ACP-204 Development Program for Alzheimer's Disease Psychosis: Population Pharmacokinetic Modeling

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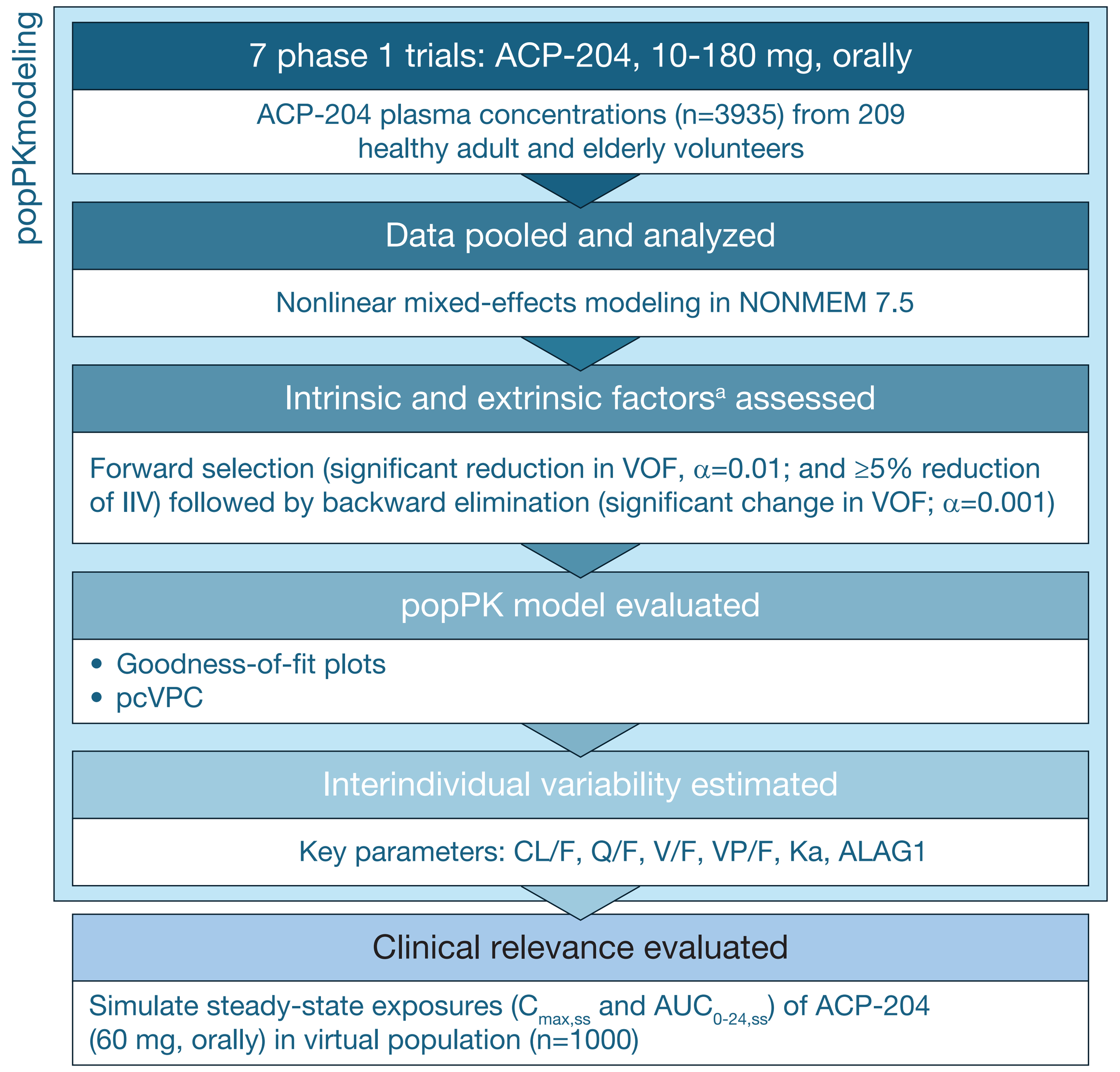
INTRODUCTION

