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Safety, Pharmacokinetics, and Pharmacodynamics of Avoralstat, an Oral Plasma Kallikrein

Inhibitor: Phase 1 Study

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List of Abbreviations:

HAE	Hereditary angioedema
q8h	every 8 hours
AE	adverse event
EC ₅₀	concentration of drug required to produce 50% of the maximal inhibition
HK	high-molecular weight kininogen
C1INH	C1 esterase inhibitor
IC ₅₀	50% inhibitory concentration
ANOVA	analysis of variance
CI	confidence interval
GLSM	geometric least square mean
PT	prothrombin time
aPTT	activated partial thromboplastin time
C _{max}	maximum observed concentration of drug
T _{max}	time of maximum observed concentration of drug
t _{1/2}	estimate of the terminal elimination half-life of the drug
C _{tau}	observed drug concentration at the end of the dosing interval
AUC _{0-t}	area under the concentration versus time curve from time zero to time “t” (time of the last measurable concentration)
AUC _{tau}	area under the plasma concentration versus time curve over the dosing interval
CL/F	apparent oral clearance
V _z /F	apparent volume of distribution of the drug
CL _r	renal clearance of unchanged drug
A _e	amount eliminated
%Dose _{excreted}	percentage of given dose excreted in the urine as unchanged drug
CV	coefficient of variance
E _{max}	maximal inhibition
R	correlation coefficient

ABSTRACT

Background: Avoralstat is a potent small-molecule oral plasma kallikrein inhibitor under development for treatment of hereditary angioedema. This first-in-human study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of avoralstat.

Methods: This double-blind, placebo-controlled, ascending-dose cohort trial evaluated avoralstat single doses of 50, 125, 250, 500, and 1000 mg and multiple doses up to 2400 mg daily (100, 200, 400, and 800 mg every 8 hours [q8h] up to 7 days).

Results: Avoralstat (n=71) was generally well tolerated with no signals for a safety concern; there were no serious adverse events or discontinuations due to adverse events (AEs), and compared to placebo (n=18), no notable difference in AEs. Four moderate-severity AEs were reported in 2 subjects; syncope after a single 250 mg dose (1 subject) and abdominal pain, back pain, and eczema after multiple doses of 800 mg avoralstat (1 subject). For multiple-dose cohorts, the incidence of gastrointestinal AEs was highest at the 2400 mg/day dose. Elimination of avoralstat was bi-exponential with a terminal half-life of 12-31 hours. Inhibition of plasma kallikrein was observed at all doses, and the degree of inhibition was highly correlated to avoralstat concentrations ($R=0.93$). Mean avoralstat concentrations at doses ≥ 400 mg q8h met or exceeded plasma kallikrein EC_{50} values throughout the dosing interval.

Conclusion: Avoralstat was well tolerated, and drug exposure was sufficient to meet target levels for inhibition of plasma kallikrein. Based on these results, the 400 mg q8h dose was selected for further evaluation in patients with hereditary angioedema.

Text:

INTRODUCTION

Hereditary angioedema (HAE) is a serious, potentially life-threatening, rare autosomal dominant disorder that is characterized by recurrent acute episodes of swelling of the skin, pharynx, larynx, gastrointestinal tract, genitals, and extremities (1). Animal models and clinical studies have identified bradykinin as the principal mediator of the signs and symptoms of acute attacks of HAE [reviewed in (2, 3)]. Plasma kallikrein, a serine protease integral to the contact activation pathway on vascular endothelial cells, cleaves high-molecular weight kininogen (HK), releasing bradykinin; the primary inhibitor of plasma kallikrein is the *SERPING1* gene product, C1 esterase inhibitor (C1INH), with α -2 macroglobulin playing a secondary role (2, 3). Mutations in the affected *SERPING1* allele in patients with HAE result in reduced production of C1INH or elaboration of nonfunctional C1INH (2, 3); the capacity of plasma to inhibit plasma kallikrein activity is greatly reduced in patients with HAE (4).

