Double-blind, placebo-controlled, randomized, single-ascending dose study to investigate the tolerability, safety, pharmacokinetics, pharmacodynamics, absolute bioavailability, mass balance, and metabolism of ACT-541468 in healthy male subjects

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• To evaluate the tolerability and safety of ascending single oral doses of ACT-541468 in healthy male subjects.• To investigate the single oral dose pharmacokinetic (PK) and PD of ACT-541468 in healthy male subjects.• To investigate dose…

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

Summary

ID

NL-OMON41910

Source
ToetsingOnline

Brief title
Safety and tolerability of ACT-541468

Condition

- Other condition

Synonym
insomnia, Sleeping disorders

Health condition

Sleep disorders

Research involving
Human

Sponsors and support

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

Intervention

Keyword: First in Man, Pharmacokinetics&Pharmacodynamics, Safety&Tolerability, Sleeping disorders

Outcome measures

Primary outcome

Concentrations of ACT-541468 and its metabolites and radioactivity in whole blood and plasma per time point will be summarized by dose presenting number of observations, arithmetic mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and 95% confidence interval (CI) of the mean.

Dose proportionality will be assessed across ACT-541468 doses (formulation A) using the power model described by Gough et al., [Gough 1995] which will be applied to the loge AUC0-* and Cmax data. A point estimate and 90% CI will be determined for the population mean slope.

Differences between formulation A (reference) and formulation B (test) for AUC0-8, AUC0-24, AUC0-t, AUC0-*, Cmax, Cu/C, and t* will be explored using the ratio of geometric means (absolute) and its 90% CI. Differences between

formulation A and formulation B for tmax will be explored using the median difference and its 90% CI.

• Individual absolute bioavailability will be listed by subject number and summarized overall presenting number of observations, arithmetic mean and its 95% CI, minimum, median, maximum, SD, and CV(%).
• Absolute bioavailability (F) will be calculated using the geometric means of AUC0-*
All PK parameters of 14C-labeled ACT-541468 (including CL, Vss, and cumulative excretion in urine and feces) will be presented as described above.

If applicable, individual concentrations of ACT-541468 in urine will be listed per collection interval by dose and subject and summarized by dose presenting number of observations, arithmetic mean, minimum, median, maximum, SD, SE, CVb(%), and 95% CI of the means. Percentage of total dose excreted (unchanged and metabolized) in urine and CLR will be similarly listed and summarized with the exception that also the geometric mean and 95% CI will be provided.

Individual PD data will be listed by dose, formulation, and subject. At each time point, absolute values and change from baseline of PD variables will be summarized with arithmetic mean, median, SD, SE, 95% CI, minimum, and maximum.

The All-treated set will be used to perform all safety analyses.
All AEs and SAEs are to be coded using the MedDRA dictionary (Version 17.1 or a

more recent version, if available).

ECG abnormalities will be coded using the clinical data interchange standards

consortium terminology.

Safety and tolerability data will be listed and summarized descriptively.

Secondary outcome

NA

Study description

Background summary

The neuropeptides orexin-A and orexin-B are synthesized by a discrete number of neurons (~3500 in rat, ~70,000 in man) in lateral hypothalamic areas (LHA) and act at the interface of sleep, energy homeostasis, and reward/aversion systems of the brain. Endogenous orexins activate two closely related G protein-coupled receptors, the orexin-1 (OX1) and the orexin-2 (OX2) receptors, leading to transient increases in intracellular calcium levels in projection neurons expressing orexin receptors. In insomnia patients, the dual orexin receptor antagonist almorexant dose-dependently increased sleep efficiency and total sleep time by decreasing latency to persistent sleep and wake after sleep onset. Repeat-dose animal studies showed no loss of efficacy over time. The dual orexin receptor antagonist suvorexant is approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Insomnia (as inappropriate nocturnal wakefulness) affects 10-15% of the US population chronically, with up to a third suffering from it occasionally. Insomnia has a wide range of effects on quality of life and is associated with increased accident risk and chronic health problems. Currently, standard insomnia treatments are mainly γ-aminobutyric acid-A receptor modulators, which evoke sleep by increasing non-REM sleep but decreasing REM sleep. They can also impair cognitive performance, locomotor skills, and balance when waking. The latter is of particular concern for older adults as falls are a primary cause of injury in this population. Orexin receptor antagonists are expected to minimize these side effects, as orexin receptors are not present in the cerebellum or in the vestibular nuclei, where balance and locomotor activity are controlled. ACT-541468 is a potent and selective orexin receptor antagonist that blocks the actions of the orexin neuropeptides at both OX1 and OX2 receptors. The orexin system is involved in the regulation of sleep and arousal by the central nervous system and is currently being targeted in the development of new therapies for sleep disorders. ACT-541468

decreases wakefulness while maintaining natural sleep patterns in rat and dog and, thus, is a potential candidate for the treatment of insomnia.