- Pharmacotherapy for Alzheimer's disease psychosis and Lewy Body Dementia psychosis traditionally involves off-label use of atypical antipsychotics despite limited evidence of efficacy and adverse effects such as cognitive or motor impairment[1]
- Pimavanserin, a selective 5-HT_{2A} receptor inverse agonist/antagonist, is the only US Food and Drug Administration–approved treatment for hallucinations and delusions associated with Parkinson's disease[2,3]
- ACP-204, a similar 5-HT_{2A} receptor inverse agonist, is under investigation for treatment of Alzheimer's disease psychosis
- The current study aimed to develop and refine a population pharmacokinetics (popPK) model for ACP-204, identify intrinsic and extrinsic factors affecting PK variability, and assess the clinical relevance of these effects in a large virtual population

METHODS

- A popPK model was developed (**Figure 1**), and the clinical relevance of intrinsic and extrinsic factors on steady-state exposures (maximum plasma concentration at steady state [$C_{max,ss}$] and area under the plasma concentration-time curve over the last 24-hour dosing interval at steady state [$AUC_{0\text{-}24,ss}$]) was evaluated using a virtual population (n=1000; 60 mg/d) based on geometric mean ratios and 90% CI within a 0.8-1.25 boundary[4]

Figure 1. Development of a PopPK Model for ACP-204 in Adults

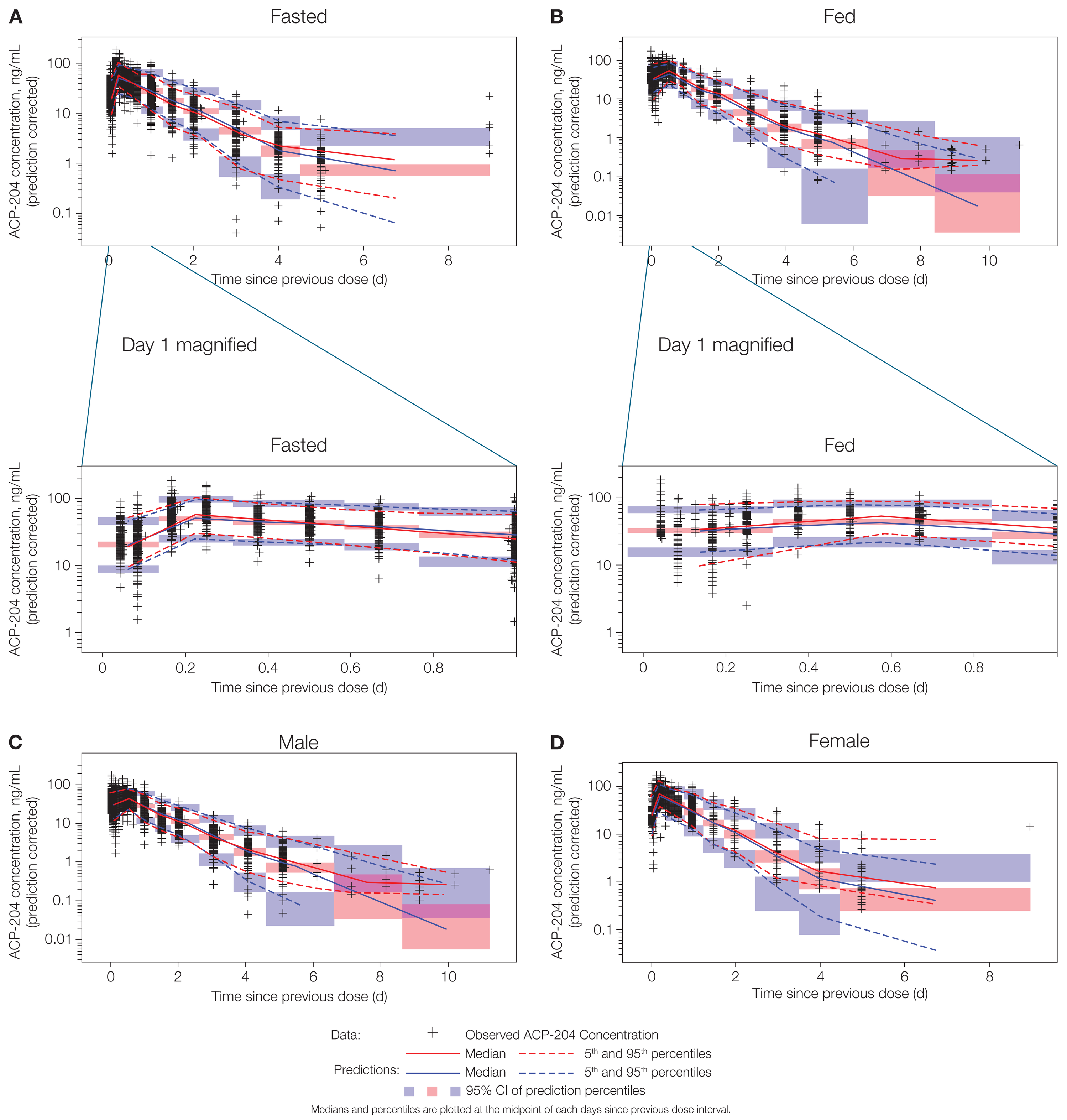

popPKmodeling
7 phase 1 trials: ACP-204, 10-180 mg, orally
ACP-204 plasma concentrations (n=3935) from 209 healthy adult and elderly volunteers
Data pooled and analyzed
Nonlinear mixed-effects modeling in NONMEM 7.5
Intrinsic and extrinsic factors[a] assessed
Forward selection (significant reduction in VOF, α=0.01; and ≥5% reduction of IIV) followed by backward elimination (significant change in VOF; α=0.001)