Plasma kallikrein is a proven pharmacologic target in the treatment of HAE; plasma-derived purified C1INH (Cinryze[®], Berinert[®]) and a human recombinant C1INH intravenous treatment (Ruconest[®]) as well as a recombinant engineered polypeptide noncovalent plasma kallikrein inhibitor (ecallantide) are licensed in the European Union and/or United States for acute treatment of angioedema attacks in patients with HAE (5, 6).

Licensed therapy for prevention of angioedema attacks in patients with HAE is limited to a purified plasma-derived C1INH administered intravenously every 3 to 4 days and oral attenuated androgens. Given the intravenous mode of administration of C1INH and the virilizing and dose-limiting adverse effects of orally administered androgens, clinical use of these therapies for prevention of angioedema attacks has been limited (5-7). Patients managed with on-demand

treatment of acute attacks continue to have disrupted lives with significantly reduced quality of life (8-10) and risk of death from laryngeal edema (11). Thus, new oral prophylactic therapies are needed to effectively manage patients with HAE.

The synthetic small molecule avoralstat (RN: 918407-35-9) is a potent inhibitor of plasma kallikrein (12) that suppresses HK/kallikrein-dependent bradykinin production on human endothelial cells (13). The effect of avoralstat on kallikrein activity in human plasma has been demonstrated using a novel assay developed by the authors (13-15), in which contact activation is stimulated by ellagic acid and enzyme activity is measured with a specific fluorogenic substrate. In an ex vivo study of plasma samples from 51 healthy human subjects, the EC₅₀ values for avoralstat in this assay were 1.14 nM to 11.1 nM (14). This sensitive and selective fluorogenic assay can be used to monitor the intended pharmacodynamic effects of avoralstat in human plasma.

We report on the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple ascending oral doses in this first in human study of avoralstat in healthy volunteers.

METHODS

Subjects

Healthy male and female subjects 18 to 50 years of age were enrolled. Subjects were required to have a body mass index 19 to 32 kg/m², a creatinine clearance of ≥ 80 mL/min (Cockcroft-Gault equation), and no history or family history of angioedema or coagulopathies. Subjects who were not surgically sterile, or female subjects who were not postmenopausal for >2 years and of childbearing potential, were required to follow protocol-specified contraceptive methods.

Subjects were excluded for any clinically significant coexisting medical condition.

Study Design

This phase 1, double-blind, randomized, placebo-controlled, single- and multiple-ascending-dose study (EudraCT 2013-000032-10) evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of oral doses of avoralstat in healthy volunteers. Avoralstat (25, 50, and 100 mg strength) and matching placebo were prepared in liquid formulations with 45% polyethylene glycol 600, 18% propylene glycol, 18% Vitamin E TPGS (D- α -tocopherol polyethylene glycol 1000 succinate), 4% ethyl alcohol, and 2% sodium lauryl sulfate, and filled into hard gelatin capsules. Subjects were randomized to receive avoralstat or placebo; for single-dose cohorts, subjects were randomized 3 to 1 (6 active; 2 placebo). Single doses of blinded study drug were administered orally after an 8 hour fast in 5 ascending dose cohorts: 50 mg, 125 mg, 250 mg, 500 mg, and 1000 mg (Table 1). Escalation to the next dose level proceeded provided that clinical and laboratory safety were satisfactory and predicted drug exposures for the next cohort did not exceed exposure at the no observed adverse effect level dose in the monkey. Subjects in Cohort 4 (500 mg) returned to the clinic and received a second single oral dose of avoralstat 500 mg or placebo following a high-fat meal.

Subjects enrolled into multiple-dose cohorts were randomized 5 to 1 (10 active; 2 placebo) and administered blinded study drug orally every 8 hours (q8h) for 6 days followed by a morning dose on Day 7. The 4 multiple-dose cohorts were: 100 mg, 200 mg, 400 mg, and 800 mg q8h (Table 2). Subjects fasted for 8 hours prior to and 4 hours after morning dosing on Days 1 and 7.

