European Neuropsychopharmacology (2019) 29, 847–857

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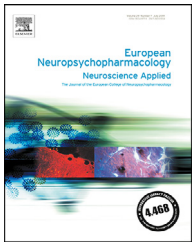

Multiple-dose clinical pharmacology of ACT-541468, a novel dual orexin receptor antagonist, following repeated-dose morning and evening administration

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Received 21 November 2018; received in revised form 22 May 2019; accepted 29 May 2019

KEYWORDS
Multiple-dose;
Pharmacokinetics;
Pharmacodynamics;
Orexin receptor antagonist;
Insomnia

Abstract
ACT-541468 is a dual orexin receptor antagonist with sleep-promoting effects in humans. Following entry-into-humans, its pharmacokinetics (PK) including dose-proportionality and accumulation, pharmacodynamics (PD), safety, and tolerability following multiple-ascending oral dose (MAD) administration in the morning, and next-day residual effects after repeated evening administration were investigated in a double-blind, placebo-controlled, randomized study. 31 healthy male and female subjects in 3 dose-groups (10, 25, and 75 mg) received study drug in the morning for 5 days (MAD part), and 20 healthy subjects received 25 mg in the evening for 1 week (evening part). PK, PD (saccadic peak velocity (SPV), adaptive tracking, body sway, Bond and Lader visual analogue scales (VAS), Karolinska Sleepiness Scale (KSS), VAS Bowdle for assessment of psychedelic effects), Digit Symbol Substitution Test (DSST), and Simple Reaction Time Test (SRTT), safety, and tolerability were assessed. ACT-541468 was absorbed with a median t_{max} of 1.0–2.0 h across the 3 dose groups. The geometric mean elimination half-life ($t_{½}$) on Day 5 was between 5.6 and 8.5 h, and the exposure (area under the curve (AUC)) showed dose proportionality. No accumulation and no influence of sex on the multiple-dose PK parameters of ACT-541468 was observed. No effects were observed at 10 mg. Administration of 25 and 75 mg during the day showed clear dose-dependent effects on the PD parameters, while next-day effects were absent after evening administration of 25 mg. The drug was safe and well tolerated.

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https://doi.org/10.1016/j.euroneuro.2019.05.009

In conclusion, multiple-dose PK/PD of ACT-541468 were compatible with a drug designated to treat insomnia.

1. Introduction

Insomnia is a common health problem, affecting up to 30% of the general population who complain of sleep disruption and approximately 10% of the general population have complaints of sleep disruption with associated symptoms of distress or day-time functional impairment (NIH, 2005; Roth, 2007). These symptoms are consistent with Insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; APA, 2013), which include a dissatisfaction with sleep quantity, associated with difficulty initiating or maintaining sleep, or early morning awakening. Non-pharmacological (psychological and behavioural) standard-of-care therapies of insomnia include cognitive-behavioural therapy, stimulus control, relaxation training, and sleep hygiene measures which typically are the first of these measures to be applied (Schutte-Rodin et al., 2008). Current pharmacologic treatments include benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists (so-called z-drugs), melatonin agonists, and the dual orexin receptor antagonist suvorexant. Although there are safe and effective drugs available to treat insomnia (Schutte-Rodin et al., 2008), a better tolerability, improved efficacy, and the absence of next-day sleepiness is envisaged when pursuing the approach of targeting and antagonizing the orexin receptors.

The discovery of the orexin system in 1998 is a remarkable story that involved 2 independent research teams in the US (de Lecea et al., 1998; Sakurai et al., 1998). Orexin A and B are two hypothalamic neuropeptides that promote wakefulness and mediate behaviour under situations of high motivational relevance such as feeding, reward opportunities, and exposure to stress (Hoyer and Jacobson, 2013; Mahler et al., 2014). Nerve fibers from the orexin neurons make wide projections to those brain regions (forebrain, corticolimbic structures, brainstem) related to the regulation of the wake-sleep cycle. Orexins bind and activate two different orexin receptors (OX_1 and OX_2), promoting alertness and maintaining wakefulness (Sakurai, 2007). The first clinical data of an orexin receptor antagonist were presented less than 10 years after its discovery by Brisbare-Roch et al., 2007, a paper in which results on the dual orexin receptor antagonist (DORA) almorexant in rats, dogs, and humans were reported. More recently in 2014, the DORA suvorexant (Belsomra® USPI) was approved for the treatment of insomnia after extensive review by the US Food and Drug Administration (Michelson et al., 2014).

The identification and development of new sleep drugs poses particular challenges owing to disease-specific requirements such as rapid onset of action, sleep maintenance throughout major parts of the night, and the need for absence of residual next-day effects. In the particular case of ACT-541468, these challenges were addressed by applying physiologically-based PK and PD modelling and estimated the initial therapeutic dose range of ACT-541468 to be within 25–75 mg, and by accelerating Phase 1 development with a multi-layer first-in-humans (FIH) study (Treiber et al., 2017; Muehlan et al., 2018). In the FIH study, over the tested oral dose range (5 to 200 mg), the PK and PD were compatible with a potential treatment for insomnia. The exposure parameters maximum plasma concentration (C_{max}) and area under the curve (AUC) increased slightly less than proportionally to the dose administered, the time to maximum plasma concentration (t_{max}) appeared to increase with dose, ranging from 0.8 to 2.8 h, while the $t_{½}$ was 5.9–8.8 h. Starting at a dose of 25 mg and above, clear dose-dependent effects on the central nervous system (CNS) including reduction in vigilance, attention, alertness, and motor coordination were obtained using a validated PD test-battery. Administration of the drug as single doses of up to 200 mg was safe and well tolerated (Muehlan et al., 2018). In 2 dose groups of that study, a microdose of ^{14}C-labelled ACT-541468 (250 nCi) was administered either orally (in combination with 50 mg 'cold' ACT-541468) to investigate absorption, distribution, metabolism, and excretion (ADME), or intravenously (in combination with 100 mg 'cold' ACT-541468) to evaluate absolute bioavailability. Levels of ^{14}C were determined with the ultrasensitive accelerator mass spectrometry method. Only traces of non-metabolized drug were found in excreta, while the cumulative recovery of radioactivity (drug-related material) was 85% with the majority excreted in faeces. In total 77 metabolites were identified, whereof the 3 major metabolites were shown not to contribute to the pharmacological activity of ACT-541468. Administration of the intravenous microdose revealed an absolute bioavailability of 62%, a low clearance (5.0 L/h), and a volume of distribution of 31 L.