popPK model evaluated
• Goodness-of-fit plots
• pcVPC
Interindividual variability estimated
Key parameters: CL/F, Q/F, V/F, VP/F, Ka, ALAG1
Clinical relevance evaluated
Simulate steady-state exposures ($C_{max,ss}$ and $AUC_{0\text{-}24,ss}$) of ACP-204 (60 mg, orally) in virtual population (n=1000)

ALAG1, lag time for first-order absorption; $AUC_{0\text{-}24,ss}$, area under the plasma concentration-time curve over the last 24-hour dosing interval at steady state; BMI, body mass index; CL/F, apparent central clearance; $C_{max,ss}$, maximum plasmaconcentration at steady state; IIV, interindividual variability; Ka, absorption rate constant; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; popPK, population pharmacokinetics; Q/F, apparent intercompartment clearance; V/F, apparent central volume of distribution; VOF, value of the objective function; VP/F, apparent peripheral volume of distribution.
[a]Via covariate analysis; factors included age, weight, BMI, sex, race, liver and kidney function, and fed/fasted status.

RESULTS

- The final popPK model for ACP-204 was a 1-compartment model with first-order absorption with lag time and linear elimination
- Categorical factors of food status (fed vs fasted) and sex (male vs female) were statistically significant (*P*<0.001) predictors of ACP-204 PK
 - Each explained ≥5% of interindividual variability in the parameter of interest
 - However, there was no clinically relevant impact on $C_{max,ss}$ or $AUC_{0\text{-}24,ss}$
- Prediction-corrected visual predictive checks confirmed that the model adequately captured central tendency and variability in ACP-204 concentrations in the virtual population (**Figure 2**)