The study received regulatory and ethics committee approvals and all subjects provided written informed consent prior to the conduct of study-related procedures. The study was conducted at Quotient Clinical in the UK in compliance with the protocol, Good Clinical Practice guidelines,

the ethical principles of the Declaration of Helsinki, and all applicable local laws and regulatory requirements.

Activity of Plasma Kallikrein

Plasma kallikrein activity was measured with a contact activation assay that used ellagic acid as the activator and a fluorogenic artificial substrate specific for plasma kallikrein (15, 16). On-treatment results are expressed as percent inhibition compared to baseline enzyme activity and reflect inhibition additional to the activity of normal levels of relevant plasma components (C1INH and α -2 macroglobulin) in healthy subjects.

Pharmacokinetics

Plasma and urine samples for determination of avoralstat concentrations were analyzed using a validated liquid chromatography-mass spectrometry assay (LGC, Fordham Cambridgeshire UK). Avoralstat plasma and urine pharmacokinetic parameters were determined by noncompartmental analysis of by-subject concentration-time results using WinNonlin, version 6.3 (Pharsight Corporation, Mountain View, CA).

Safety and Tolerability Assessments

Safety and tolerability were assessed by analysis of treatment emergent adverse events (AEs) reported from the first dose through the last follow up visit; and clinical laboratory assessments, vital signs, 12-lead electrocardiograms, and physical examinations conducted throughout the

study. All AEs and clinical laboratory abnormalities were graded using the Division of Microbiology and Infectious Diseases (DMID) criteria for grading events (DMID Adult Toxicity Table, 2007).

Statistical Analyses

Standard summary statistics were calculated for continuous variables, and n and percent for categorical variables. PK analyses were performed on $\log_e$ -transformed concentrations, where appropriate, using analysis of variance (ANOVA).

Dose proportionality for single and multiple doses was assessed for AUC_{0-inf} (single dose only), AUC_{tau} (multiple dose only), AUC_{0-t} , and C_{max} using two methods. A power model was used to estimate the mean slope and corresponding 90% confidence intervals (CIs) across the exposure and dose range. An ANOVA mixed-effects model compared exposure of each test dose to a reference dose (250 mg for the single dose cohorts and 200 mg for the multiple dose cohorts) on a pairwise basis. In each model, treatment was fitted as a fixed effect.

Accumulation of avoralstat was evaluated by comparing AUC_{tau} on Day 7 with AUC_{0-t} on Day 1. The $\log_e$ -transformed point and interval estimates were back-transformed to give estimates of the geometric least-squares means (GLSMs) AUC_{tau}/AUC_{0-t} ratio and its associated 90% CIs.

The effect of a high-fat meal on avoralstat exposure in the 500 mg cohort was assessed from estimates of the fasted/fed ratios of the GLSMs and 90% CIs for AUC_{0-inf} and C_{max} .

The exposure-response analyses of kallikrein inhibition as a function of avoralstat concentrations were performed using WinNonlin. Different exposure-response models were evaluated, and the simple E_{max} model was selected based on goodness-of-fit, parameter estimates and their

precision, and the Akaike Information criterion. The form of the model is:

$$E = E_0 + \frac{E_{\max} \times \text{Concentration}}{EC_{50} + \text{Concentration}}$$

RESULTS

Subject Disposition

Eighty-nine subjects were enrolled between March and August 2013; 41 subjects (31 avoralstat:10 placebo) in single dose cohorts and 48 subjects (40 avoralstat:8 placebo) in multiple dose cohorts. Two subjects prematurely discontinued the study; 1 subject randomized to avoralstat 1000 mg was withdrawn for noncompliance and subsequently replaced, and 1 subject randomized to placebo (200 mg q8h cohort) withdrew consent on Day 2 and was not replaced.

Baseline Characteristics

The baseline demographics were generally comparable across cohorts and active and placebo groups; notable differences included a higher proportion of female and nonwhite or black subjects in the 1000 mg (single dose) and 200 mg q8h (multiple dose) cohorts (Supplemental Tables 1 and 2).

