A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTIPLE DOSE, PARALLEL ARM STUDY TO EVALUATE THE EFFECT OFMEAL TIMING AND FOOD- VERSUS THE FASTED STATE ON THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF REPETITIVE DAILY DOSES OF TONABERSAT (USL260) IN HEALTHY SUBJECTS

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

Summary

ID

NL-OMON35227

Source
ToetsingOnline

Brief title
FE Tonabersat

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: Migraine, Tonabersat, USL260

Outcome measures

Primary outcome

Safety, tolerability and pharmacokinetic profile.Food effect.

Secondary outcome

Not applicable.

Study description

Background summary

The drug to be given Tonabersat (USL260) is a new, investigational compound that may eventually be used for the treatment of migraine. Migraine is a disorder characterised by attacks of throbbing headache
lasting from 4 to 72 hours (most commonly around 24 hours) accompanied by nausea, vomiting and sensitivity to light and sounds. Tonabersat is a new compound which has a broader range of activity than the commonly used anti-migraine agent, sumatriptan.

Current treatment of migraine with sumatriptan gives cardiovascular- and neurotoxic effects. It is expected that treatment with Tonabersat (USL260) is expected to give less cardiovascular (faster -or slower hartbeat,

heartpalpitations) and neurotoxic effects (cold fingers and/or cold feet).

Study objective

The purpose of the study is to investigate how safe the compound USL260 is and how well the compound USL260 is tolerated under fasting and fed conditions. The study will also investigate how quickly and to what extent the compound USL260 is absorbed and eliminated from the body (this is called pharmacokinetics) under fasting and fed conditions.
This study is not intended to improve your health, but is necessary for the further development of the compound.

Study design

A Phase 1 Randomized, Placebo-controlled, Double-Blind, Multiple Dose, Parallel Arm Study to Evaluate the Effect of Meal timing and Food versus the Fasted State on the Safety, Tolerability and Pharmacokinetics of Repetitive Daily Doses of USL260.

In Group 1 and 2 you will receive the study drug or placebo 30 minutes after the start of a standard high fat breakfast. Group 3will receive the study drug or placebo after a period of minimal 10 hours fasting. If you take part on Group 4 you will receive a breakfast at 1 hour post dose, which you have to eat completely. Group 5 will receive the study drug or placebo 2 hours after the start of a breakfast, that the volunteers have to eat completely. All doses will be administrated as one or more tablets together with 240 ml of water at room temperature.
In each group 10 volunteers will receive the drug USL260 and 2 volunteers will receive placebo.

The screening will include a physical examination including measurement of blood pressure and pulse rate, a heart trace (electrocardiogram) recording, and a number of blood and urine tests. You will also be screened for drugs of abuse and alcohol. Hepatitis A, B and C, and HIV (= AIDS test). In case of female participants a pregnancy test will be performed. The volunteer will be asked to complete a questionnaire (CSSR) about potential depressive feelings.

The post-study examination will include a complete physical examination including measurement of blood pressure and pulse rate, a heart trace (electrocardiogram) recording, and a number of blood and urine tests, alcohol, drug of abuse and a pregnancy test. You will also be asked to complete a questionnaire (CSSR) about potential depressive feelings.

Both for the pre-study screening and the post-study follow-up examination, the volunteer will have to be fasted (not to have eaten or drunk anything, except water). For the pre-study screening the volunteer will have to be fasted for at

least 4 hours and for the post-study follow-up you will have to be fasted for at least 10 hours.

Intervention

Group Day Study drug Dose Frequency Condition

(4*80mg)
1 1-14 USL260/Placebo 320 mg Once daily Fed state
2 1-14 USL260/Placebo 80 mg Once daily Fed state
3 1-14 USL260/Placebo 320 mg Once daily Fasted state
4 1-14 USL260/Placebo 320 mg Once daily 1 hour before a breakfast
5 1-14 USL260/Placebo. 320 mg Once daily 2 hours after a breakfast.

All doses will be administrated as one or more tablets together with 240 ml of water at room temperature.

In each group 10 volunteers will receive the drug USL260 and 2 volunteers will receive placebo.

Study burden and risks

Previous clinical studies were conducted with the same compound in 221 healthy volunteers (148 males and 73 females), and 44 patients with migraine (9 males and 35 females). In addition, multiple dose studies have been conducted in 39 patients with a diagnosis of migraine with aura (10 males and 29 females). Migraine with aura is a migraine that's preceded or accompanied by a variety of sensory warning signs or symptoms, such as flashes of light, blind spots or tingling in your hand or face. In these studies doses up to 200 mg daily for a maximum of 14 days have been administered to volunteers and the following adverse effects were reported or observed: nausea, dizziness, sleepiness, headache and vertigo. Scotoma described as an area of lost vision or a *blind spot* in the field of vision was also reported. In addition the following serious adverse events have been reported: low blood pressure and epileptic seizure ; lowering of blood potassium with vomiting, dehydration and dizziness; sigmoid diverticulitis, complex migraine and left sided weakness, all considered to be possibly related to the study medications and the subjects were withdrawn.