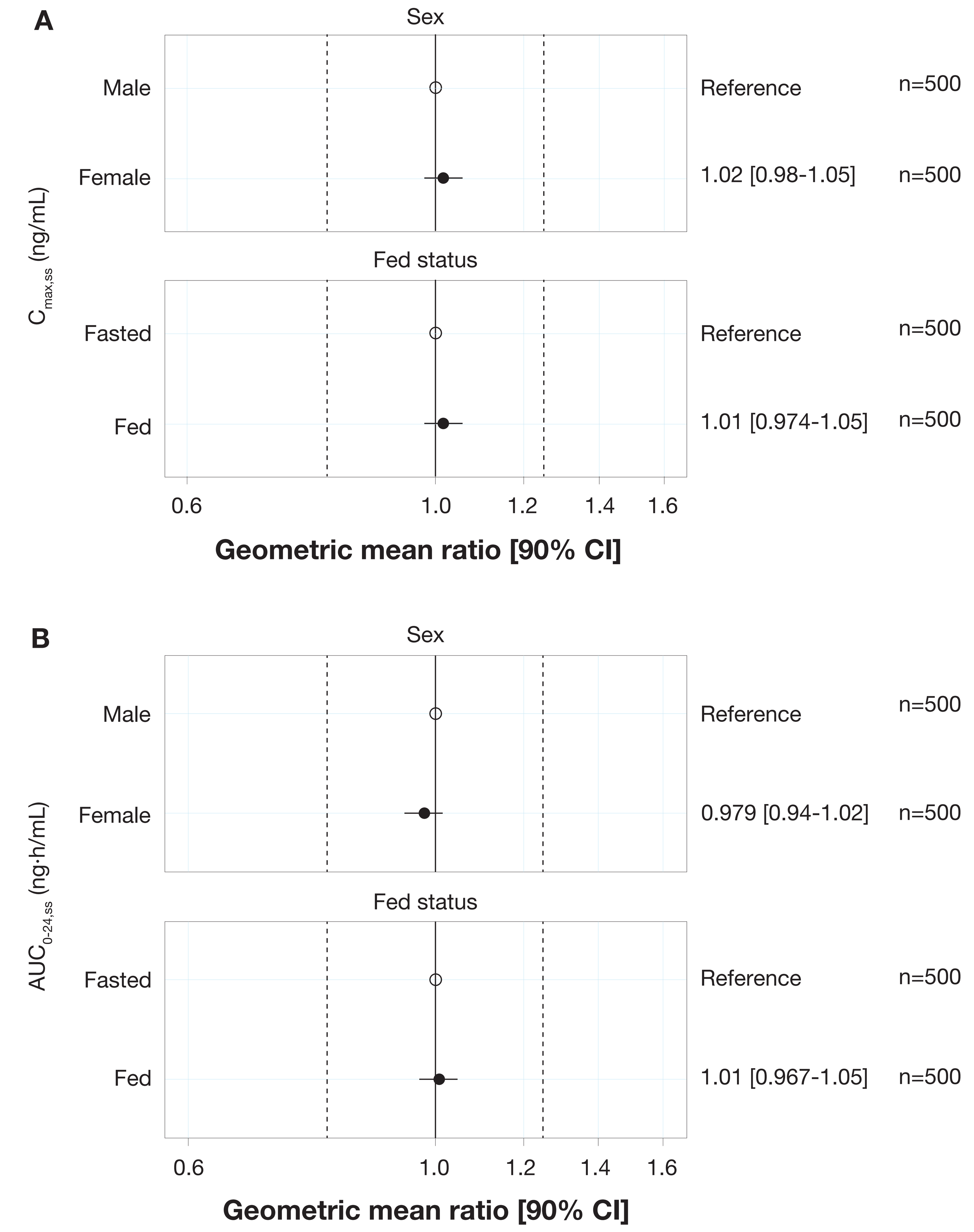
Figure 2. Prediction-Corrected Visual Predictive Check Plots for the Final PopPK Model, Stratified by Fasted (A) vs Fed (B) Status and Male (C) vs Female (D) Sex


A
Fasted
B
Fed
Day 1 magnified
Fasted
Fed
C
Male
D
Female
ACP-204 concentration, ng/mL (prediction corrected)
Time since previous dose (d)
Data: Observed ACP-204 Concentration
Predictions: Median 5th and 95th percentiles
Median 5th and 95th percentiles
95% CI of prediction percentiles
Medians and percentiles are plotted at the midpoint of each days since previous dose interval.

