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

PII-013

Margaux Boehler[1]*, Clemens Muehlan[1], Pierre-Eric Juif[1], Stephen English[2], Joop van Gerven[3], Pierre Peeters[3], Jules Heuberger[3], and Jasper Dingemanse[1]

[1]Department of Clinical Pharmacology, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [2]Xceleron Inc., Germantown, MD, USA; [3]Centre for Human Drug Research, Leiden, The Netherlands

Presenting author

INTRODUCTION

Background

- The orexin system is an important regulator of sleep and arousal.[1-4]
- ACT-541468 is a potent dual orexin receptor antagonist under development for the treatment of sleep disorders.

Objectives

- Mass balance part: to investigate the mass balance in urine and feces, and the pharmacokinetics (PK) of total radioactivity (i.e., parent ^{14}C-labeled ACT-541468 and metabolites) in whole blood and plasma, following oral administration of a microtracer.
- Absolute bioavailability part: to estimate the absolute bioavailability (F), clearance (CL), and volume of distribution at steady state (V_{ss}) of ACT-541468, as well as the PK of total radioactivity (i.e., parent ^{14}C-labeled ACT-541468 and metabolites) and parent ^{14}C-labeled ACT-541468, following intravenous (i.v.) administration of a microtracer.

METHODS

Study design

- A first-in-human, double-blind, placebo-controlled, randomized, single-ascending dose study (five dose groups).[5]
- Mass balance and F determined in two selected dose groups.
- Eight healthy male subjects per group (six on active drug and two on placebo).

Study treatments

- Mass balance part: a single oral dose of 50 mg ACT-541468 in combination with 15 mL of an oral solution of 2.02 µg (nominal dose, 250 nCi) ^{14}C-labeled ACT-541468 administered to six subjects. Two subjects received the matching placebos.
- Absolute bioavailability part: 2.02 µg ^{14}C-labeled ACT-541468 (nominal dose, 250 nCi) administered as a short i.v. infusion (15 mL in 15 min) starting 2.5 h after oral 100 mg ACT-541468 to four subjects. Two subjects received the matching placebos.

Bioanalytics

Sampling duration

- Mass balance part: blood, urine, and feces over 168 h.
- Absolute bioavailability part: blood over 96 h.

Sample analysis

- Plasma concentrations of ACT-541468 determined by LC-MS/MS.
- Mass balance part: plasma, whole blood, urine, and feces samples analyzed for total ^{14}C-content by accelerator mass spectrometry (AMS). The radioactivity concentrations in dpm/mL (plasma, whole blood, and urine) or dpm/g (feces) were converted to ng eq/mL or ng eq/g, respectively, based on the specific activity of the total oral dose ACT-541468 administered (tracer plus capsule; 10386 dpm/mg).
- Absolute bioavailability part: plasma samples analyzed for total ^{14}C-content by AMS and for parent ^{14}C-labeled ACT-541468 by HPLC followed by AMS. The specific activity of the tracer (274.4 dpm/ng) allowed for a conversion of radioactivity concentration (dpm/mL) in pg eq/mL (total radioactivity) or pg/mL (parent compound).

REFERENCES

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2. Sakurai T. Nat Rev Neurosci. 2007;8(3):171-81.
3. Carter ME, Schaich Borg J, de Lecea L. Curr Opin Pharmacol. 2009;9(1):39-45.
4. Tsujino N, Sakurai T. Pharmacol Rev. 2009;61(2):162-76.
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RESULTS: MASS BALANCE PART

- Terminal half-life ($t_{½}$) of total radioactivity was longer and exposure higher in plasma than in whole blood (Table 1 and Figure 1).
- Partitioning of total radioactivity into red blood cells determined based on total ^{14}C-concentration measured at t_{max} in plasma and whole blood, with an estimated blood/plasma ratio of 0.64.
- Mean (95% confidence interval [CI]) cumulative excretion of the administered radioactive dose in feces and urine of 56.6 (49.6, 63.5)% and 27.9 (23.4, 32.4)%, respectively, corresponding to a total cumulative recovery of 84.5 (78.3, 90.6)% at 168 h (Figure 2).