Currently there is an ongoing study with single ascending doses up to 400 mg in 60 subjects and multiple ascending doses up to 400 mg in 48 subjects. The most common adverse events in the single- and multiple ascending dose parts of this study that were possibly or probably related were; dizziness, impaired coordination, reduced concentration, headache intermittent orthostatic intolerance, light headiness, bad taste, nausea and vomiting, hot flushes, sleepiness, restlessness, and gastrointestinal disorders. Most adverse events

were of mild or moderate intensity. In the multiple ascending part one subject experienced a rash of severe intensity. This adverse event is possibly related to the study medication.

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. However, chances these complications will occur are limited.

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

* Age 18 to 65 years, inclusive. ;* Male or non-pregnant and not breast feeding female (non-

pregnancy will be confirmed by a serum pregnancy test conducted at Screening and prior to any dosing period).;Female subjects of childbearing potential must be:;o On oral contraceptive therapy; or,;o Practicing acceptable double-barrier methods of birth control during the course of the study (e.g., a barrier method using a condom with spermicide, diaphragm with spermicide, or cervical cap with spermicide); or ;o Surgically sterile (bilateral tubal ligation 90 days or more prior to dosing, bilateral oopherectomy, or hysterectomy).;Female subjects who are post- menopausal must be:;o Postmenopausal (no menses) for at least 1 year and have a documented follicle stimulating hormone (FSH) level *30 mIU/ml.;o Post-menopausal females may be on hormone replacement therapy.;* Have a body mass index (BMI) between 18 and 30 kg/m2, inclusive, and weigh at least 50 Kg (110 lbs.).;* Physical examination is within normal limits; a subject with a clinical abnormality could be included only if the investigator considers that it would not introduce any additional risk to the subject nor interfere with study procedures.;* Grapefruit juice is not allowed 7 days prior to dosing, throughout the entire clinic period (through Day 21), and until after the completion of Day 28 PK blood samples are collected. ;* Theobromide-, alcohol-, caffeine-, and xanthine-containing beverages or food (coffee, tea, cola beverages, chocolate, *power drinks*) are not allowed for 48 hours (2 days) prior to dosing, throughout the entire clinic period, until the morning of Day 28.;* All hematology and clinical chemistry values for blood and urine are within the normal range or show no relevant deviations as judged by the medical investigator.;* Subject is a *light smoker*, i.e., he/she smokes no more than 5 cigarettes (1/4 pack) per day.;* Is able to communicate effectively with study personnel and are considered reliable, able, willing and cooperative with regard to complying with protocol-defined requirements as assessed by the study investigator.;* Can voluntarily give written informed consent to participate in the study prior to the completion of any study-related procedures.

Exclusion criteria

* Have a clinically relevant current illness (within 4 weeks prior to dosing) or history of a medical condition that would interfere with the subject*s ability to complete the study or would confound the results of this study, as determined by the clinical investigator(s).;* Have a predisposing condition that could interfere with the absorption, distribution, metabolism, or excretion of drugs or any condition that may confound the analyses to be conducted in this study. ;* Have evidence of clinically relevant pathology.;* Have a clinically significant history of renal or hepatic disease or gastrointestinal disease.;* Have history of malignancy, suspicious or undiagnosed skin lesions, or a history of melanoma.;* Have history of psychoses, depression, suicidal ideation (as determined by CSSR assessment) or tendencies (within 1 year of the Screening Visit).;* Have past history of or current, severe cardiovascular or pulmonary disease, bronchial asthma, or endocrine disease including diabetes or hypoglycemia.;* Have history of lactose intolerance or lactose sensitivity. ;* Have a history of, or currently observed, clinically significant arrhythmias as evidenced on Screening ECG, or history of myocardial infarction that has residual atrial, nodal, or ventricular arrhythmias, or any other clinically significant cardiac disease ;* a systolic blood pressure of above 140 mm Hg or diastolic blood pressure of above 90 mm Hg or a systolic blood pressure of below 90 mm Hg or diastolic blood pressure of below 50 mm Hg.;* Have a history of, or currently

observed, clinically significant CNS disorder.;* Have history of complications from venipunctures.;* Have donated blood or plasma within 60 days prior to the Screening Visit.;* Have a history of clinically significant alcohol or significant psychoactive substance use disorder (abuse, dependence, and/or withdrawal) within the past 12 months (within 1 year of the Screening Visit).;* Have a positive drug screen for drugs of abuse at Screening or upon admission.;* Have a positive test for human immunodeficiency virus (HIV), HAV IgM (to assess recent hepatitis A infection), hepatitis B, or hepatitis C.;* Have taken a prescription medication, including MOA inhibitors, within 14 days prior to the initial PK study period or taken over-the-counter oral preparations, including dietary and herbal supplements, 3 days prior to dosing.;* Previous exposure to USL260 or its metabolite. Have required continuation of previous concomitant medications other than those allowed (see Section X.X) during the study.;* Have participated in another clinical trial with any other investigational drug within 30 days prior to the first PK study period.

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):	24-10-2011
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	Tonabersat

Ethics review

Approved WMO Date:	11-10-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2011
Application type:	First submission
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	EUCTR2011-004837-15-NL
CCMO	NL38357.056.11