In this article, we report the results of the first multiple-dose administration of ACT-541468 following morning and evening administration to healthy subjects (ClinicalTrials.gov: NCT02571855).

2. Experimental procedures

2.1. Subjects

In total 51 subjects were included in this study: In the MAD part, 31 healthy male and female subjects (1:1 sex ratio) between 18 and 45 years of age received multiple daily doses of ACT-541468 for 5 days in the morning. In the evening part, 20 male and female subjects (1:1 sex ratio) of the same age range received an oral dose of 25 mg ACT-541468 once daily (o.d.) in the evening for 7 days. The protocol was approved by the Dutch health authorities and by the local ethics committee, the Foundation Beoordeling Ethiek Biomedisch Onderzoek, Assen, the Netherlands. Written informed consent was given by each individual prior to any screening procedures. This study was performed in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki. Being healthy was the main inclusion criterion, and the main exclusion criteria for these subjects were history or presence of substance abuse (based

on urine drug screen) or any other psychiatric illness. Absence of any history of narcolepsy was verified with the modified Swiss Narcolepsy Scale questionnaire (Sturzenegger and Basetti, 2004) which was electronically completed by the subject at screening.

2.2. Study design

This was a double-blind, randomized, placebo-controlled, MAD study including an evening administration part. Following a screening period of 3 weeks, subjects in the MAD part were treated with a daily dose of ACT-541468 for 5 days, formulated as the hydrochloride salt in hard gelatin capsules, in 3 dose groups (10, 25, and 75 mg), administered in the morning (between 9:00 and 12:00) under fasting conditions. Each dose was investigated in a new group of 10 healthy subjects (8/2 active/placebo), PK and PD were assessed on Day 1 and on Day 5 (at steady-state). Subjects in the evening part received a daily dose of 25 mg of ACT-541468 before going to sleep (between 22:00 and 24:00) for 7 days, whereas 6 subjects (4/2 active/placebo) had an additional 8th study drug administration to determine PK parameters at night. The design of both study parts is graphically depicted in Fig. 1.

2.3. Blood sampling and PK

MAD part (morning administration): PK samples were taken on Day 1 (single-dose PK profile, sampling time points: pre-dose, 30 min, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose) and on Day 5 (steady-state PK profile, sampling time points as on Day 1 plus 36, 48, and 72 h post-dose). Additional trough (pre-dose) samples were taken on Days 3, and 4. PK parameters C_{max}, t_{max}, $t_{½}$, AUC zero to 24 h ($AUC_{0\text{-}24}$) were determined for Days 1 and 5. In addition, the accumulation index (AI) based on $AUC_{0\text{-}24}$ Day 5/Day 1 was calculated. Dose proportionality was assessed across the dose range for C_{max} and AUC using the method described by Gough et al., 1995.

Evening part: After study drug administration in the evening of Days 1–7, the following PK samples were collected:

- Pre-dose plasma concentration in the evening of Day 1, 3, 5, and 7.
- plasma concentration the next morning (8 h post-dose) on Day 2, 4, 6, and 8.

After the last study drug administration in the evening of Day 7, $t_{½}$ was determined (morning of Day 8 until 60 h post-dose).

- For subjects with night-time PK that had an additional 8th study drug administration in the evening of Day 8, samples were collected at pre-dose, 1, 2, 4, 6, 8, 10, 12, 24, and 36 h post-dose to obtain a night-time PK profile and the parameters C_{max}, $t_{½}$, and $AUC_{0\text{-}24}$ were derived.

2.3.1. Bioanalytics and PK evaluations

Collected blood samples (4 mL) were immediately cooled in ice water. Within 30 min of collection, the tubes were centrifuged at 2000 g for 4 min at 4 °C. Plasma was transferred into polypropylene tubes and was stored at −70 °C and protected from light. After shipment to the bioanalytical laboratory (Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland), the samples could thaw at room temperature, followed by vortex-mixing for 3 s. After further vortex-mixing for 30 s at room temperature, the samples were centrifuged at 3250 g and 4 °C. 150 μL of the supernatants were transferred into a new microtiter plate, and 10 μL were injected onto the column. Concentrations of ACT-541468 were determined using liquid chromatography coupled to tandem mass spectrometry (Mass spectrometer API 4000, AB SCIEX, Concord, ON, Canada), as previously described (Muehlan et al., 2018).

For PK analysis, concentrations below the level of quantification (0.5 ng/mL) were set to '0'. PK parameters were determined by non-compartmental analysis using Professional WinNonlin version 6.4 (Pharsight, Mountain View, CA, USA).

2.4. PD assessments

MAD part (morning administration): PD were assessed on Day 1 (single-dose assessment) and Day 5 (at steady-state) for 10 h using a battery of validated tests (Neurocart®, Centre for Human Drug Research, Leiden, the Netherlands), including the objective psychomotor performance tests SPV, adaptive tracking, the 2-min body sway test, and the VAS Bond and Lader for alertness, mood, and calmness. In previous studies, the Neurocart® test battery had been proven to be sensitive to measure sedation in subjects who had been administered a DORA (Hoever et al., 2010, 2012; Muehlan et al., 2018). In addition, sleepiness was evaluated using the KSS and potential psychedelic effects were assessed with the VAS Bowdle.

Evening part (evening administration): to evaluate next-day effects of ACT-541468 on CNS performance, the objective PD parameters SPV, adaptive tracking performance, body sway, as well as VAS Bond and Lader for subjective alertness, mood, and calmness were evaluated in the morning of Day 2 (after single dose) and Day 8 (at steady state). In addition, on each morning during the treatment period (Days 2–8), sleepiness, cognitive performance, reaction time, and subjective psychedelic effects were evaluated, using the KSS, DSST, SRTT, and the VAS Bowdle, respectively.

The SPV measurement was performed as previously described (van Steveninck et al., 1999; Zuurman et al., 2008). The target screen with a horizontal moving light for assessment of eye movements was fixed 50 cm in front of the head support. The head was restrained from movements and disposable silver chloride electrodes (Mediscore, Rotterdam, the Netherlands) were applied on the forehead and beside the lateral canthi of both eyes of the subject for the registration of the electrooculographic signals. Fifteen saccades were recorded with interstimulus intervals varying randomly between 3 and 6 s recorded for stimulus amplitudes of 15° to either side. Average values of SPV (°/s) were recorded.

