A single-center, randomized, placebo-controlled, two-way crossover study to investigate the drug-drug interaction on the pharmacokinetics and pharmacodynamics of ACT-078573 and single-dose desipramine in healthy male subjects

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Evaluation of the pharmacodynamic and pharmacokinetic effects of multiple doses of ACT-078573 on the pharmacokinetics of a single dose of desipramine

Ethical review	Approved WMO
Status	Pending
Health condition type	Sleep disturbances (incl subtypes)
Study type	Observational invasive

Summary

ID

NL-OMON32097

Source
ToetsingOnline

Brief title
Study to investigate the interaction of ACT-078573 and desipramine

Condition

- Sleep disturbances (incl subtypes)

Synonym
insomia, sleeplessness

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Actelion pharmaceuticals

Intervention

Keyword: ACT-078573, desipramine, pharmacodynamics, pharmacokinetics

Outcome measures

Primary outcome

Pharmacokinetic variables/outcomes:

• Maximum concentration (Cmax) of desipramine

• Area under the plasma concentration-time curve from zero to infinity (AUC0-*)

of desipramine

Secondary outcome

Pharmacokinetic variables/outcomes:

• Maximum concentratie (Cmax) of the metabolite 2-OH desipramine

• Area under the plasma concentration-time curve from zero to infinity (AUC0-*)

of the metabolite 2-OH desipramine

• Time to reach Cmax (tmax) of desipramine (and the metabolite 2-OH

desipramine).

• Area under the plasma concentration-time curve from zero to time t of the

last measured concentration above the quantificationlimit (AUC0 t) of

desipramine (and the metabolite 2-OH desipramine).

• The halflife (t*) of desipramine (and the metabolite 2-OH desipramine).

• Maximum concentration (Cmax) of ACT 078573.

• Area under the plasma concentration-time curve from zero to 24 hours

(AUC0-24) of ACT 078573.

• Time to reach Cmax (tmax) of ACT 078573.

Pharmacodynamic outcomes/variables:

Eye Movements:

• Saccadic peak velocity

Adaptive tracking:

• Adaptive tracking performance

Body Sway

Pupillometry:

• Pupil / iris ratio

Visual analog scale (VAS) Bond & Lader:

• Alertness

• Mood

• Calmness

Study description

Background summary

ACT-078573 is a selective orally active orexine-antagonist. Orexine peptiden play a central role in het sleep-wake rhythm. Preclinical data have shown that this compound increased the REM and non-REM sleep in animal models. Earlier phase I research in healthy volunteers has brought no serious side effects to light.

ACT-078573 is being developed for the treatment of insomnia. Earlier preclinical research has shown that this compound can inhibit CYP2D6 in vitro. Drug-drug interaction studies are therefore needed to determine the clinical relevance of this. Desipramine was chosen because this drug is also a substrate for CYP2D6

Study objective

Evaluation of the pharmacodynamic and pharmacokinetic effects of multiple doses of ACT-078573 on the pharmacokinetics of a single dose of desipramine

Study design

A single-center, randomized, placebo-controlled, two-way cross-over study to determine drug-drug interaction on the farmacokinetics and farmacodynamics of ACT-078573 and a single dose of desipramine in healthy male volunteers

Study burden and risks

Possible side effects of study medication

ACT-078573
For ACT-078573 the most common side effects reported to date are tiredness, dizziness, disturbed concentration, and headache.
Double vision, nausea and muscle weakness (during emotional moments or at waking up) have been reported a few times. These symptoms may be frightening for persons not familiar with them. Other healthy volunteers have reported dry or irritated eyes after multiple doses.

Desipramine
The most common side effects include problems to focus on close objects, constipation, tiredness, dry mouth and low blood pressure.
In rare occasions sleep disorders and related tiredness, urinary dysfunction, restlessness, thirst, exanthema, allergies and sexual function disorders may occur.

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

Signed informed consent prior to any study-mandated procedure.;Male aged between 18 and 45 years (inclusive) at screening.;CYP2D6 extensive metabolizer (EM) genotype.;No clinically significant findings on the physical examination at screening.;Body mass index (BMI) between 18 and 30 kg/m2 (inclusive) at screening.;Systolic blood pressure (SBP) 100-145 mmHg, diastolic blood pressure (DBP)
50-90 mmHg, and heart rate (HR) 45-90 bpm (all inclusive), measured at screening on the leading arm after 5 minutes in the supine position.;12-lead electrocardiogram (ECG) without clinically relevant abnormalities at screening and meeting the following criteria: QTcB interval * 430 msec, QRS interval * 110 msec, and PR interval * 220 msec.;Hematology and clinical chemistry results not deviating from the normal range to a clinically relevant extent at screening.;Negative results from urine drug screen at screening.;Ability to communicate well with the investigator in the local language, and to understand and comply with the requirements of the study.

Exclusion criteria

History of cardiovascular disease (e.g., arrhythmia, congenital long QT syndrome).;History of seizures disorders.;Clinically significant findings at baseline assessments for pupillometry.;Any contraindication to desipramine or any tricyclic antidepressant

(TCA).;Known hypersensitivity to desipramine, or any TCA, Ponceau 4R, or any other excipients of the drug formulations.;Treatment with any prescribed or OTC medications (including herbal medicines such as St John*s Wort) within 2 weeks prior to screening.;Treatment with another investigational drug within 3 months prior to screening or more than 4 times within the year prior to screening.;History or clinical evidence of alcoholism or drug abuse within the 3-year period prior to screening.;Excessive caffeine consumption (more than 800 mg per day) at screening .;History or clinical evidence of any disease, and/or existence of any surgical or medical condition, which might interfere with the absorption, distribution, metabolism or excretion of the study drugs.;Smoking within 3 months prior to screening and inability to refrain from smoking during the course of study.;Loss of 250 mL or more of blood within 3 months prior to screening.;Positive hepatitis serology, except for vaccinated subjects, at screening.;Positive HIV serology at screening.;Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol.;Legal incapacity or limited legal capacity at screening

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-06-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ACT 078573

Generic name:	ACT 078573
Product type:	Medicine
Brand name:	Norpramin
Generic name:	Desipramine

Ethics review

Approved WMO Date:	13-05-2008
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-07-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2008-001607-35-NL
CCMO	NL23235.058.08