First-in-human study of ACT-541468, a novel dual orexin receptor antagonist: characterization of its pharmacokinetics, pharmacodynamics, safety, and tolerability

PII-102

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INTRODUCTION

Background

- The orexin system plays a central role in maintaining wakefulness.[1-4]
- The dual orexin receptor antagonist ACT-541468 promotes sleep in animal models and is currently being developed to treat sleep disorders.

Objectives

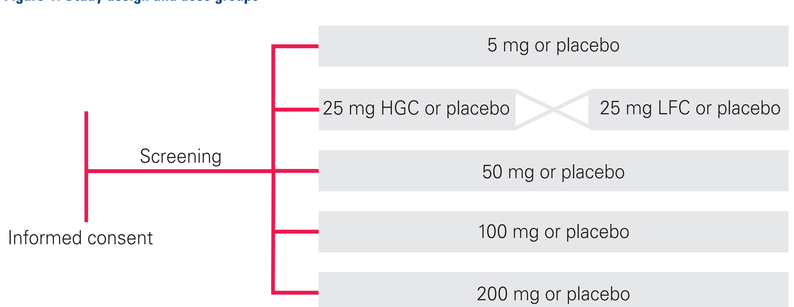
- This first-in-human trial investigated the single ascending oral dose pharmacokinetics (PK) including dose-proportionality, pharmacodynamics (PD), safety, and tolerability.
- The mass balance and metabolism and the absolute bioavailability were investigated in two additional study parts, following oral and intravenous administration of a ^{14}C-labeled ACT-541468 microtracer [see poster PII-013, Mass balance and absolute bioavailability of ACT-541468, a dual orexin receptor antagonist, by administration of a microtracer dose and AMS analysis in a first-in- human study].

METHODS

Study design, treatments, and assessments

- This was a double-blind, placebo-controlled, randomized, single-ascending dose study in 40 healthy male subjects in five dose groups (5, 25, 50, 100, and 200 mg ACT-541468 as hard gelatin capsules (HGC), six on active and two on placebo/group).
- At 25 mg, subjects received ACT-541468 as a HGC and as a liquid-filled capsule (LFC), in a cross-over design.
- Plasma samples were collected over 96 h. Concentrations of ACT-541468 were determined by LC-MS/MS.
- PK, PD, safety, and tolerability were assessed.
- The following PK parameters of ACT-541468 were derived by noncompartmental analysis of the plasma concentration–time profiles:
  - Maximum plasma concentration (C_{max})
  - Time to reach C_{max} (t_{max})
  - Terminal half-life ($t_{½}$)
  - Area under the plasma concentration-time curve from 0–24 h (AUC_{0-24}) and extrapolated to infinity ($AUC_{0-\infty}$)
    - Ratio of free (unbound) to total plasma concentration (Cu/C) 1.5 h post-dose
    - Dose proportionality
    - PK parameters were explored using geometric means and their 95% confidence intervals (CI), except t_{max} which is expressed as median (range).
- The PD (change from baseline) of ACT-541468 were assessed at specific timepoints for 10 h using a battery of validated objective tests (Neurocart®), including body sway, saccadic peak velocity, and adaptive tracking.
- Subjective effects were assessed using the 16-item Bond and Lader visual analog scale (VAS) for alertness, mood, and calmness.

Figure 1. Study design and dose groups



RESULTS

Demographics

- All 40 subjects included received study drug and were evaluable for PK, PD, safety, and tolerability. The mean (range) age was 23.9 (18–44) years and the mean (SD) BMI of subjects was 22.97 (2.52) kg/m^2. Demographic characteristics were similar across dose groups.

Pharmacokinetics

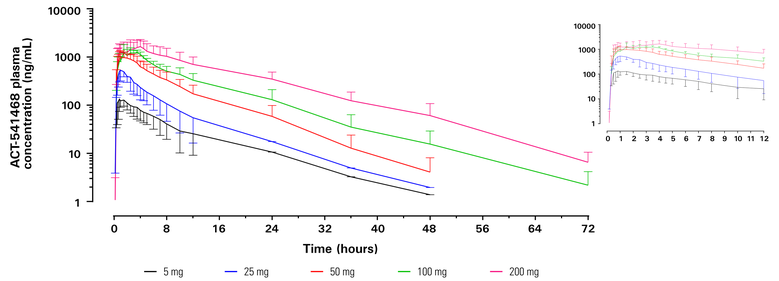
- ACT-541468 was quickly absorbed (median t_{max} 0.7–2 h for the 5–50 mg doses and 2.5 and 2.8 h for the 100 and 200 mg dose, respectively) (Table 1, Figure 2).
- The geometric mean $t_{½}$ was between 5.9 and 6.5 h for the 5–50 mg doses, and 7.5 and 8.8 h for the 100 and 200 mg dose, respectively (Table 1).
- C_{max} and AUC increased slightly less than proportionally to the dose administered.
- The ratio of free (unbound) to plasma protein-bound concentrations (Cu/C) at 1.5 h post dose was 0.1% in the 25 and 200 mg dose groups (Table 1).
- LFC formulation showed slightly shorter t_{max} and higher C_{max} but same exposure as HGC.