Table 1. Summary of PK parameters of total radioactivity in whole blood and plasma, after oral administration of 50 mg ACT-541468 in combination with oral tracer (n = 6)

Parameter	50 mg + oral tracer (plasma)	50 mg + oral tracer (whole blood)
C_{max}, ng eq/mL	3590 (3353, 3845)	2329 (2062, 2630)
t_{max}, h	0.4 (0.3, 1.0)	0.5 (0.3, 1.0)
$AUC_{0\text{-}t}$, ng eq·h/mL	28971 (20400, 41143)	18287 (12442, 26879)
$AUC_{0\text{-}\infty}$, ng eq·h/mL	29478 (20790, 41797)	19337 (13224, 28274)
$t_{1/2}$, h	25.5 (14.0, 46.6)	14.0 (11.5, 16.9)

Data are presented as geometric mean (95% confidence interval) for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ and as median (range) for t_{max}. $AUC_{0\text{-}\infty}$ = area under the plasma/whole blood concentration-time curve from zero to infinity, $AUC_{0\text{-}t}$ = area under the plasma/whole blood concentration-time curve from zero to time t of the last measured concentration above the limit of quantification, C_{max} = maximum plasma/whole blood concentration, $t_{1/2}$ = terminal half-life, t_{max} = time to reach C_{max}.

Figure 1. Mean (SD) concentration-time profile of total radioactivity in whole blood and plasma after oral administration of 50 mg ACT-541468 in combination with oral tracer (linear scale, inset semi-logarithmic scale, n = 6)

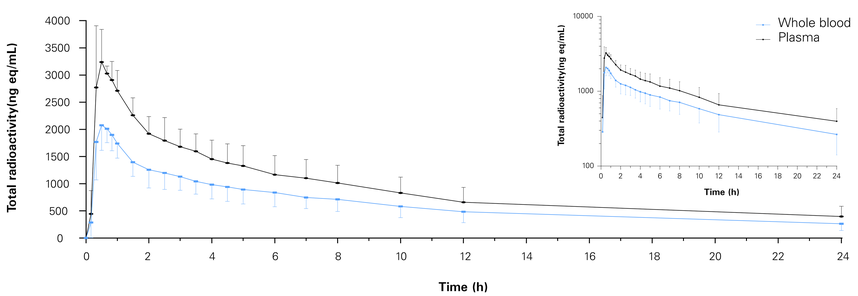
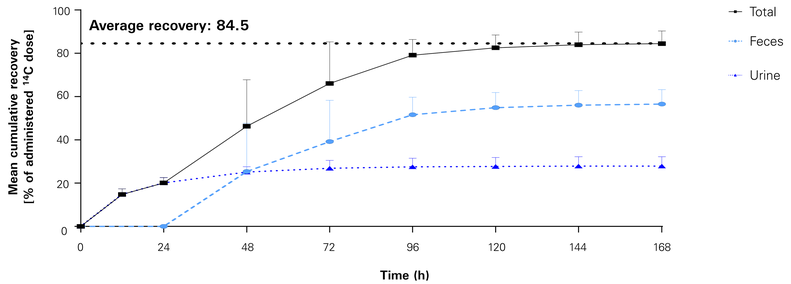


Figure 2. Mean (SD) cumulative recovery of total radioactivity following oral administration of the tracer (n = 6)



CONCLUSION: MASS BALANCE PART

- **After 168 h, total recovery of 85% with approximately 2/3 in feces and 1/3 in urine.**

RESULTS: ABSOLUTE BIOAVAILABILITY PART

- Following i.v. infusion, ^{14}C-labeled ACT-541468 quickly distributed and was eliminated with metabolites exhibiting a longer $t_{½}$ than the parent compound (Table 2 and Figure 3).
- No marked differences in $t_{½}$ between i.v. and oral administered ACT-541468 (Figure 4).
- Comparison of the total exposure following the i.v. microtracer to oral ACT-541468 showed a geometric mean (95% CI) F of 62.1 (51.6, 74.8)%.
- Geometric mean (95% CI) CL and V_{ss} of 5.0 (3.0, 8.1) L/h and 31.0 (26.3, 36.5) L, respectively.