The adaptive tracking test is a pursuit-tracking task in which a circle is moving randomly on a screen. The subject had to try to keep a dot inside the moving circle by operating a joystick. The speed of the moving circle increased when the dot was contained in the circle, and the speed was reduced if the dot could not be maintained in the circle. The test was performed as previously described (Borland and Nicholson 1984; van Steveninck et al., 1999; Zuurman et al., 2008; de Haas et al., 2010; Hoever et al., 2010).

Postural stability/body sway was assessed while subjects had to stand in the body sway meter, keeping their eyes closed, with a string attached to the waist, similar to the previously described Wright ataxia meter (Wright, 1971, Zuurman et al., 2008). All body movements in the anteroposterior direction over a period of 2 min were recorded as mm sway.

The KSS has been widely used to assess next-day alertness (Åkerstedt and Gillberg, 1990; Gillberg et al., 1996). The subject was asked to mark his/her current sleepiness on a 9-point scale, where 1 is "very alert", 3 is "alert – normal level," 5 is "neither alert nor sleepy," 7 is "sleepy, but no effort to keep awake," 9 is "very sleepy, great effort to keep awake, fighting sleep," and 2, 4, 6, and 8 are unlabeled. The response was recorded in the subject's source documentation.

The DSST is a widely used cognitive sub-test of the Wechsler Adult Intelligence Tests (Wechsler, 1981). The DSST assesses visual perception but also measures other cognitive functions including attention, short-term memory, and psychomotor speed (Reed et al., 1994; Grünberger et al., 1993). With the computerized version of the DSST, selected symbols appeared in random order in the

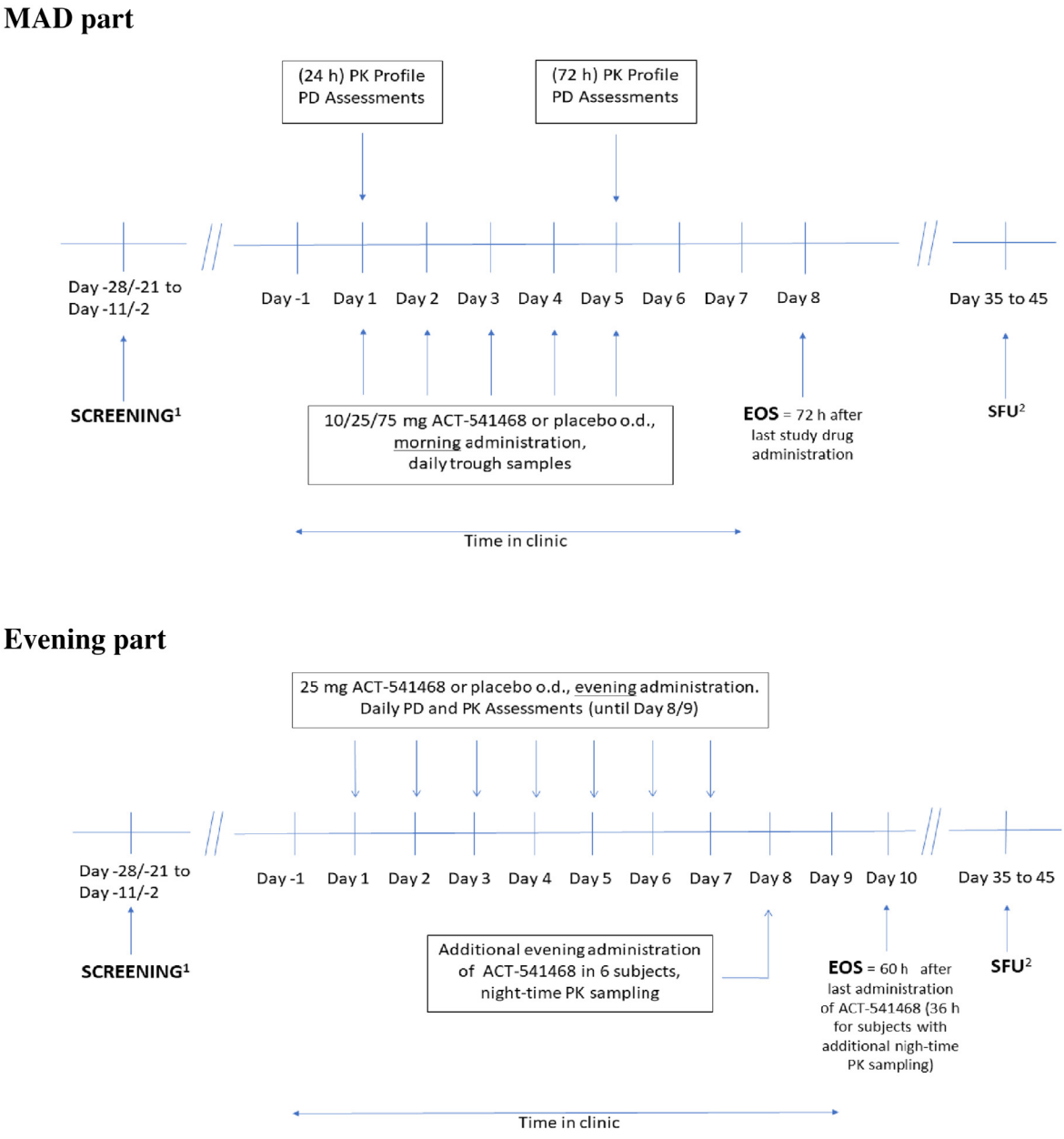

Fig. 1 Study design: MAD and evening part.
EOS = end of study; MAD = multiple-ascending dose; o.d. = once daily; PD = pharmacodynamics; PK = pharmacokinetics; SFU = safety follow up.
[1]Screening between Day −28 and Day −11 for women of childbearing potential and between Day −21 and Day −2 for the other subjects. [2]SFU = 30 to 40 days after last study drug administration.

centre of the computer screen. Subjects used a numeric pad of the keyboard to reproduce the digits associated with the symbol by using the symbol-digit code as presented at the top of the screen. Each symbol-digit association constituted one response. Numbers of correct and incorrect responses were recorded with an average response time per array. The number of correct and incorrect responses within the allowed time and the response time of each array were measured and recorded in the subject's source documentation.

