Rising Single Dose Safety, Tolerability and Pharmacokinetic Study of SCH 900229 in Healthy Adult Subjects

Published: 30-11-2009
Last updated: 04-05-2024

- to evaluate the safety and tolerability of a single oral dose of SCH 900229 administered to healthy adult volunteers- to characterize the pharmacokinetic (PK) profile of SCH 900229 in plasma of healthy adult volunteers after a single oral dose- to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cognitive and attention disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON34885

Source
ToetsingOnline

Brief title
SCH 900229 SAD study

Condition

- Cognitive and attention disorders and disturbances

Synonym
Alzheimer's disease

Research involving
Human

Sponsors and support

Primary sponsor: Schering-Plough
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Alzheimer, SCH 900229

Outcome measures

Primary outcome

Pharmacodynamics: A*40 concentrations in plasma

Pharmacokinetics: SCH 900229 concentrations in plasma, metabolite profiling in plasma and urine, pharmacokinetic parameters

Safety: adverse events, vital signs, ECG-parameters, laboratory parameters (including Hes 1 gene expression and PHF-based Notch signalling), physical examination

Secondary outcome

N/A

Study description

Background summary

The drug to be given, SCH900229, is a new investigational compound that may eventually be used for the treatment of Alzheimer*s disease. This compound is still in the development phase. Alzheimer*s disease is characterized by specific plaques in the brain, composed primarily of certain proteins. These plaques contribute to the progress of the disease. The experimental drug used in this study, SCH900229, has shown (in animals) to significantly reduce this specific protein in the blood, brain and spinal fluid with possible beneficial effects on disease course in Alzheimer*s disease, both on the effects on the nervous system and on complaints.

Study objective

- to evaluate the safety and tolerability of a single oral dose of SCH 900229 administered to healthy adult volunteers
- to characterize the pharmacokinetic (PK) profile of SCH 900229 in plasma of healthy adult volunteers after a single oral dose

- to evaluate the potential effects of a high fat diet on the safety, tolerability, bioavailability and pharmacokinetics of SCH 900229 administered to healthy adult volunteers as a single oral dose
- to evaluate the relative bioavailability of SCH 900229 when administered as blend in capsule formulation
- to evaluate the relative bioavailability of SCH 900229 when administered as an active (liquid emulsion) in capsule formulation
- to explore the utility of whole blood Hes1 gene expression levels as a safety biomarker
- to explore the utility of pooled hair follicle-based Notch signalling gene expression levels as a safety biomarker.

Study design

Design:
a randomized, placebo-controlled, third party blind, rotating panel, single ascending dose study with four cohorts of ten healthy male and/or female (postmenopausal/sterilized) subjects each receiving a single oral dose of SCH 900229 or placebo (eight verum and two placebo) in three periods(two periods for Cohort 4); in the third period one cohort will receive SCH 900229 after a high fat meal, the other two panels will receive SCH 900229 in capsule form; one panel will receive a blend in capsule formulation and the other an active liquid emulsion in capsule formulation; a washout of approximately two weeks between successive dose levels; in the first dose level two subjects will be dosed at least one day prior to the rest of the cohort (one verum and one placebo).

Procedures and assessments
Screening and follow-up:
clinical laboratory, occult blood, vital signs (including oral temperature), physical examination, 12-lead ECG; at eligibility screening: medical history, elbow breadth measurement, height, weight, drug screen, FSH and estradiol (females only), HBsAg, anti HCV, anti-HIV 1/2 and pregnancy test (females only); drug screen, clinical laboratory, 12-lead ECG and vital signs (including oral temperature) to be repeated upon each admission.

Observation period:
3 periods (2 periods for Cohort 4), first and second period in clinic from -17 h up to 72 h after drug administration followed by ambulatory visits on Days 6 and 8 and third period in clinic from -17 h up to 72 h after drug administration with optional ambulatory visits on Days 6 and 8.

Blood sampling:
for pharmacokinetics of SCH 900229 in plasma: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, 48, 72 (all periods), 120 (Periods 1 and 2 only) and 168 h (Periods 1 and 2 only, optional in period 3) post-dose
for pharmacodynamics of A*40 in plasma: pre-dose and 1, 2, 4, 6, 10, 14, 24, 48

and 72 h post-dose and once on Day 8 (Periods 1 and 2 only)
for metabolite profiling in plasma: pre-dose and 1, 3, 6, 12, 24, 36, 48, 72 and 120 h post-dose (Period 2 only)
for Hes1 gene expression: once on Days -1 to 4 and once on Day 8 (Periods 1 and 2)
for genotyping: pre-dose (Period 1 only)

Urine sampling:
For metabolite profiling: pre-dose and interval 0-48 h post-dose (in 24 h block intervals; Period 2 only).