Table 1. Summary of main PK parameters after single-dose administration

Parameter [unit]	5 mg	25 mg	50 mg	100 mg	200 mg
t_{max} [h]	0.8 (0.5, 2)	1.0 (0.8, 2.5)	2.0 (0.7, 3)	2.5 (1.5, 3.5)	2.8 (1.5, 4)
C_{max} [ng/mL]	160 (123, 208)	632 (516, 774)	1232 (962, 1576)	1557 (1245, 1946)	1869 (1179, 2962)
AUC_{0-24} [ng·h/mL]	894 (556, 1439)	2568 (1612, 4092)	6947 (4838, 9976)	10998 (8488, 14248)	17864 (10891, 29302)
$t_{1/2}$ [h]	6.5 (4.8, 8.9)	6.1 (4.1, 9.1)	5.9 (4.8, 7.4)	7.4 (5.3, 10.5)	8.8 (6.6, 11.8)
C_u/C (1.5 h post-dose) [%]	–	0.1 N/A	–	–	0.1 N/A

Data are expressed as geometric mean (95% CI) except for t_{max} which is expressed as median (range); n = 6 per dose group.

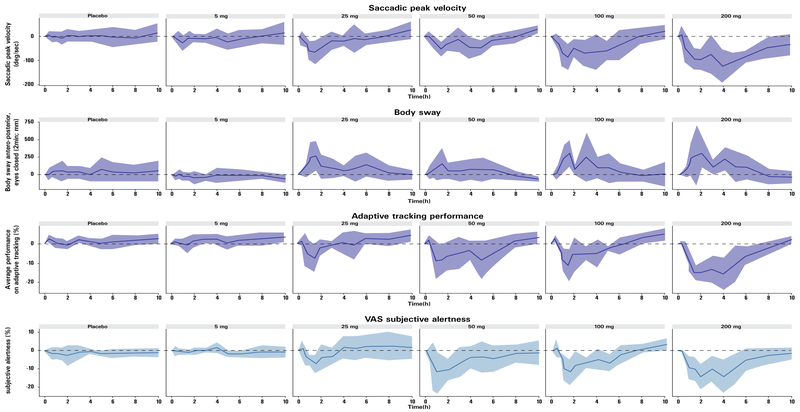
Figure 2. Mean (±SD) plasma concentration-time profile of ACT-541468 following oral administration (semilogarithmic scale, inset shows first 12 h post-dose with frequent sampling, n = 6)



Pharmacodynamics

- Results of PD assessments showed a barely detectable effect of ACT-541468 at 5 mg.
- At doses ≥ 25 mg, PD data revealed a clear effect on the central nervous system (CNS), i.e., reduced vigilance and attention, visuomotor coordination and postural stability indicated by decreased saccadic peak velocity (Figure 3), adaptive tracking performance, and increased body sway.
- Starting at 25 mg a dose-dependent decrease in VAS subjective alertness was observed. There was no change in alertness in the placebo and 5 mg groups (Figure 3).
- PD effects with LFC formulation were similar to HGC.
- The onset of effect started within 1 h and the maximum effect occurred around 1.5 h following treatment intake for doses up to 100 mg. At 200 mg, the maximum effect generally occurred after 2 h. Overall, the effects of 25 and 50 mg returned to baseline within 3–6 h and 6–8 h after drug intake, respectively. Following doses of 100 mg and 200 mg, the time required to return to baseline values was within 8 h and 10 h, respectively.

Figure 3. Saccadic peak velocity, body sway, adaptive tracking, and VAS Bond & Lader subjective alertness) after administration of a single dose of ACT-541468 (mean change from baseline ± SD; n = 6 for ACT-541468 doses; n = 10 for placebo)



Safety and tolerability

- Adverse events (AEs) observed were in line with the expected PD effects of a sleep-inducing drug. The total number of AEs reported in the study (whether or not related to study drug) was 56, of which 15 were reported after placebo administration (Table 2).
- The duration of AEs related to depression of the CNS showed a trend to increase with dose.
- All AEs were of either mild or moderate intensity.
- No clinically significant treatment-emergent abnormalities in clinical laboratory, vital sign, body temperature, or ECG variables were observed.

Table 2. Summary of main AEs (reported in ≥ 10% of subjects)

Preferred term	5 mg (n = 6)	25 mg (n = 6)	25 mg LFC (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	Placebo (n = 10)	Overall (N = 40)
Somnolence	–	2	4	5	4	5	3	23
Fatigue	–	3	1	1	3	1	–	9
Headache	1	–	–	–	–	1	4	6
Disturbance in attention	1	1	2	1	–	–	–	5
Muscular weakness	–	–	–	–	–	4	–	4

CONCLUSION

- **The PK and PD of ACT-541468 are compatible with a drug for the treatment of insomnia.**
- **ACT-541468 was generally well tolerated at single doses of up to and including 200 mg.**
- **Data from this first-in-human study warrant further investigation in humans.**

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