SRTT: slowed reaction time can be an indication of lack of concentration and reduced alertness (Grünberger et al., 1993). To assess reaction time, subjects viewed a black computer screen, and at random intervals (0.5–1.5 s), a white circle appeared in the centre of the screen. Subjects were instructed to press the space bar of the keyboard with the index finger of their dominant hand each time the circle appeared. They were instructed to respond as quickly as possible when they saw the circle. A total of 40 circles were presented, and the duration of the task was approximately 1 min. Reaction times (in ms) were captured in an electronic log file during the test and recorded in the subject's source documentation.

The VAS Bowdle (Bowdle et al., 1998) assesses psychedelic effects. It consists of 13 items, for which the subject was asked to rate on a 10-cm horizontal line how the items applied to his/her current feelings. The VAS was scored from 0 to 100, with 0 reflecting "not at all" and 100 reflecting "extremely". The 13 measurements were recorded into the subject's source documentation. Items 1,

2, 3, 5, 6, and 7 were combined to assess the derived variable "subjective internal perception". Items 4, 8, 9, 10, and 13 were combined to assess the derived variable "subjective external perception". Items 11 and 12 assessed if the subjects were "feeling high" or "drowsy". The algorithm to derive the variables has been described previously (Zuurman et al., 2008).

Dutch versions of the VAS Bond and Lader (Bond and Lader, 1974) to assess subjective alertness, mood, and calmness have been frequently employed at the Centre for Human Drug Research (CHDR) for a variety of sedative agents and are described elsewhere (de Haas et al., 2010; Hoever et al., 2010). Completing the set of VAS required approximately 2 min.

2.5. Safety and tolerability

Safety and tolerability were continuously assessed with respect to frequency, nature, and intensity of treatment-emergent adverse events (AEs). On Days 1 and 5, vital signs (blood pressure and pulse rate) were assessed at pre-dose, and at 30 min, 1, 2, 3, 4, 6, 8, 10, and 12 h post-dose, and daily in the morning of Days 2, 3, 4, 6, 7, and 8 (end of study = EOS). Effects on cardiac function were assessed with 12-lead electrocardiograms (ECGs) at pre-dose, and at 1, 2, and 4 h post-dose on Days 1 and 5 and at EOS. Clinical laboratory parameters (hematology, clinical chemistry) were evaluated at pre-dose and at EOS.

2.6. Statistical analysis

Dose proportionality of the estimated PK parameters was tested across ACT-541468 doses using linear regression of log-transformed parameters as described by Gough et al. (1995). The continuous PD variables were analyzed separately by mixed model with dose, sex, time, and dose by time as fixed effects, with subject as random effect, and with the average baseline value as covariate.

Treatment effects were analyzed as the contrasts between placebo and the different ACT-541468 doses. The contrast between Day 1 and "at steady-state" conditions (Day 5 of the MAD part and Day 8 of the evening part) was analyzed. The PD effects were also assessed on the basis of mean changes from baseline. Safety and tolerability were analyzed descriptively by study part and treatment group, whereas subjects treated with placebo in the different dose groups were pooled for this analysis.

3. Results

3.1. Subjects

A total of 51 (25 male / 26 female) subjects were included into this study. In the MAD part, 31 subjects (24/7 active/placebo) were randomized into 3 dose groups, and 20 subjects (16/4 active/ placebo) in the evening part. In the study parts, including placebo, the mean age was 23.4 and 24.1 years (range: 18–44 years), and mean body mass index was 22.2 and 22.8 kg/m^2 (range: 18.0–29.4 kg/m^2). The majority of subjects (83.5%) were White. All subjects received study treatment. Two subjects in the MAD part discontinued study drug (withdrawal of informed consent). A subject on placebo discontinued study drug on Day 1 prior to any pivotal PD assessment and was replaced. A subject treated with 75 mg discontinued study drug (withdrawal of informed consent) after an AE of sleep paralysis (i.e., a short-lasting [seconds] inability to move and react) on Day 4 and was not replaced.

Table 1 Summary of main PK parameters of ACT-541468 (MAD part, $N = 8$ per dose group).

Parameter		10 mg	25 mg	75 mg
t_{max} [h]	Day 1	**1.00** (0.5-1)	**1.17** (1-1.03)	**1.98** (1-4)
	Day 5	**1.00** (0.5-1.1)	**1.00** (1-4)	**1.07** (1-1.1)
C_{max} [ng/mL]	Day 1	**256** (224-294)	**614** (466-810)	**1225** (766-1960)
	Day 5	**280** (214-366)	**616** (445-852)	**1308** (885-1933)
AUC_{0-24} [ng•h/mL]	Day 1	**1156** (962-1388)	**3502** (2413-5084)	**8583** (5797-12,707)
	Day 5	**1293** (1069-1563)	**3805** (2695-5371)	**8940** (6441-12,410)
$t_{1/2}$ [h]	Day 1	**5.9** (4.5-7-6)	**5.9** (4.8-7.2)	**9.2** (6.3-13.6)
	Day 5	**5.6** (4.2-7-4)	**6.7** (5.1-8.9)	**8.5** (6.8-10.8)
AI	Day 5	**1.1** (1.0-1-3)	**1.1** (1.0-1.3)	**1.1** (0.9-1.3)

Data are expressed as geometric mean (95% confidence interval) except for t_{max} which is expressed as median (range); AI = accumulation index; AUC_{0-24} = area under the plasma concentration-time curve from time zero to 24 h; C_{max} = maximum plasma concentration; MAD = multiple-ascending dose; t_{max} = time to reach maximum plasma concentration; $t_{1/2}$ = terminal half-life.

3.2. Pharmacokinetics

The mean concentration-time profiles and the PK parameters following administration of 10, 25, and 75 mg ACT-541468 in the MAD part are depicted in Fig. 2 and summarized in Table 1. Median t_{max} for ACT-541468 ranged from 1.00 to 1.98 h, and the geometric mean $t_{½}$ on Day 5 ranged from 5.6 to 8.5 h across the dose groups. Steady-state was reached within 3 days, with minimal accumulation, which was estimated by the geometric mean ratio of AUC_{0-24} on Days 5 and 1, yielding an AI of 1.1 after administration of 10, 25, and 75 mg (Table 1). AUC_{0-24} showed dose-proportionality on Day 1 and on Day 5 (steady-state), with the 90% CIs of the slopes (0.83, 1.16 and 0.81, 1.11, for Day 1 and Day 5, respectively) contained within the critical interval (0.66, 1.34). C_{max} increased slightly less than proportionally with dose, with the lower bound of the 90% CIs of the slopes (0.62, 0.93 and 0.60, 0.93 for Day 1 and Day 5, respectively) just outside the critical interval (0.66, 1.34).