Table 2. Summary of PK parameters of ^{14}C-labeled ACT-541468 in plasma, following i.v. administration of the tracer (n = 4)

Parameter	100 mg + i.v. tracer (plasma)
C_{max}, pg/mL	154.5 (101.9, 234.3)
t_{max}, h	0.3 (0.3, 0.3)
$AUC_{0\text{-}t}$, pg·h/mL	295.9 (158.9, 551.1)
$AUC_{0\text{-}\infty}$, pg·h/mL	315.0 (174.2, 569.9)
$t_{1/2}$, h	6.2 (3.5, 11.0)

Data are presented as geometric mean (95% confidence interval) for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ and as median (range) for t_{max}. $AUC_{0\text{-}\infty}$ = area under the plasma concentration-time curve from zero to infinity, $AUC_{0\text{-}t}$ = area under the plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification, C_{max} = maximum plasma concentration, i.v. = intravenous, $t_{1/2}$ = terminal half-life, t_{max} = time to reach C_{max}.

Figure 3. Mean (SD) plasma concentration-time profile of total radioactivity and ^{14}C-labeled ACT-541468, following i.v. administration of the tracer (linear scale, inset semi-logarithmic scale, n = 4)

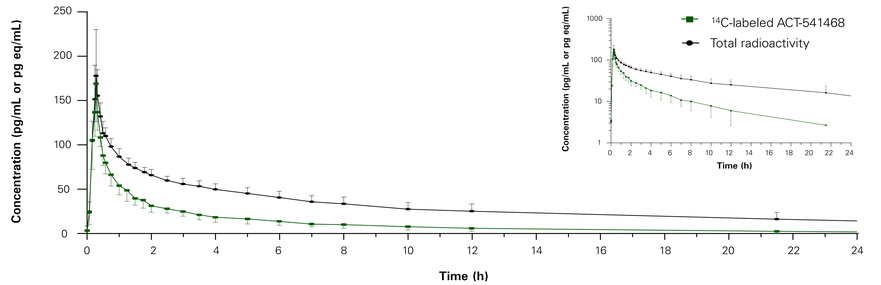
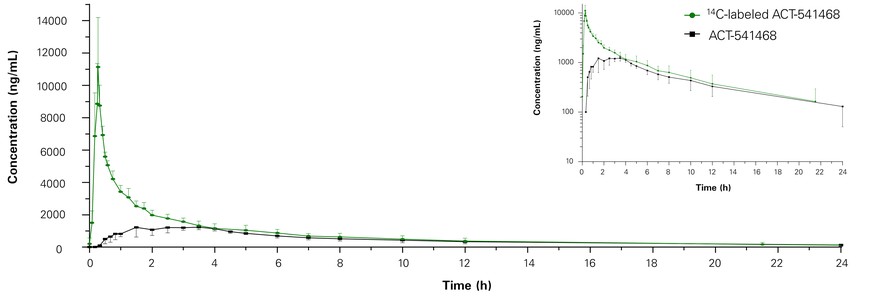


Figure 4. Mean (SD) plasma concentration-time profile after oral administration of 100 mg ACT-541468 vs. dose-adjusted i.v. administered tracer (linear scale, inset semi logarithmic scale, n = 6 for ACT-541468, n = 4 for i.v. tracer)



CONCLUSION: ABSOLUTE BIOAVAILABILITY PART

- **ACT-541468 is characterized by moderate F of approximately 60% and low CL and V_{ss}.**

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