated. Part 3 is in younger men and Part 4 in elderly men and women.

Study objective

to assess the tolerability and safety after single oral ascending doses of SAR501788 in healthy young male subjects (Part 1)
to assess the tolerability and safety after repeated oral ascending doses of SAR501788 in healthy young male subjects (Part 3)
to assess the pharmacokinetic parameters after single (Part 1) and repeated oral ascending doses of SAR501788 (Part 3) in healthy young male subjects
to assess the tolerability and safety after repeated oral ascending doses of SAR501788 in healthy elderly male and female subjects (Part 4)
to asses the pharmacokinetic (PK) parameters after repeated oral ascending doses of SAR501788 in healthy elderly male and female subjects (Part 4)
to obtain preliminary information on the effect of a high fat meal on the pharmacokinetics of SAR501788 in healthy young male subjects (Part 2)
to provide preliminary information regarding the potential renal excretion of

the compound
(Parts 1, 3 and 4)
to evaluate the potential of SAR501788 1) to induce CYP3A4, 2) to interact with the Renin Angiotensin Aldosterone System, 3) to alter steroid hormone levels
(Parts 3 and 4)

Study design

Part 1 (TDU6964)
Design :
a double-blind, randomized, placebo-controlled, sequential single ascending dose part with seven cohorts of eight subjects each receiving a single oral dose of SAR501788 or placebo (six verum and two placebo)

Procedures and assessments
Screening and follow-up :
clinical laboratory (including INR and aPTT), physical examination, vital signs (supine and standing), oral body temperature, body weight, 12-lead ECG; at eligibility screening: height, medical history, alcohol and drug screen, HBsAg, anti HCV, anti-HIV 1/2; physical examination, body weight, alcohol and drug screen, vital signs (supine and standing), oral body temperature, 12-lead ECG and clinical laboratory (including INR and aPTT) to be repeated upon admission

Observation period :
one period in clinic from -24 h up to 48 h after drug administration

Blood sampling :
for pharmacokinetics of SAR501788: 0.5 h pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 h post-dose
for genotyping and archival blood sampling: 0.5 h pre-dose

Urine sampling :
for pharmacokinetics of SAR501788: pre-dose and intervals 0-24 h and 24-48 h post-dose

Safety assessments :
adverse events: throughout the study; physical examination: 48 h post-dose; vital signs (supine and standing): 0.5 h pre-dose and 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose; oral body temperature: 0.5 h pre-dose and 24 h post-dose; 12-lead ECG: 0.5 h pre-dose (in triplicate) and 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose; clinical laboratory (including INR and aPTT): 24 and 48 h post-dose; telemetry: from 24 h pre-dose until 12 h post-dose

Bioanalysis :
analysis of plasma and urine SAR501788 samples using validated methods by Sponsor

Part 2 (FED6965)
Design :
an open label, randomized, two-way crossover part in eight healthy male subjects receiving a single oral dose of SAR501788 in the fed state in one period and a single oral dose of SAR501788 in the fasted state in the other period; a washout of seven days between dosing

Procedures and assessments
Screening and follow-up :
clinical laboratory (including INR and aPTT), physical examination, vital signs (supine and standing), oral body temperature, body weight, 12-lead ECG; at eligibility screening: height, medical history, alcohol and drug screen, HBsAg, anti HCV, anti-HIV 1/2; physical examination, body weight, alcohol and drug screen, vital signs (supine and standing), oral body temperature, 12-lead ECG and clinical laboratory (including INR and aPTT) to be repeated upon each admission

Observation period :
2 periods, each period in clinic from -24 h up to 48 h after drug administration

Blood sampling :
for pharmacokinetics of SAR501788: 0.5 h pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 h post-dose
for genotyping and archival blood sampling: 0.5 h pre-dose (period 1 only)

Safety assessments :
adverse events: throughout the study; physical examination: 24 and 48 h post-dose; vital signs (supine and standing): 0.5 h pre-dose and 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose; oral body temperature: 48 h post-dose; 12-lead ECG: 0.5 h pre-dose (in triplicate) and 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h post-dose; clinical laboratory: 24 and 48 h post-dose; telemetry: from 24 h pre-dose until 12 h post-dose

Bioanalysis :
analysis of plasma and urine SAR501788 samples using validated methods by Sponsor

Parts 3 (TDR6966) and 4 (TDR6967)
Design :

Part 3: a double-blind, randomized, placebo-controlled, sequential fourteen day repeated ascending dose part with three cohorts of twelve healthy male subjects each receiving oral doses of SAR501788 or placebo (nine verum and three placebo) for fourteen days

Part 4: a double-blind, randomized, placebo-controlled, sequential fourteen day

repeated ascending dose part with two cohorts of twelve healthy elderly male and female subjects each (at least five of each gender in each dose group) receiving oral doses of SAR501788 or placebo (nine verum and three placebo) for fourteen days
Procedures and assessments