In the evening part in which 25 mg was administered in the evening, geometric mean concentrations at trough ranged from 20.3 to 24.1 ng/mL, and from 142.4 to 169.2 ng/mL when measured the next morning at 8 h post-dose. The geometric mean $t_{½}$ of ACT-541468 following the last dose in the evening of Day 7 was 6.1 h [Fig. 3, left panel]. When ACT-541468 PK parameters were determined

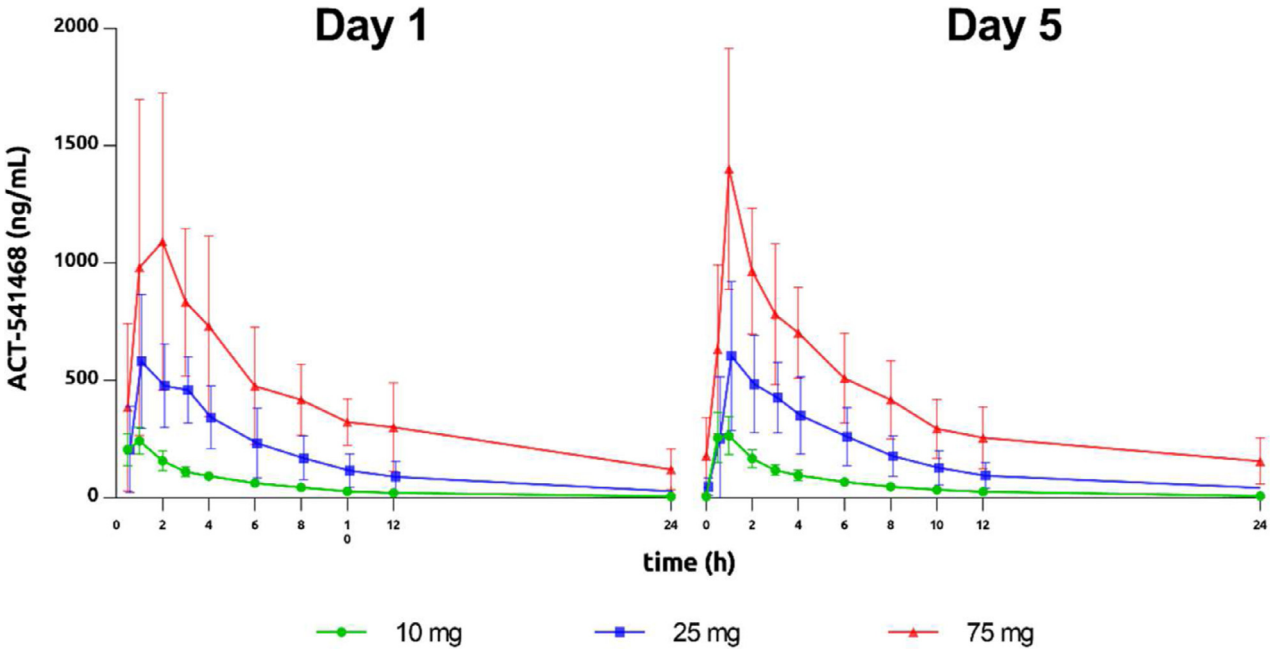

Fig. 2 MAD part: Arithmetic mean (± SD) plasma concentration-time profiles of ACT-541468 following morning administration of 10, 25, or 75 mg o.d. in the fasted state for 5 days on a linear scale; (Day 1 = single dose, Day 5 = at steady state; $N = 8$ per group). PK = pharmacokinetics; SD = standard deviation.

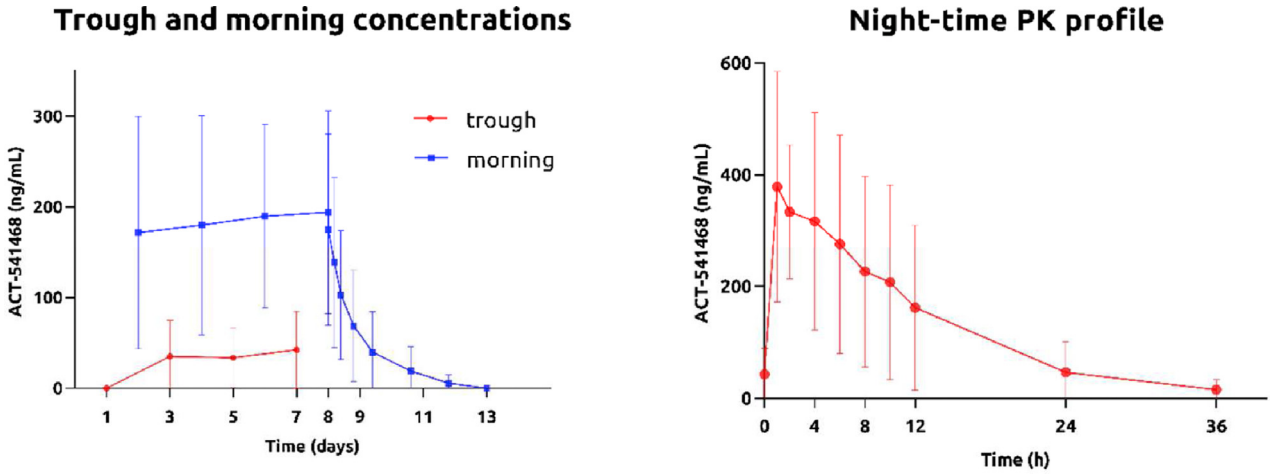

Fig. 3 evening part, left panel*: Arithmetic mean (±SD) plasma concentrations in the morning (8 h post-dose) and evening (trough), following oral administration of 25 mg ACT-541468 in the evening for 7 days to healthy subjects ($n = 16$). Right panel: Mean (±SD) night-time plasma concentration-time profile following an additional administration of 25 mg ACT-541468 to healthy subjects ($n = 4$). PK = pharmacokinetics; SD = standard deviation

*Following evening administration on day 8, a plasma concentration-time profile was collected (Days 9–13) to estimate the terminal half-life ($t_{1/2}$).

during the night, the drug was absorbed with a median (range) t_{max} of 1.5 h (1–4 h) and the geometric mean $t_{½}$ was 6.1 h, while C_{max} and $AUC_{0\text{-}24}$ were 475 ng/mL and 3729 ng h/mL, respectively [Fig. 3, right panel]. In both study parts (MAD and evening administration), no trend with respect to the influence of sex on ACT-541468 PK was observed.

