A single-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 4-way cross-over study to assess next-day driving performance following single and multiple evening administrations of ACT-541468 in middle-aged and elderly subjects.

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Primary objective- To evaluate the effects of ACT-541468 on objective simulated driving performance, i.e., the standard deviation of the lateral position (SDLP), after single- and multiple dose administrations (i.e., on Day 1 and Day 4) in the...

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

Summary

ID

NL-OMON48154

Source
ToetsingOnline

Brief title
Driving performance of ACT-541468

Condition

- Sleep disorders and disturbances

Synonym
Insomnia; sleeplessness

Research involving
Human

Sponsors and support

Primary sponsor: Idorsia Pharaceuticals Ltd.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Driving performance, Insomnia, Orexin antagonist, Sleep disorder

Outcome measures

Primary outcome

Driving performance as measured by the SDLP (difference from placebo, cm) on

Day 2 and 5 at 9 h post dose following administration of ACT-541468.

Secondary outcome

Effects of ACT-541468 on Days 2 and 5 on other driving performance parameters 9

h post dose:

- Mean lateral position (MLP).

- Mean speed (MS).

- SD of the mean speed (SDMS).

- Number of lapses (lapses are short periods of inattention and reduced

alertness which may be a risk factor for car crashes. A lapse is defined as

change from the steady lateral position of * 100 cm for * 4 s.)

- Drive safety score (DSS), a 24-item composite safety score.

- Subjective driving performance and effort scale.

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 WHO has identified motor vehicle accidents (MVAs) as one of the major causes of injury and death around the world [who.int]. An important factor contributing to traffic accidents is inattention of the driver due to reduced alertness or increased sleepiness. It has been estimated that fatigue/sleepiness plays a role in 10*30 % of traffic accidents [Horne 1995, Maycock 1996, Verster 2003]. In the US, the FDA considers the reduction of the incidence of MVAs that occur because of drug-impaired driving a public health priority [FDA 2017]. Assessing the ability to operate a motor vehicle following drug intake is a critical component of the FDA-guided assessment of drug risks and related strategies to reduce these risks.

Drugs that have pronounced CNS impairing effects and are intended to be administered primarily at night are of concern because residual daytime effects can impair driving ability [FDA 2017].Driving studies that included the dual orexin receptor antagonist suvorexant have been performed in non-elderly [Vermeeren 2015] and elderly subjects [Vermeeren 2016], with no clinically meaningful residual effects as assessed by overall mean changes of the SDLP. However, some individuals in the non-elderly study who were treated with suvorexant had to stop the next-day driving test due to drowsiness [Vermeeren 2015].

Following oral administration, ACT-541468 has been shown to cause distinct adverse effects on the CNS due to the drug*s expected pharmacological effects [Section 1.2.2]. Therefore, the next level of evaluation in this tiered approach [FDA 2017] is the application of various driving tasks to assess the potential effects of ACT-541468 on the ability to drive a car in the morning after evening administration.

Study objective

Primary objective
- To evaluate the effects of ACT-541468 on objective simulated driving performance, i.e., the standard deviation of the lateral position (SDLP), after single- and multiple dose administrations (i.e., on Day 1 and Day 4) in the

evening.

Secondary and exploratory objectives
- To evaluate the effects of ACT-541468 on other objective simulated driving performance parameters.
- To evaluate the effects of ACT-541468 on subjective simulated driving performance.
- To evaluate the potential relationship between driving performance parameters and plasma concentrations of ACT-541468.
- To evaluate tolerability and safety of multiple oral doses of ACT-541468 (multiple oral doses) and zopiclone (two separate doses).

Study design

This is a single-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 4-way cross-over study.

Intervention

Subject will be randomized into any of the four treatment sequences (A, B, C, D) in a cross-over fashion.

A: ACT-541468 50 mg, zopiclone 7.5 mg, Placebo, ACT-541468 100 mg
B: ACT-541468 100 mg, Placebo, zopiclone 7.5 mg, ACT-541468 50 mg
C: zopiclone 7.5 mg, ACT-541468 100 mg, ACT-541468 50 mg, Placebo
D: Placebo, ACT-541468 50 mg, ACT-541468 100 mg, zopiclone 7.5 mg

Study burden and risks

Administration of ACT-541468 has been evaluated in several preclinical toxicology and pharmacology studies and in phase I and phase 2 studies. ACT-541468 was found to be generally safe and well tolerated. It is however, unsure what the effect on next-day driving ability is. This study will provide valuable human data on driving ability, both objectively as well as subjectively. 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

Public
Idorsia Pharaceuticals Ltd.

Hegenheimermattweg 91
Allschwil CHD-4123
CH
Scientific
Idorsia Pharaceuticals Ltd.

Hegenheimermattweg 91
Allschwil CHD-4123
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Be male or female (of nonchildbearing potential) aged 50 to 80 years, inclusive, at the Screening Visit.
2. Have a body mass index *18.5 and *30.0 kg/m2 at the Screening Visit.
3. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety
tests, medical history, physical examination and vital sign measurements performed at the screening visit and before the first dose of study drug.

Exclusion criteria

1. Pregnant or lactating women.
2. Known hypersensitivity to ACT-541468, zopiclone, or treatments of the same class, or any of their excipients.
3. Unstable medical condition, significant medical disorder, or acute illness within 2 months prior to Screening.
4. Current heavy tobacco user (* 15 cigarettes per day) or smoker with an urge to wake up during the night to smoke.

5. No history of narcolepsy, cataplexy or fainting.
6. Mini Mental State Examination (MMSE) score < 25 at Screening.
7. Current or previous diagnosis of insomnia-related disorder according to the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) criteria.
8. Modified Swiss Narcolepsy Scale total score < 0 at Screening.
9. Activities that disturb the circadian rhythm (e.g., working night shift, travelling across 3 time zones) within 2 weeks before (each) study treatment.

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):	16-03-2019
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACT-541468
Generic name:	NA
Product type:	Medicine
Brand name:	zopiclone
Generic name:	zopiclone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-02-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2019
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	EUCTR2018-003773-97-NL
CCMO	NL68520.056.19

Study results

First publication
02-07-2020