Study objective

• To evaluate the tolerability and safety of ascending single oral doses of ACT-541468 in healthy male subjects.
• To investigate the single oral dose pharmacokinetic (PK) and PD of ACT-541468 in healthy male subjects.
• To investigate dose proportionality across different doses of ACT-541468.
• To evaluate the relative PK properties of two oral formulations of ACT-541468 after single-dose treatment in healthy male subjects.
• To investigate the absolute bioavailability of a single oral dose of ACT-541468 compared to an i.v. 14C-labeled ACT-541468 tracer.
• To investigate the rate and routes of elimination of a single oral dose of a 14C-labeled ACT-541468 tracer and the mass balance in urine and feces.
• To investigate the PK of total radioactivity (tracer) in whole blood and in plasma following oral administration of 14C-labeled ACT-541468.
• To identify and quantify ACT-541468 metabolites in plasma, urine, and feces.

Study design

This is a single-center, double-blind, randomized, placebo-controlled, ascending single oral dose Phase 1 study. In addition, the study includes a biocomparison part, an absolute bioavailability part, and a mass balance and metabolism part. Each dose group will be investigated in a new group of eight healthy male subjects (six on active drug and two on placebo). If seven dose groups will be performed, 56 healthy male subjects will be enrolled.

Intervention

At each dose level, six subjects will receive a single oral dose of ACT-541468 (formulation A) and two subjects will receive a single oral dose of matching placebo.

For the biocomparison part in the second dose group subjects will participate in two different treatment periods, separated by a washout period of 10-14 days between study drug administrations. In a double-blind, randomized, crossover design six subjects will receive a single oral dose of ACT-541468 formulation A and a single oral dose of ACT-541468 formulation B. Subjects on placebo (two) will receive the matching placebos in both treatment periods.

Subjects in the absolute bioavailability part in the fourth dose group will receive a single oral dose of ACT-541468 (formulation A) followed by 2.3 µg (250 nCi) of the 14C-labeled ACT-541468 tracer as a short i.v. infusion.

Subjects in the mass balance part in the third dose group will receive a single oral dose of ACT-541468 (formulation A) followed by 15 mL of 2.3 µg (250 nCi) of the 14C-labeled ACT-541468 tracer orally.

Formulation A:
ACT-541468 as the hydrochloride salt, as hard capsules for oral administration formulated at strengths of 5 mg, 25 mg, and 100 mg.

Formulation B:
ACT-541468 as the free base, lipid-based liquid-filled soft capsules for oral administration formulated at the strength of 25 mg.

Study burden and risks

Burden:

-The subjects will remain fasted from at least 10 h prior to (each) study drug administration until 3.5 h thereafter.
-The intake of liquids is not allowed from 1 h before until 1 h after oral study drug administration.
-Smoking and consumption of any grapefruit or grapefruit juice is not permitted from screening until the EOS. Drinking of alcoholic beverages and xanthine containing beverages (e.g., coffee, tea, cola, cocoa, Red Bull) or food is not permitted from at least 48 h prior to clinic admission and during the treatment period(s).
-From screening until the EOS, the subjects must refrain from strenuous physical exercise, physical work, strenuous sports activities (endurance sports), and activities disturbing the circadian rhythm.
-On the day(s) of the study drug administration, the subjects must remain in a sitting position from approximately 5 min before and until 4 h after intake of study drug, except for the body sway measurement (conducted in standing position), measurement of vital signs (two pre-dose measurements, conducted in supine position), ECG and EEG (conducted in supine position), or going to the toilet.
-Subjects will have to perform different pharmacodynamic tests and questionnaires.