3.3. Pharmacodynamics

No clear PD effects were observed on both Day 1 and 5 following administration of 10 mg ACT-541468 in the morning. In the 25 and 75 mg groups, when compared to placebo, effects on all PD variables assessing motor and cognitive functions of the CNS (i.e., reduced vigilance and attention,

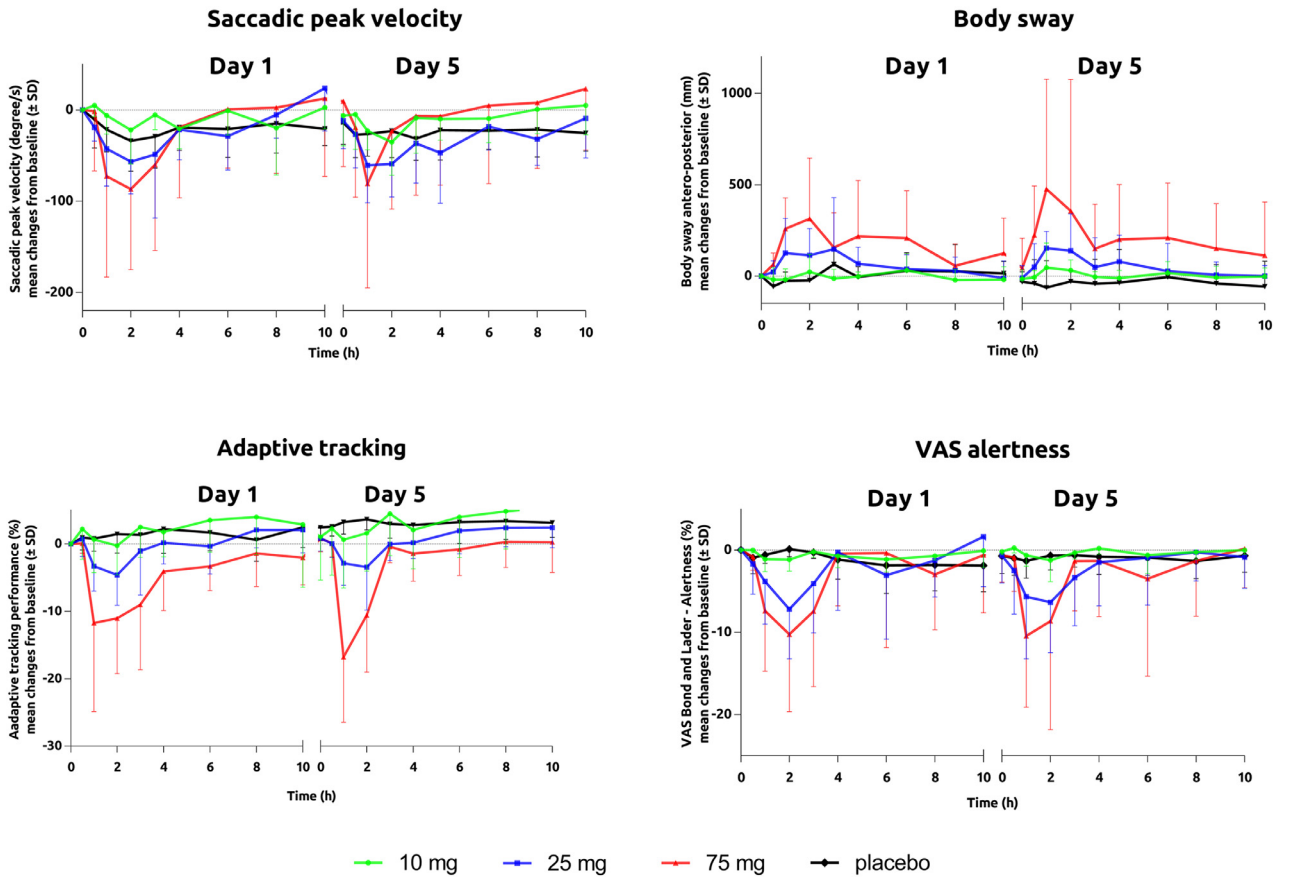

Fig. 4 MAD part: Effects on PD variables saccadic peak velocity, body sway, adaptive tracking, and VAS subjective alertness on Days 1 and 5 after multiple-dose administration of 10, 25, and 75 mg ACT-541468 (mean change from baseline ± SD; $N = 8$ for ACT-541468 doses; $N = 7$ for placebo).
MAD = multiple-ascending dose; PD = pharmacodynamic; SD = standard deviation; VAS = visual analogue scale.

as well as visuomotor coordination and postural stability), were observed (Fig. 4 and supplemental Table 1). The onset of effects on the objective PD assessments was within 1 h after study drug administration and the maximum effect occurred around 2 h post-dose, with return to baseline within 4–10 h post-dose. On Day 1, in the 25 and 75 mg dose groups, decreased SPV compared to placebo was observed with a maximum mean reduction (±SD) of 57 (35.5) and 87 (88.2) °/s, for 25 and 75 mg, respectively. On Day 5, the maximum mean reduction in SPV was observed at 1 h post-dose, with a similar magnitude than on Day 1, and return to baseline at approximately 10 h post-dose.

When compared to placebo, administration of 25 and 75 mg ACT-541468 resulted in a decrease of adaptive tracking performance in a dose-dependent manner with a maximum mean reduction (±SD) on Day 1 of 4.6 (4.5) and 16.8% (9.7) on Day 5, and an increase in body sway with maximum mean values (±SD) observed on Day 5 of 154 (91.4) and 476 (601.8) mm for 25 and 75 mg of ACT-541468, respectively. When compared to placebo, subjective alertness decreased dose-dependently with a maximum mean reduction of 7.4 and 10.4% for 25 and 75 mg, respectively. At 25 and 75 mg, small mean maximum effects on the KSS of 1.5 - 3 were observed on Day 1 and Day 5 (supplemental Fig. 1). At 75 mg, small mean maximum increases from baseline in the range 0.1–0.5 on all four components of the VAS Bowdle were observed on Day 1 and Day 5 (supplemental Fig. 2). There were no relevant differences in the magnitude of effects on Day 1 and Day 5 for any of the PD parameters.