Hair sampling:
15 hair follicles will be collected at Predose (0 hour), and at 8, 24, 48, and 72 hours post-dose. An additional sample will be collected on Day 8.

Safety assessments:
adverse events: throughout the study; clinical laboratory: pre-dose and once on Days 2-4 (all periods) and once on Day 8 (Periods 1 and 2); occult blood: on all stool samples from Days -1 to 4 (all periods) and once on Day 8 (Periods 1 and 2 only); 12-lead ECG: pre-dose and 1, 2, 4, 8, 12, 24, 48 and 72 h post-dose and once on Day 8 (Periods 1 and 2 only); vital signs (including oral temperature): pre-dose and 1, 2, 4, 8, 12, 24, 48 and 72 h post-dose (all periods) and once on Days 6 and 8 (Periods 1 and 2 only, optional for Period 3).

Bioanalysis:
- analysis of plasma SCH 900229 samples using a validated method by Sponsor
- analysis of plasma A*40 samples using a validate method by Sponsor
- genotyping by Sponsor
- metabolite profiling in plasma and urine using validated methods by Sponsor
- analysis of Hes1 gene expression using validated method by Sponsor

Intervention

Study Medication:
Active substance: SCH 900229
Activity: *-secretase (GS) inhibitor
Indication: Alzheimer*s disease (AD)
Strength: 0.1 and 1 mg/mL (oral solution); 2 mg (powder capsule) and 12 mg (liquid emulsion capsule)
Dosage form: oral solution, powder capsule (Period 3) and liquid emulsion capsule (Period 3)

Treatments:
Cohort 1
Period 1: a single oral dose of A mg SCH 900229 or placebo on Day 1
Period 2: a single oral dose of D mg SCH 900229 or placebo on Day 1

Period 3: a single oral dose of G mg SCH 900229 or placebo on Day 1*

Cohort 2
Period 1: a single oral dose of B mg SCH 900229 or placebo on Day 1
Period 2: a single oral dose of E mg SCH 900229 or placebo on Day 1
Period 3: a single oral dose of H mg SCH 900229 or placebo on Day 1*

Cohort 3
Period 1: a single oral dose of C mg SCH 900229 or placebo on Day 1
Period 2: a single oral dose of F mg SCH 900229 or placebo on Day 1
Period 3: a single oral dose of I mg SCH 900229 or placebo on Day 1*

Cohort
Period 1: a single oral dose of J mg SCH 900229 or placebo on Day 1
Period 2: a single oral dose of K mg SCH 900229 or placebo on Day 1

*In this period subjects will participate in two formulations investigations and a food effect investigation. The assignment of investigations of (Food or Formulation) to a particular cohort will be determined based upon available PK, safety and tolerability results from previous periods and considerations

Formulation 1: SCH 900229 blend in capsule or placebo
Formulation 2: SCH 900229 active (liquid emulsion) in capsule or placebo
Food effect: SCH 900229 or placebo in the fed state

Study burden and risks

Procedures: pain, light bleeding, heamatoma, possibly an infection.

Medication: As SCH900229 will be administered to man for the first time in this study, adverse effects in man have not been reported up to now. In previous studies with mice, in which SCH900229 was administered daily in (very) high doses over a period of one month, an increase of mean body weight was observed. In previous studies with dogs (dosing for 8 days) there were abnormal stool findings in higher doses (lack of stool, soft/loose, red streaked stool). In a one month study with dogs these stool findings were also present.

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

Healthy men and women, between 30 and 65 years of age (inclusive), BMI between 18 and 30 kg/m2, no more cigarettes than 10 per day, female have been surgically sterilized for at least 3 months before screening or post-menopausal for at least one year.

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor (50 mL or more) within 60 days from the start of the study. In case of donating more than 1.5 liters of blood (for men) / more than 1.0 liters of blood (for women) in the 10 months preceding the start of this study.

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):	09-12-2009
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	30-11-2009
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-12-2009
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2010
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-05-2010
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	EUCTR2009-016665-28-NL
CCMO	NL30676.056.09