Safety

Avoralstat was well tolerated, with no subject discontinuing due to an AE. No severe or serious AEs or deaths were reported. For both placebo and active cohorts, most AEs were mild in severity. After single doses, headache was the most frequently reported AE (12.9% avoralstat and 20.0% placebo subjects). A summary of AEs for subjects in multiple dose cohorts is presented in Table 3 and all AEs of at least moderate severity (single and multiple dose cohorts)

are presented in Supplemental Table 3. Gastrointestinal events were most frequent overall, and in subjects who received 800 mg avoralstat (90.0%); the most common AEs were diarrhea and flatulence (avoralstat), and diarrhea and nausea (placebo). Additionally, one of two placebo subjects enrolled in the 800 mg cohort experienced gastrointestinal events. The only Grade 2 AEs in multiple dose cohort subjects were back pain, abdominal pain, and eczema experienced by a single subject in the 800 mg avoralstat group; abdominal pain was considered possibly related to study drug. Serial vital signs and ECGs showed no significant adverse findings. No clinically significant activated partial thromboplastin time (aPTT) or prothrombin time (PT) abnormalities were observed for any cohort. One avoralstat subject had grade 1 elevation of ALT and GGT on study Day 7.

Pharmacokinetics

Mean avoralstat concentrations over time on Day 7 are shown in Figure 1; avoralstat concentrations peaked at approximately 2 hours postdose (Table 4, multiple ascending dose cohorts, and Supplemental Table 4, single ascending dose cohorts), then declined bi-exponentially with a terminal elimination half-life on Day 7 that ranged from approximately 12 hours to 31 hours. Variability in exposure (CV%) for AUC and $C_{\max}$ after multiple-day dosing ranged from approximately 50-70% (Table 2).

After single dose administration at doses ranging from 50 to 1000 mg, avoralstat $C_{\max}$ values showed a less than dose proportional increase (slope [90%CI] of 0.68 [0.57, 0.80]), while a dose-proportional increase in $AUC_{0-\infty}$ values was generally observed over the dose range of 50 to 500 mg (slope [90%CI] of 0.93 [0.80, 1.07]). After multiple dose administration, $C_{\max}$ and AUC_{τ} values increased in a less than dose proportional manner from 100 to 800 mg q8h (slope [90%CI] of 0.50 [0.31, 0.68] and 0.53 [0.34, 0.72], respectively) with the possible exception of

the 200 to 400 mg q8h dose range which was reasonably linear. Significant overlap in plasma exposure was observed among subjects treated with 400 and 800 mg avoralstat q8h.

Slight avoralstat accumulation occurred after 7 days of dosing, with an accumulation ratio of 1.3, over all dose levels combined. Plasma accumulation was less than predicted based on the terminal elimination half-life.

Renal excretion of avoralstat as a proportion of administered dose was low; the dose recovered as avoralstat ranged from 0.05% to 0.10% on Day 7. Renal clearance values were less than estimated glomerular filtration rate and similar across dose cohorts; values ranged from 555 to 677 mL/h on Day 7 (Table 4).

Administration of avoralstat with a high-fat meal reduced AUC_{0-inf} and C_{max} by approximately 28% and 47%, respectively, compared to fasting conditions. Mean C_{9h} point estimates were not affected, however variance for this parameter was increased under fed conditions (Supplemental Table 4).

Pharmacodynamics

The degree and time course of plasma kallikrein inhibition after 7 days of dosing was generally similar to that observed after single doses, with a high degree of inhibition observed around the time of avoralstat C_{max} (Figure 2).

Significant inhibition of plasma kallikrein was observed for all active dose groups combined compared to placebo ($p < 0.0001$). The degree of inhibition plateaued for single doses ≥ 500 mg and on Day 7 for multiple doses ≥ 400 mg q8h. For multiple doses, significant inhibition of plasma kallikrein ($p < 0.01$) was observed from predose to 8 hours postdose with avoralstat 400

mg q8h.