In the evening part, in which next-day effects of ACT-541468 on PD parameters (SPV, adaptive tracking, body sway, VAS Bond and Lader) were assessed at 8 h post-dose in the morning of Day 2 and Day 8, no relevant mean changes from baseline when compared to placebo were observed (supplemental Fig. 3). Other PD variables (KSS, DSST, SRTT, and VAS Bowdle, data not shown) which were assessed every morning at 8 h post-dose, also showed no relevant changes from baseline when compared to placebo. No influence of sex on the PD parameters of ACT-541468 was observed.

3.4. Tolerability and safety

Most frequently reported treatment-emergent AEs are presented in Tables 2 and 3. In the MAD part, 18 of the 24 subjects (75.0%) in the 10, 25, and 75 mg ACT-541468 dose groups had at least 1 treatment-emergent AE, and 4 of the 7 subjects (57.1%) treated with placebo had at least 1 AE. All AEs were of either mild or moderate intensity, there were neither severe nor serious AEs reported. Somnolence was

Table 2 Summary of treatment-emergent adverse events that occurred in more than 1 subject, shown by frequency (MAD part).

Preferred term	10 mg (N = 8)		25 mg (N = 8)		75 mg (N = 8)		Placebo (N = 7)	
	AEs	*N*	*AEs*	*N*	*AEs*	*N*	*AEs*	*N*
Subjects with at least one AE		**6**		**5**		**7**		**4**
Somnolence	1	**1**	9	**5**	22	**6**	2	**2**
Sudden onset of sleep	-	**-**	1	**1**	13	**6**	-	**-**
Headache	1	**1**	3	**1**	2	**2**	5	**2**
Dizziness	1	**1**	1	**1**	2	**2**	-	-
Muscular weakness	1	**1**	-	**-**	2	**2**	-	-
Abdominal pain	-	**-**	1	**1**	1	**1**	-	-
Back pain	1	**1**	1	**1**	-	**-**	-	-
Feeling cold	-	**-**	-	-	2	**2**	-	-
Insomnia	-	**-**	-	-	2	**2**	-	-
Sleep paralysis	-	-	-	-	2	**2**	-	-

AE = adverse event; MAD = multiple-ascending dose.

Table 3 Summary of treatment-emergent adverse events that occurred in more than 1 subject, shown by frequency (evening part).

Preferred term	25 mg (N = 16)		Placebo (N = 4)	
	AEs	*N*	*AEs*	*N*
Subjects with at least one AE		**14**		**4**
Headache	12	**8**	2	**2**
Somnolence	9	**5**	-	**-**
Insomnia	2	**2**	1	**1**
Nausea	2	**2**	2	**2**
Dizziness	-	**-**	2	**2**

AE = adverse event.

the most frequently reported AE in the MAD part across all active dose groups (12 subjects, 50.0%) compared to 2 subjects (28.6%) on placebo. Somnolence was reported by 1, 5, and 6 subjects treated with 10, 25, and 75 mg, respectively. Other frequently reported AEs in the MAD part included headache, sudden onset of sleep, and dizziness (Table 2).

Muscular weakness was reported in 3 subjects in the MAD part: Two female subjects in the 75 mg dose group reported mild muscular weakness of short duration (seconds) on Day 2 at approximately 2–3 h post-dose that was considered by the investigator to be related to the study drug but not associated with narcolepsy. In addition, 1 female subject in the 10 mg dose group reported muscular weakness which was considered by the investigator as not related to the study drug. Sleep paralysis was reported in 2 subjects (1 female on Day 4 and 1 male on Day 1) in the 75 mg dose group. Both events were mild in intensity, reported at approximately 2–3 h post-dose, with a duration of a few seconds. Although related to study drug, these events were considered by the investigator to be not associated with narcolepsy. The female subject experiencing sleep paralysis on Day 4 withdrew from the study thereafter (withdrawal of consent).

In the evening part, 14 of the 16 subjects (87.5%) on ACT-541468 and all 4 placebo subjects had at least 1 treatment-emergent AE (Table 3). Headache was the most frequently reported AE, with 8 subjects (50.0%) on ACT-541468 and 2 subjects (50.0%) on placebo. Other AEs reported in at least 2 subjects on ACT-541468 or placebo were somnolence (5 on active), insomnia (2 on active and 1 on placebo), nausea (2 subjects each), and dizziness (0 on active and 2 on placebo). All reported AEs were of mild intensity. In both study parts (MAD and evening administration), the incidence of subjects who reported at least one AE was higher in females compared to males.

In both study parts, safety parameters (i.e., mean changes from baseline to EOS in clinical laboratory variables, vital signs or ECG variables) were unremarkable. Out-of-range post-baseline values were reported for some subjects. These observations were incidental, no treatment-related pattern was detected, and none of these findings were considered by the investigator to be clinically significant.

4. Discussion

ACT-541468 is a dual orexin receptor antagonist with a nonclinical profile indicative of sleep-promoting properties (Treiber et al., 2017). After the successful conduct of the FIH single-ascending dose (SAD) study (Muehlan et al., 2018), we report here the first multiple-dose and the first evening administration of ACT-541468 in healthy young adult male and female subjects.

The PK profile of ACT-541468 following multiple-dose administration of 10, 25, or 75 mg o.d. in the morning in the fasted state was characterized by an absorption with a median t_{max} ranging from 1 to 2 h, and a geometric mean $t_{½}$ on Day 5 ranging from 5.6 to 8.5 h across the dose groups. PK parameters t_{max}, C_{max}, $t_{½}$, and AUC were similar to those observed in the SAD study. Following daily multiple-dose administration, no relevant accumulation of ACT-541468 was observed.

In the evening part, 25 mg ACT-541468 was administered in the evening for 7 days, and PK samples were taken pre-dose (at trough) and at 8 h post-dose (next morning). Following the last study drug administration (on Day 7), the geometric mean plasma concentration at 8 h post-dose on

Day 8 was 169 ng/mL. The geometric mean $t_{½}$ was 6.1 h, which was similar to the $t_{½}$ following morning administration in the MAD part. For evaluation of night-time PK, 6 subjects had an additional eighth study drug administration, followed by a PK profile to determine PK parameters during the night. When administered in the evening, ACT-541468 was absorbed with a median (range) t_{max} of 1.5 h (1–4 h), a geometric mean C_{max} of 475 ng/mL, and a geometric mean $t_{½}$ of 6.1 h. The lower C_{max} observed during the night was most likely influenced by the less frequent PK sampling schedule during the night. The exposure and $t_{½}$ observed after evening administration were comparable to the parameters observed in subjects under multiple-dose conditions following morning administration in the MAD part, which is demonstrated when parameters of the evening part are compared to morning administration values on Day 5 of the MAD part: $AUC_{0\text{-}24}$ 3729 ng h/mL vs 3805 ng h/mL and $t_{½}$ 6.1 h vs 6.7 h (Table 1).