Screening and follow-up :
clinical laboratory (including INR and aPTT), physical examination, vital signs, oral body temperature, body weight, 12-lead ECG; at eligibility screening: height, medical history, alcohol and drug screen, HBsAg, anti HCV, anti-HIV 1/2; physical examination, body weight, alcohol and drug screen, vital signs (supine and standing), oral body temperature, 12-lead ECG and clinical laboratory (including INR and aPTT) to be repeated upon admission

Observation period :one period in clinic from -41 h before drug administration on Day 1 up to 48 h after drug administration on Day 14

Blood sampling :
for pharmacokinetics of SAR501788: 0.5 h pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 16 h post-dose on Day 1, pre-dose on Days 2, 3, 4, 7, 8, 11 and 13 and pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 h post-dose on Day 14
for pharmacodynamics of plasma pregnenolone, pregnenolone sulphate, testosterone, DHEA, DHEA sulphate and serum prolactin and plasma renin, AcSDKP and aldosterone: 22, 20 and 16 h pre-dose and pre-dose and 2, 4 and 8 h post-dose on Day 1, pre-dose on Day 2 and pre-dose and 2, 4, 8 and 24 h post-dose on Day 14

for genotyping and archival blood sampling: pre-dose on Day 1

Urine sampling :
for pharmacokinetics of SAR501788: pre-dose on Day 1 and pre-dose until 24 h post-dose on Day 14
for 6-beta-OH cortisol and cortisol: from 24 h pre-dose until pre-dose on Day 1 and from pre-dose until 24 h post-dose on Day 14

Safety assessments :
adverse events: throughout the study; physical examination: pre-dose on Days 2 and 7 and 0.5 h pre-dose and 48 h post-dose on Day 14; vital signs: pre-dose and 1, 2, 3, 4, 6, 8 and 12 h post-dose on Day 1, pre-dose and 2 h post-dose on Days 2-13, 0.5 h pre-dose and 1, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dose on Day 14; oral body temperature: 0.5 h pre-dose and 4 and 8 h post-dose on Day 1, pre-dose on Days 2 and 7 and 0.5 h pre-dose and 4, 8 and 48 h post-dose on Day 14; 12-lead ECG: pre-dose (in triplicate) and 1, 2, 3, 4, 6, 8 and 12 h post-dose on Day 1, pre-dose and 2 h post-dose on Day 2, pre-dose on Days 4, 7, 11 and 0.5 h pre-dose and 1, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dose on Day 14 (all time points on Days 14 and 15 in triplicate); clinical laboratory:

pre-dose on Days 2, 4, 7 and 11 and 0.5 h pre-dose and 24 h post-dose on Day 14; telemetry: from 24 h pre-dose until 12 h post-dose on Day 1 and from pre-dose until 12 h post-dose on Day 14

Bioanalysis :
analysis of plasma and urine SAR501788 samples using validated methods by Sponsor
analysis of urine 6-beta-OH cortisol and cortisol using a validated method by Sponsor
analysis of plasma pregnenolone, pregnenolone sulphate, DHEA, DHEA sulphate and plasma renin, AcSDKP and aldosterone using validated methods by Sponsor
analysis of serum prolactin and plasma testosterone using clinical laboratory methods by Sponsor

Study burden and risks

Procedures: pain, light bleeding, haematoma.

As SAR501788 will be administered to man for the first time in this study, adverse effects in man have not been reported up to now. In animal studies, in which SAR501788 was administered daily in (very) high doses,no target organ toxicity was induced by SAR501788 following repeated administrations at doses of up to 2000mg/kg/day in rat, monkey or dog for up to 1 month. Apart from white material in the feces (consistent with unabsorbed compound) in all species, the only other effect seen was slight transient weight loss in monkeys during the first week of the 1 month study.

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 male subjects, between 18 and 45 years inclusive.
2. Body weight between 50.0 and 95.0 kg inclusive, body mass index between 18.0 and 28.0 kg/m2 inclusive
10. Healthy male or post-menopausal female subjects, between 60 and 75 years of age inclusive.
11. Body weight between 50 kg and 105 kg if male, between 40 kg and 95 kg if female, body mass index between 18 and 33 kg/m2.

Exclusion criteria

Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, psychiatric, systemic, ocular or infectious disease, or signs of acute illness.
2. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month).

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-08-2008
Enrollment:	152
Type:	Actual

Ethics review

Approved WMO Date:	24-06-2008
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-07-2008
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-07-2008
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-09-2008
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-09-2008
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2008
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-10-2008
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-03-2009
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2009
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2008-001627-65-NL
CCMO	NL23897.056.08