Exposure-response Analyses

The exposure-response relationship following multiple dose administration is shown in Figure 3, and associated $E_{\max}$ model-estimated parameters are presented in Table 5. The degree of kallikrein inhibition was highly correlated to avoralstat levels ($r=0.93$), and based on the model estimation, the EC_{50} value was 13.7 ng/mL. Mean plasma avoralstat concentrations following multiple doses were at or above EC_{50} values over the entire dosing interval for avoralstat doses ≥ 400 mg q8h.

DISCUSSION

In this first-in-human study of an orally administered plasma kallikrein inhibitor, multiple ascending doses of avoralstat up to 800 mg q8h were generally well tolerated, with no dose-limiting toxicities or clinical or laboratory safety signals. Generally, the incidence and severity of AEs was similar between placebo and avoralstat, and most AEs were mild in severity. Subjects enrolled in the 800 mg dose cohort experienced a higher incidence of gastrointestinal events; however, one of the 2 placebo subjects in this cohort also experienced gastrointestinal events. At other dose levels, the incidence of gastrointestinal AEs was similar to placebo, further suggesting that gastrointestinal events were related to vehicle.

Although the safety of chronic pharmacologic plasma kallikrein inhibition will require evaluation in long term studies, naturally occurring human deficiencies of either prekallikrein (17-19), HK (20, 21) or FXII/Hageman factor (22) are not associated with a discernable disease phenotype or clinical abnormalities of hemostasis, although in each case the aPTT is prolonged.

No clinically meaningful changes in aPTT were observed in this study.

Avoralstat exposure with doses greater than 400 to 500 mg per administration was significantly less than predicted based upon linear extrapolation of exposure seen with lower doses.

Bioavailability of avoralstat in nonclinical species was low, approximately 3-5%, and the less than proportional dose-exposure relationship observed in this study may reflect constraints resulting from biophysical characteristics of the drug, or saturable absorption mechanisms.

After q8h dosing of avoralstat, accumulation (33%) was much lower than predicted from the calculated terminal half-life of 12-31 hours; the terminal concentrations influencing this calculated half-life were in the beta slope of the elimination phase near the lower quantification limit (10 ng/mL), and contributed little to overall systemic exposure.

The time course of plasma kallikrein inhibition following avoralstat dosing generally followed avoralstat pharmacokinetics, with maximum inhibition seen at avoralstat T_{max} . The high correlation between kallikrein inhibition activity and avoralstat plasma concentrations is expected, since the effect and sampling compartments are identical. This PD parameter could be investigated as a potential surrogate marker for clinical benefit in studies of avoralstat in HAE patients.

A dose of 400 mg q8h of avoralstat has been chosen for a proof-of-concept clinical study in HAE patients based on the results of the current study. Relative to 800 mg q8hr, this dose regimen provided similar inhibition of plasma kallikrein together with a lower incidence of gastrointestinal adverse events, and avoralstat concentrations were maintained at or above the plasma kallikrein EC_{50} throughout the dosing interval. Based on the reduced exposure and increased variability in the fed state compared to the fasting state, avoralstat is not being administered with food in current clinical studies in HAE.

Surveys of both patients and expert physicians indicate that there is a significant unmet medical need for a safe, effective, and convenient therapy for the prevention of angioedema attacks in HAE patients (8, 10, 23, 24). The safety profile, pharmacokinetics, and pharmacodynamic properties of the oral plasma kallikrein inhibitor, avoralstat, strongly support its further clinical investigation for the prevention of angioedema attacks in patients with HAE.

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Author Contributions

All authors approved the final manuscript and were involved in either drafting or providing critical revision to the article; MC, PC, JC, and WS contributed to the concept and design of the study; MC, PC, YSB, RW, J. Zhang, J. Zong, LF, and WS contributed to analysis and interpretation of study results; and MC, PC, YSB, RW, WS, and JC were involved in the acquisition of data.

Conflicts of Interest

All authors are employed by BioCryst Pharmaceuticals except JC, J. Zong and LF. JC (Quotient Clinical employee), J. Zong and LF (Pharstat employees) received research funding to conduct (JC) and analyze (J. Zong and LF) the study.