The similarities of the ACT-541468 PK parameters after morning and evening administration are in contrast with the observations made earlier with the DORA almorexant, for which evening administration resulted in a different PK profile, characterized by a delayed absorption (median t_{max} 2.0–4.0 h after evening administration vs 1.0 h during after morning administration) and a 60% decrease in C_{max} (Hoever et al., 2012). This difference between the two drugs is probably explained by the difference in bioavailability, i.e., 62% for ACT-541468 and only 11% for almorexant (Muehlan et al., 2018; Hoch et al., 2012). Drugs with a low bioavailability are more sensitive to changes in liver blood flow which in turn is influenced by body posture (Culbertson et al., 1951; Klotz and Ziegler, 1982; Ohnishi et al., 1985).

In the MAD part, in which the drug was administered in the morning, clear CNS-related effects, i.e., reduced vigilance and attention, visuomotor coordination, and postural stability were observed in the 25 and 75 mg dose groups.

The onset of effects on the objective PD assessments was within 1 h after study drug administration and the maximum effect occurred around 2 h post-dose, with return to baseline within 4–10 h post-dose. There were no relevant differences in the magnitude of the PD effects measured on Day 1 and Day 5; however, Fig. 1 indicates a trend for a slightly earlier maximum mean effect on Day 5 (1–1.5 h post-dose) when compared to Day 1 (2 h post-dose). In the evening part, no next-day residual effects, i.e., no relevant changes from baseline when compared to placebo on any of the objective and subjective PD variables were observed when assessed the next morning. However, one should be cautious when interpreting these results in view of the relatively small subject numbers, the inherent inter-subject variability, and the differences in placebo response. It remains to be seen if the observed PD effects in healthy subjects will translate into efficacy in the target population (i.e., patients suffering from insomnia disorder) that will be included in future studies. In addition, future trials will need to address the fact that use of sleep medication increases with age and is highest in the elderly (Ohayon and Smirne, 2002), and as elderly people exhibit a different sleep pattern compared to younger adults (Ohayon et al., 2004), the sensitivity of elderly and younger adults to the PD properties of a compound may differ.

With regards to the PK-PD relationship in this study, the occurrence of maximum PD effects at 1–2 h post-dose (i.e., around C_{max}) and the time course of the effects, i.e., the return to baseline within 4–10 h, are in agreement with the observed PK characteristics of ACT-541468, both after single and multiple dosing. The absence of PD effects 10 h after administration of the study drug also suggests that there is no accumulation of any active metabolites, although in the human ADME study, metabolites with a significantly longer $t_{½}$ than the parent compound (25 vs 6 h) were present in plasma (Muehlan et al., 2018).

Multiple-dose administration of ACT-541468 was safe and well-tolerated in healthy male and female subjects, all treatment-emergent AEs were of mild or moderate intensity. The AE profile of 10 mg was similar to placebo whereas for 25 and 75 mg CNS-related AEs such as somnolence or sudden onset of sleep were reported more frequently for ACT-541468 than for placebo, which was expected when a sleep-promoting drug is administered to healthy subjects in the morning of a busy day with frequent PK, PD, and safety assessments. Two cases of sleep paralysis and 2 cases of muscle weakness, without loss of consciousness, were observed at the highest dose level of 75 mg and were considered by the investigator as related to study drug. Sleep paralysis is thought to occur in up to 25% of (healthy) people. It is characterized by a discrete period of time during which voluntary muscle is inhibited, yet ocular and respiratory movements are intact, and the sensorium remains clear. These episodes can occur when falling asleep or upon awakening (Sharpless and Barber, 2011). The AE of muscular weakness reported in the 10 mg dose group was not related to study drug. Notably, these events occurred during morning administration of an orexin receptor antagonist, thus, may be related to a typical reduction in motor tone that can occur with brief transitions to sleep or while awakening, and did not result in premature withdrawal of subjects. All 4 subjects completed the Narcolepsy 2nd Step Questionnaire (which was required to be completed by subjects who had potential narcolepsy-like events) without any indication of an emotional trigger, which would classify these events as narcolepsy-like. However, narcolepsy, a neurological condition mostly characterized by excessive daytime sleepiness and uncontrollable sleep attacks, could in theory be a side effect of an orexin receptor antagonist (Hoever et al., 2012), given the finding that an orexin deficiency causes narcolepsy in humans and animals (Peyron et al., 2000; Thannickal et al., 2000; Sakurai, 2007). Therefore, any AEs that are possibly related to abnormalities in muscle tone should be monitored thoroughly in future studies.

5. Conclusion

In conclusion, there are several pharmacological treatment options available for insomnia disorder, however, each has its limitations (Holbrook et al., 2000; MacCall, 2004; Buscemi et al., 2007). Improved tolerability and efficacy without negatively impacting next-day functioning is needed in clinical practice.

In this MAD/repeated evening administration study of the dual orexin receptor antagonist ACT-541468 in healthy

young subjects, effects on PD variables assessing motor and cognitive functions of the CNS (i.e., reduced vigilance and attention, as well as visuomotor coordination and postural stability) starting at a dose of 25 mg were observed. During administration of 25 mg ACT-541468 in the evening, no next-day impairment of motor and cognitive functions of the CNS was observed.

Results of this study support further development of ACT-541468 in patients with insomnia disorder.

Acknowledgements

The authors thank Margaux Boehler, Sandrine Gioria, Susanne Globig, Giancarlo Sabattini, and Cristina Maria Russo for their dedicated support.

Role of funding source

At the time of study conduct, C. Muehlan and J. Dingemanse were employees of Actelion Pharmaceuticals Ltd, the study sponsor and predecessor of Idorsia Pharmaceuticals Ltd. These authors own stocks or stock options of Idorsia Pharmaceuticals Ltd.

R. Zuiker and J. van Gerven were the study Investigators and employees at CHDR, S. Brooks was the project manager at CHDR. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this article.

Contributions

C. Muehlan: Conceptualization, methodology, data curation, formal analysis, writing - original draft. S. Brooks, R. Zuiker, J. van Gerven: Investigation, project administration, data curation, writing - review and editing. J. Dingemanse: Conceptualization, methodology, supervision, writing - review and editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.05.009.

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