A double-blind, randomized, placebo-controlled, double-dummy, four-way crossover study to investigate the drug-drug interactions between ACT-541468 and ethanol in healthy subjects

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To evaluate the pharmacodynamic (PD) effects of the study treatments (ACT-541468 50 mg, ethanol at a blood level of 0.6 g/L for 5 h) as co-administration in 4 different combinations (ACT-541468 plus ethanol, ACT-541468 alone, ethanol alone, and…

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

Summary

ID

NL-OMON45918

Source
ToetsingOnline

Brief title
Interaction study with ACT-541468 and ethanol in healthy subjects.

Condition

- Sleep disorders and disturbances

Synonym
Insomnia, Sleeping disorders

Research involving
Human

Sponsors and support

Primary sponsor: Idorsia Pharmaceuticals LTD
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Insomnia, PK & PD, Safety and tolerability, Sleep disorder

Outcome measures

Primary outcome

Change from baseline for:

* Saccadic peak velocity (degrees/sec) to assess sedation.

* Smooth pursuit (%) to assess eye movement coordination and attention.

* Adaptive tracking (%) to assess visuo-motor control and vigilance.

* Body sway (antero-posterior in mm / 2 min) to assess postural stability.

* Visual analog scales (VAS) Bond & Lader to assess subjective alertness, mood,

and calmness.

* VAS for alcohol intoxication to assess subjective effects of ethanol.

Secondary outcome

ACT-541468 PK endpoints for treatments A and B:

* The area under the plasma concentration-time curve (AUC) from time zero to 24

h (AUC0*24).

* The AUC from zero to infinity (AUC0**).

* The maximum plasma concentration (Cmax).

* The time to reach Cmax (tmax).

* The terminal elimination half-life (t*).

Ethanol PK endpoints for treatments A and C:

* Breath ethanol concentrations (BrEC).

* Total ethanol dose (in grams) required to maintain the 0.6 g/L ethanol clamp.

Safety endpoints:

* Treatment-emergent AEs from study treatment administration up to EOT in each

treatment period.

* Treatment-emergent SAEs from study treatment administration up to EOT in each

treatment period.

Study description

Background summary

The neuropeptides orexin-A and orexin-B are synthesized in the lateral hypothalamic areas [De Lecea 1998] and activate the orexin-1 and orexin-2 receptors [Kilduff 2000]. Nerve fibers from orexin neurons make projections to the basal forebrain, corticolimbic structures, and brainstem, particularly to those regions related to waking and regulation of sleep [Hagan 1999, Sakurai 2007]. Infusing exogenous orexins into cerebral ventricles in rats leads to enhanced behavioral activity, arousal, delayed onset of sleep, and maintenance of cortical activation

ACT-541468 is a new potent and selective compound that blocks the actions of the orexin neuropeptides at both orexin-1 and orexin-2 receptors. Due to the wide connections of the orexin system with brain areas involved in sleep/arousal regulation, ACT-541468 is being evaluated for the treatment of insomnia disorders. In humans, ACT-541468 has a dose-dependent effect on wake after sleep onset (WASO) and shows pharmacodynamic effects on a battery of CNS tests, including adaptive tracking, VAS alertness and body sway. In contrast to the commonly used drugs (e.g. benzodiazepines) for the treatment of insomnia, ACT-541468 preserves a normal sleep architecture.

Ethanol is often used by insomnia patients as self-medication to help them falling asleep. It is currently unknown if there is an interaction between ACT-541468 and ethanol. And in case there is an interaction, whether this

results in additive or synergistic effects. Therefore, a clinical study to investigate the possible interaction of ACT-541468 and ethanol on PK and PD has strong relevance.

Study objective

To evaluate the pharmacodynamic (PD) effects of the study treatments (ACT-541468 50 mg, ethanol at a blood level of 0.6 g/L for 5 h) as co-administration in 4 different combinations (ACT-541468 plus ethanol, ACT-541468 alone, ethanol alone, and placebo) in healthy subjects.

To explore the magnitude of interaction effect between ACT-541468 and ethanol on PD variables.

To evaluate the potential pharmacokinetic (PK) interactions between a single dose of ACT-541468 (50 mg) and ethanol (at a blood level of 0.6 g/L for 5h) in healthy subjects.

To evaluate the safety and tolerability of the co-administration of a single dose of ACT-541468 (50 mg) and ethanol (at a blood level of 0.6 g/L for 5 h) in healthy subjects.

Study design

Single-center, double-blind, randomized, placebo-controlled, double-dummy, 2x2 factorial design, four-way crossover Phase 1 study.

Intervention

There will be 4 study treatments (A, B, C, and D) and each subject will receive all 4 treatments in a blinded crossover fashion. Each subject will be randomized to one of the sequences defined using a Williams square design balanced for first order carry-over effects.

Treatment A (ethanol + ACT-541468) will consist of a 5 h i.v. ethanol clamp at a level of 0.6 g/L in combination with a single oral dose of ACT-541468 (50 mg).

Treatment B (ethanol placebo + ACT-541468) will consist of a 5 h i.v. placebo clamp in combination with a single oral dose of ACT-541468 (50 mg).