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Table 1. Treatments Administered for Part 1, Single Ascending Dose

Cohort	Regimen	Dose	Capsule Strength	No. of Capsules	Fasted/Fed Status
1	A	50 mg BCX4161 or placebo	50 mg or placebo	1 capsule of BCX4161 or placebo	8 h fast
2	B	125 mg BCX4161 or placebo	25 mg or placebo	5 capsules of BCX4161 or placebo	8 h fast
3	C	250 mg BCX4161 or placebo	50 mg or placebo	5 capsules of BCX4161 or placebo	8 h fast
4	D	500 mg BCX4161 or placebo	100 mg or placebo	5 capsules of BCX4161 or placebo	8 h fast
		500 mg BCX4161 or placebo	100 mg or placebo	5 capsules of BCX4161 or placebo	High-fat meal
5	E	1000 mg BCX4161 or placebo	100 mg or placebo	10 capsules of BCX4161 or placebo	8 h fast

Table 2. Treatments Administered for Part 2, Multiple Ascending Dose

Cohort	Regimen	Dose	Total Dose over 7 days (mg)	Capsule Strength	No. of Capsules for each Dose
1	F	100 mg BCX4161 or placebo	1900	100 mg or placebo	1 capsule of BCX4161 or placebo
2	G	200 mg BCX4161 or placebo	3800	100 mg or placebo	2 capsules of BCX4161 or placebo
3	H	400 mg BCX4161 or placebo	7600	100 mg or placebo	4 capsules of BCX4161 or placebo
4	J	800 mg BCX4161 or placebo	15200	100 mg or placebo	8 capsules of BCX4161 or placebo

Table 3. Treatment-emergent adverse events – multiple dose cohorts

System Organ Class Preferred term ¹	Dose of Avoralstat					
	All Placebo (N = 8)	All Active (N = 40)	100 mg q8h (N = 10)	200 mg q8h (N = 10)	400 mg q8h (N = 10)	800 mg q8h (N = 10)
Number (%) of Subjects reporting at least 1 AE	6 (75%)	27 (67.5%)	4 (40.0%)	7 (70.0%)	6 (60.0%)	10 (100.0%)
Total Number of AEs	10	41	5	10	11	15
GI Disorders	4 (50.0)	16 (40.0)	1 (10.0)	3 (30.0)	3 (30.0)	9 (90.0)
Constipation	0	3 (7.5)	0	0	3 (30.0)	0
Diarrhea	2 (25.0)	6 (15.0)	0	2 (20.0)	0	4 (40.0)
Flatulence	0	5 (12.5)	0	0	0	5 (50.0)
Nausea	2 (25.0)	2 (5.0)	1 (10.0)	1 (10.0)	0	0
Musculoskeletal and Connective Tissue Disorders						
Back pain	1 (12.5)	5 (12.5)	0	2 (20.0)	1 (10.0)	2 (20.0)
	1 (12.5)	4 (10.0)	0	1 (10.0)	1 (10.0)	2 (20.0)
Nervous System Disorders	0	6 (15.0)	2 (20.0)	2 (20.0)	2 (20.0)	0
Dizziness	0	3 (7.5)	2 (20.0)	0	1 (10.0)	0
Headache	0	2 (5.0)	0	1 (10.0)	1 (10.0)	0
Infections and Infestations	2 (25.0)	2 (5.0)	0	1 (10.0)	0	1 (10.0)
Upper respiratory tract infection	1 (12.5)	1 (2.5)	0	0	0	1 (10.0)
Skin and Subcutaneous Tissue Disorders	1 (12.5)	3 (7.5)	1 (10.0)	0	1 (10.0)	1 (10.0)
Papule	1 (12.5)	1 (2.5)	1 (10.0)	0	0	0
Immune System Disorders	0	2 (5.0)	0	0	1 (10.0)	1 (10.0)
Seasonal allergy	0	2 (5.0)	0	0	1 (10.0)	1 (10.0)

Table 3 footnotes: Adverse events were coded using MedDRA version 15.1. Treatment-

emergent adverse events (TEAEs) are presented by System Order Class with preferred terms for any TEAEs that occurred in at least 2 subjects. TEAEs occurring in only 1 placebo-treated subject and not presented in the table were: vomiting, infection, and dysmenorrhea. TEAEs occurring in only 1 avoralstat-treated subject and not included in the table were: hepatic enzyme increased (Cohort 1); pain in extremity, presyncope, sinusitis, and urine odor abnormal (Cohort 2); arthralgia, dry skin, and ocular hyperemia (Cohort 3); abdominal pain and eczema (Cohort 4).

