A double-blind, placebo controlled, randomized study to evaluate the safety, tolerability, pharmacokinetic profile and cytochrome P450 interaction potential of single and multiple doses of Tonabersat over the dose range of 240 mg to 480 mg in healthy adult subjects.

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to assess the single-dose safety, tolerability and pharmacokinetic profile of (6) individual doses of tonabersat ranging from 160 mg to 480 mg (or to dose-limiting toxicity (DLT)) in healthy subjects under the fasted or fed conditionsto assess the...

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

Summary

ID

NL-OMON36253

Source
ToetsingOnline

Brief title
SAD/MAD/DDI study.

Condition

- Headaches

Synonym
Migraine

Research involving
Human

Sponsors and support

Primary sponsor: Upsher-Smith Laboratories, Inc.
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Cytochrome P450, Tonabersat

Outcome measures

Primary outcome

Pharmacodynamics : cognitive and psychomotor performance

Pharmacokinetics : plasma tonabersat, SB-277726, midazolam and

1-hydroxymidazolam, metoprolol and

*-

hydroxymetoprolol, omeprazole plus 5'-hydroxy-omeprazole, caffeine

paraxanthine

and tolbutamide, 4-hydroxytolbutamide and carboxyltolbutamide concentrations,

pharmacokinetic

parameters

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

laboratory parameters, physical examination,

telemetry, suicidality, EEG parameters, audiometric parameters

Secondary outcome

Not applicable.

Study description

Background summary

The drug to be given tonabersat is a new, investigational compound that may eventually be used for the treatment of migraine. Migraine is a syndrome characterised by attacks of throbbing headache lasting from 4 to 72 hours (commonly around 24 hours) accompanied by nausea, vomiting and sensitivity to light and sounds. Tonabersat is a new compound which has broader spectrum of activity than the commonly used anti-migraine agent, sumatriptan. Additionally, tonabersat lacks some of the unwanted neurotoxic and cardiovascular effects that were seen with sumatriptan, which might make tonabersat a potentially good drug for the treatment of migraine.

Study objective

to assess the single-dose safety, tolerability and pharmacokinetic profile of (6) individual doses of tonabersat ranging from 160 mg to 480 mg (or to dose-limiting toxicity (DLT)) in healthy subjects under the fasted or fed conditions
to assess the multiple-dose safety, tolerability and pharmacokinetic profile of (3) individual dose levels of tonabersat at steady state via a multiple ascending dose, consecutive group study in healthy subjects in fasted of fed consitions (to be determined after the SAD)
to assess the potential of tonabersat to undergo pharmacokinetic drug-drug interactions using a *cocktail* of CYP probe substrates at one of the doses of tonabersat evaluated at steady state under fasted or fed conditions
to assess the pharmacodynamics of tonabersat on CNS function using EEG measurements and cognitive and psychomotor performance testing

Study design

Design:
A randomized, two-part, double-blind, placebo-controlled, single-, multiple-ascending dose drug-drug interaction study; Part 1 consists of six cohorts of 10 healthy male and female subjects each receiving a single oral dose of tonabersat or placebo (eight verum and two placebo); Part 2 , Cohorts 1-3, consists of three cohorts of 16 healthy male and female subjects each receiving an oral dose of tonabersat or placebo (twelve verum and four placebo) once daily for fourteen days and part 2, Cohort 4 (DDI) consists 1 cohort of 16 healthy male and female subjects each receiving an oral dose of tonabersat or placebo (14 verum and 2 placebo) once daily for fourteen days a single oral dose of midazolam, metoprolol, omeprazole, caffeine and tolbutamide on Days -1 and 13.