Treatment C (ethanol + ACT-541468 placebo) will consist of a 5 h i.v. ethanol clamp at a level of 0.6 g/L in combination with a single oral dose of matching ACT-541468 placebo.

Treatment D (ethanol placebo + ACT-541468 placebo) will consist of a 5 h i.v. placebo clamp in combination with a single oral dose of matching ACT-541468

placebo.

Study burden and risks

Administration of ACT-541468 has been evaluated in several preclinical toxicology and pharmacology studies and in phase 1 and phase 2 studies. ACT-541468 was found to be generally safe and well tolerated. It is however, unsure how it will interact with ethanol, a substance that is often used as self-medication by insomnia patients.
This study will provide valuable human data on the safety, tolerability, pharmacokinetics and pharmacodynamis of ACT-541468 when given in combination with ethanol. This data will be of critical importance for further development of this compound for treatment of insomnia. Thus, it is felt that the potential benefits of the study as part of the development plan for insomnia exceed the risks. Subjects will be carefully screened and monitored.

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

1. Signed informed consent in a language understandable to the subject prior to any study-mandated procedure.
2. Healthy male and female subjects aged between 18 and 45 years (inclusive) at screening.
3. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1 pre-dose of each treatment period. They must consistently and correctly use (from screening, during the entire study, and for at least 90 days after last study treatment intake) a reliable method of contraception with a failure rate of <1% per year, be sexually inactive, or have a vasectomized partner. If a hormonal contraceptive is used, it must be initiated at least 1 month before first treatment administration.
4. Women of non-childbearing potential (i.e., postmenopausal [defined as 12 consecutive months with no menses without an alternative medical cause, confirmed by a follicle-stimulating hormone test], with previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy, or with premature ovarian failure [confirmed by a specialist], XY genotype, Turner syndrome, uterine agenesis).
5. Body mass index of 18.0 to 32.0 kg/m2 (inclusive) at screening.
6. No clinically relevant findings on the physical examination at screening.
7. Systolic blood pressure 100-145 mmHg, diastolic blood pressure 50-90 mmHg, and pulse rate 45-90 bpm (inclusive), measured on either arm, after 5 min in the supine position at screening.
8. 12-lead ECG without clinically relevant abnormalities, measured after 5 min in the supine position at screening.
9. No clinically relevant findings in clinical laboratory tests (hematology, clinical chemistry, and urinalysis) at screening.
10. Negative results from urine drug screen and breath alcohol test at screening and on Day 1 pre-dose.
11. Ability to communicate well with the investigator, in a language understandable to the subject, and to understand and comply with the requirements of the study.
12. Previous experience with alcohol consumption and, therefore, familiar with the effects of alcohol.

Exclusion criteria

1. Pregnant or lactating women.
2. Known hypersensitivity to ACT-541468 or treatments of the same class, or any of its excipients.
3. History of major medical or surgical disorders, which in the opinion of the investigator, are likely to interfere with the absorption, distribution, metabolism, or excretion of the study treatment(s) (appendectomy and herniotomy allowed, cholecystectomy not allowed).
4. Acute, ongoing, recurrent, or chronic systemic disease able to interfere with the evaluation

of the study.
5. Previous history of fainting, collapse, syncope, orthostatic hypotension, or vasovagal reactions.
6. Veins unsuitable for intravenous (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).
7. Participation in a clinical study involving study treatment administration within 3 months prior to screening or in more than 4 clinical studies within 1 year prior to screening.
8. Excessive caffeine consumption, defined as 800 mg per day at screening
9. Nicotine intake (e.g., smoking, nicotine patch, nicotine chewing gum, or electronic cigarettes) within 3 months prior to screening and inability to refrain from nicotine intake from screening until End-of-Study (EOS).
10. Previous treatment with any prescribed medications (including vaccines) or over-the-counter (OTC) medications (including herbal medicines such as St John*s Wort, homeopathic preparations, vitamins, and minerals) within 2 weeks prior to first study treatment administration.
11. Loss of 250 mL or more of blood within 3 months prior to screening.
12. Positive results from the hepatitis serology, except for vaccinated subjects or subjects with past but resolved hepatitis, at screening.
13. Positive results from the HIV serology at screening.
14. Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol.
15. Legal incapacity or limited legal capacity at screening.
16. History or clinical evidence of alcoholism or drug abuse.
17. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of more than 21 units or an average daily intake of more than 3 units (males), or defined as an average weekly intake of more than 14 units or an average daily intake of more than 2 units (females). One unit is equivalent to a half-pint (220 mL) of beer or 1 measure (25 mL) of spirits or 1 glass (125 mL) of wine.
18. Individuals of Asian descent or other individuals reporting ethanol intolerance (Asian descent defined as 1 or more parents or grandparents of Asian origin).
19. Modified Swiss Narcolepsy Scale total score < 0 at screening or history of narcolepsy or cataplexy.

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):	08-08-2018
Enrollment:	22
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	02-07-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2018
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	EUCTR2018-001871-19-NL
CCMO	NL66145.056.18