Table 4. Avoralstat plasma and urine pharmacokinetic parameters – multiple dose cohorts

PK Parameter	100 mg q8h (300 mg total daily dose) (N = 10)	200 mg q8h (600 mg total daily dose) (N = 10)	400 mg q8h (1200 mg total daily dose) (N = 10)	800 mg q8h (2400 mg total daily dose) (N = 10)
Day 1				
<i>Plasma PK</i>				
$C_{\max}$ (ng/mL) ¹	54.5 (34.1)	72.0 (47.5)	119.2 (39.0)	143.3 (66.2)
$T_{\max}$ (hr) ²	1.0 (1.0, 3.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)
AUC_{0-t} (ng•hr/mL) ¹	173 (48.6)	235 (53.8)	419 (49.7)	503 (76.4)
<i>Urine PK</i>				
A_e (ng) ¹	80817 (43.7)	130411 (51.3)	218127 (65.6)	324673 (61.7)
%Dose _{excreted} (%) ¹	0.08 (43.7)	0.07 (51.3)	0.05 (65.6)	0.04 (61.7)
CL_R (mL/h) ¹	539 (6.3)	554 (24.4)	520 (39.4)	646 (27.3)
Day 7				
<i>Plasma PK</i>				
$C_{\max}$ (ng/mL) ¹	72.6 (52.9)	83.6 (63.8)	152.0 (56.7)	187.2 (66.3)
$T_{\max}$ (hr) ²	2.0 (0.5, 3.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)
C_{τ} (ng/mL) ¹	8.3 (47.3)	12.9 (70.6)	17.4 (64.5)	23.7 (82.9)
AUC_{τ} (ng•hr/mL) ¹	237 (51.6)	316 (61.8)	534 (62.2)	678 (69.5)
$t_{1/2}$ (hr) ^{1,3}	17.2 (72.2)	12.2 (31.2)	31.3 (92.0)	13.9 (70.1)
CL/F (L/h) ¹	443 (51.9)	657 (67.2)	749 (62.2)	1183 (74.7)
V_z/F (L) ¹	10979 (75.7)	11590 (93.8)	33852 (131.8)	23747 (102.9)
<i>Urine PK</i>				
A_e (ng) ¹	95229 (49.7)	200622 (58.8)	361785 (52.9)	392336 (77.0)
%Dose _{excreted} (%) ¹	0.10 (49.7)	0.10 (58.8)	0.09 (52.9)	0.05 (77.0)
CL_R (mL/h) ¹	555 (15.4)	636 (10.3)	677 (15.9)	579 (32.6)

Table 4 footnotes:¹ Geometric mean (CV%).² $T_{\max}$ is reported as median (min, max).³ $t_{1/2}$ was determined from sampling out to 72 hours postdose except for 200 mg (Cohort 2) for which samples were available up to 24 hours postdose.

Table 5. Avoralstat exposure-response parameter estimates

Model Parameter	$E_{\max}$ (%)	EC_{50} (ng/mL)	R
Single Ascending Doses			
Estimate (%CV)	115 (12)	16.5 (25)	0.745
Multiple Ascending Doses			
Estimate (%CV)	104 (4)	13.7 (12)	0.933
Overall			
Estimate (%CV)	108 (6)	14.7 (14)	0.813

Table 5 Footnotes: Parameter estimates for maximum inhibition ($E_{\max}$), avoralstat 50% inhibitory concentration (EC_{50}), and correlation coefficient (R) are reported for a pharmacologically simple $E_{\max}$ model