Risk:

-In animal studies with ACT-541468 at very high doses (much higher than used in this study) a drop in body temperature and heart rate was seen. We will measure your heart rate, body temperature and blood pressure regularly during the study.
-At these high doses there were also some effects observed on the liver. As a result of this, the liver increased in size. We will measure liver function by analyzing blood samples during the study.
-As ACT-541468 has not been tested in humans so far, not all side effects are

known yet. Based on the fact that it is being developed as a sleeping agent, effects associated with this could be: drowsiness, dizziness, fatigue and decreased alertness. More severe effects could be narcolepsy like symptoms, cataplexy, or weak muscle tone. There may also be unexpected side effects.
-The radioactive exposure risk is minimal in this study because of the very small planned radioactive dose (a tracer) of 9.25 kilobecquerel (kBq), corresponding to 250 nanocurie (nCi) to be administered. As the average adult human body contains as natural 14C background around 100 nCi [Turteltaub 2000, Lappin 2010], a transient exposure to 250 nCi of a 14C-labeled compound is considered very safe - essentially comprising a negligible level of radiation. Therefore, regulatory authorities do not require a formal application with animal dosimetry data to allow such low level of 14C-study in human subjects [Lappin 2010, Sarapa 2005, ICH guideline M3 2009].

Contacts

Public
Actelion Pharmaceuticals

Gewerbestrasse 16
Allschwil CH-4123
CH
Scientific
Actelion Pharmaceuticals

Gewerbestrasse 16
Allschwil CH-4123
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Signed informed consent in the local language prior to any study-mandated procedure.
• Healthy male subjects aged between 18 and 45 years (inclusive) at screening.
• Hematology, clinical chemistry, and urinalysis results not deviating from the normal range to a clinically relevant extent at screening.
• No clinically significant findings on physical examination at screening.
• Body mass index (BMI) between 18.0 and 30.0 kg/m2 (inclusive) at screening.
• Systolic blood pressure 100-145 mmHg, diastolic blood pressure 50-90 mmHg, and pulse rate 45-90 bpm (inclusive) measured at screening on the dominant arm after 5 min in supine position.
• 12-lead ECG without clinically relevant abnormalities in supine position at screening.
• Negative results from alcohol breath test and urine drug screen at screening and at Day 1.
• Ability to communicate well with the investigator in the local language, and to understand and comply with the requirements of the study.
• Only for subjects in the mass balance and metabolism part (third dose group): subjects must have a regular (daily) defecation pattern.

Exclusion criteria

• Previous history of fainting, collapse, syncope, orthostatic hypotension, or vasovagal reactions.
• Veins unsuitable for i.v. puncture on either arm (e.g., veins that are difficult to locate, access or puncture, veins with a tendency to rupture during or after puncture).
• Treatment with any prescribed medications (including vaccines) or over-the-counter (OTC) medications (including herbal medicines such as St. John*s Wort) within 2 weeks prior to (first) study drug administration.
• Treatment with another investigational drug within 3 months prior to screening or having participated in more than four investigational drug studies within 1 year prior to screening.
• History or clinical evidence of alcoholism or drug abuse within the 3-year period prior to 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 (appendectomy and herniotomy allowed; cholecystectomy not allowed).
• Excessive caffeine consumption, defined as >= 800 mg per day at screening.
• Smoking within 3 months prior to screening and inability to refrain from smoking during the course of the study (from screening to EOS).
• Loss of 250 ml or more of blood, or an equivalent amount of plasma, within 3 months prior to screening.
• Positive results from the hepatitis serology, except for vaccinated subjects or subjects with past but resolved hepatitis, at screening.
• Positive results from the HIV serology at screening.
• Known hypersensitivity to any excipients of the drug formulations.
• Modified Swiss Narcolepsy Scale total score < 0 at screening or history of narcolepsy or

cataplexy.
• 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.
• Only for subjects in the mass balance and metabolism part (third dose group) or the absolute bioavailability part (fourth dose group): Radiation exposure, including that from the present study, excluding background radiation but including diagnostic rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. Occupationally exposed workers, as defined in the relevant Ionisation Radiation Regulations, must not participate in the study.
• Participation in any study involving administration of any 14C-labeled compound within 12 months prior to screening.
• For subjects in the mass balance and metabolism part (third dose group): Clinically relevant constipation (defined as lasting more than 3 days) in the 4-week period before screening.

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):	16-02-2015
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACT-541468
Generic name:	ACT-541468

Ethics review

Approved WMO Date:	08-01-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2015
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	EUCTR2014-003129-16-NL
CCMO	NL51750.056.14