Procedures and assessments
Screening:
Medical history, demographic data (including body weight and height), genotyping (part 2, cohort 4), clinical laboratory (incl. TSH, T4), alcohol and drug screen, pregnancy, HBsAg, anti HCV, anti-HIV 1/2, HAVIgm, vital signs, body temperature, 12-lead electrocardiogram (ECG), EEG (part 2, Cohort 1-3), physical examination, adverse events from the signing of the Informed Consent Form, previous and concomitant medication.
Admission:
Drug and alcohol screen, AEs and concomitant medication.
Study drug administration.
Part 1/Cohort 1-6 and Part 2 Cohort 1-4. In Part 4 Cohort 4 CYP Probes.
Follow-up:
Clinical laboratory, vital signs, body temperature, ECG, physical examination, AEs and concomitant medication.
Observation period:
Part 1 Cohort 1 and 3-6: 13 days plus 2 ambulatory visits
Part 1 Cohort 2: 1 or 2 periods of 13 days plus 2 ambulantory visits after each period
Part 2 Cohort 1 - 3: 26 days plus 2 ambulatory visits
Part 2 Cohort 4: 17 days

Intervention

Part 1 (SAD)
Cohort 1: a single oral dose of 240 mg tonabersat or placebo on Day 1 fasted
Cohort 2, period 1: a single oral dose of 320 mg tonabersat or placebo on Day 1 fasted
Cohort 2, period 2: a single oral dose of 320 mg tonabersat or placebo on Day 1 following a high fat breakfast
Cohort 3: a single oral dose of 360 mg tonabersat or placebo on Day 1 fasted or following a (high fat) breakfast
Cohort 4: a single oral dose of 400 mg tonabersat or placebo on Day 1 fasted or following a (high fat) breakfast
Cohort 5: a single oral dose of 440 mg tonabersat or placebo on Day 1 fasted or following a (high fat) breakfast
Cohort 6: a single oral dose of 480 mg tonabersat or placebo on Day 1 fasted or following a (high fat) breakfast
Part 2 (MAD)
Cohort 1: an oral dose of x mg tonabersat of placebo once daily on Days 1-14 fasted or following a (high fat) breakfast
Cohort 2: an oral dose of y mg tonabersat of placebo once daily on Days 1-14 fasted or following a (high fat) breakfast
Cohort 3: an oral dose of z mg tonabersat of placebo once daily on Days 1-14 fasted or following a (high fat) breakfast
Part 2 (DDI)
Cohort 4: an oral dose of xyz mg tonabersat of placebo once daily on Days 1-14

fasted or following a (high fat) breakfast, and a single oral dose of 2 mg midazolam, 50 mg metoprolol, 150 mg caffeine, 40 mg omeprazole and 500 mg tolbutamide on Days -1 and 13

Study burden and risks

Previous clinical studies were conducted with the same compound in 221healthy volunteers (148 males and 73 females), and 44 patients with migraine (9 males and 35 females). In addition, multiple dose prophylactic studies have been conducted in 39 patients with a diagnosis of migraine with aura (10 males and 29 females). In these studies doses up to 200 mg daily for a maximum of 14 days have been administered to volunteers aged < 60 years and the following adverse effects were reported or observed: nausea, diarrhoea , sleepiness, headache, dizziness, vertigo and scotoma (which is as an area of lost vision, blind spot in the field of vision). In addition the following 14 serious adverse events have been reported: low blood pressure and epileptic seizure; lowering of blood potassium with vomiting dehydration and dizziness; sigmoid diverticulitis; and complex migraine and left sided weakness.
The insertion of the indwelling canula and the venepuncture may cause some pain, and sometimes lead to a bruise, but the actual collection of blood will not be painful. Light bleeding and possibly an infection may occur. Infusion may cause oedema in the arm where the infusion is given.

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

18 - 65 years, BMI 18 - 30 kg/m2, no smoker or a moderate smoker i.e. * 5 cigarettes per day.

Exclusion criteria

Suffering from: hepatitis A, B or C, 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 within 90 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior 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):	05-01-2010

Enrollment:	129
Type:	Actual

Ethics review

Approved WMO Date:	06-12-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-11-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2012

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	EUCTR2010-023924-25-NL
CCMO	NL34545.056.10