PopPK, population pharmacokinetics.

- The forest plot assessment of covariates on $C_{max,ss}$ and $AUC_{0\text{-}24,ss}$ suggests that both fed/fasted status and sex do not exhibit a clinically relevant effect on steady-state ACP-204 exposures (**Figure 3**)

Figure 3. Clinical Relevance of Covariate Effects of Sex and Fed Status on $C_{max,ss}$ (A) and $AUC_{0\text{-}24,ss}$ (B) in the Final PopPK Model[a,b]


A
$C_{max,ss}$ (ng/mL)
Sex
Male Reference n=500
Female 1.02 [0.98-1.05] n=500
Fed status
Fasted Reference n=500
Fed 1.01 [0.974-1.05] n=500
0.6 1.0 1.2 1.4 1.6
Geometric mean ratio [90% CI]
B
$AUC_{0\text{-}24,ss}$ (ng·h/mL)
Sex
Male Reference n=500
Female 0.979 [0.94-1.02] n=500
Fed status
Fasted Reference n=500
Fed 1.01 [0.967-1.05] n=500
0.6 1.0 1.2 1.4 1.6
Geometric mean ratio [90% CI]

$AUC_{0\text{-}24,ss}$, area under the plasma concentration-time curve over the last 24-hour dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; popPK, population pharmacokinetics.
[a]Brackets indicate the respective limit is included in the interval; parentheses indicate the respective limit is not included in the interval.
[b]Vertical dashed lines at 0.8 and 1.25 are clinical relevance bounds.

- The estimated population mean absorption rate constant (Ka) of 0.692/h describes a first-order absorption half-life of approximately 1 hour for a typical participant (**Table 1**)

Table 1. Parameter Estimates and Standard Errors of the Final ACP-204 popPK Model

Parameter		Final parameter estimate: Population mean (% RSE)	Magnitude of variability: Final estimate, % CV (% RSE)
CL/F	Apparent oral clearance, L/d	849 (2.84)	42.6[a] (10.3)
V/F	Apparent central volume of distribution, L	930 (2.43)	32.1[b] (11.3)
	Additive shift in V/F for female participants	–131 (16.8)	
Ka	First-order absorption rate constant, 1/d	16.6 (4.65)	67.5 (15.2)
ALAG1	Absorption lag time, d	0.0300 (1.91)	10.7 (22.0)
	Proportional shift in ALAG1 for fed status	0.290 (10.4)	
Covariance (IIV in V/F, IIV in CL/F)		0.109[a,b,c] (11.9)	
Residual variability	Proportional	0.0388 (6.38)	19.7
Minimum VOF=15,834.209			

ALAG1, absorption lag time for a first-order absorption process; CL/F, apparent oral clearance; CV, coefficient of variation; IIV, interindividual variability; Ka, absorption rate constant; NA, not applicable; popPK, population pharmacokinetics; RSE, relative standard error; V/F, apparent volume of distribution after extravascular administration; VOF, value of the objective function.
[a]The following parameter estimates were found to be highly correlated (r^2≥0.81): covariance (IIV in V/F, IIV in CL/F), IIV in CL/F.
[b]The following parameter estimates were found to be highly correlated (r^2≥0.81): IIV in V/F, covariance (IIV in V/F, IIV in CL/F).
[c]The calculated correlation coefficient (r) associated with covariance (IIV in V/F, IIV in CL/F) was 0.852 with r^2=0.726.

LIMITATIONS

- Phase 1 trials in healthy participants (predominantly White and male; median age of 37 years) may affect the generalizability of results

CONCLUSIONS

- Following oral administration from 10 to 180 mg, the PK of ACP-204 is adequately described by a 1-compartment model having first-order absorption with lag time and linear elimination kinetics
- Intrinsic and extrinsic factors assessed—including age, body mass index, race, sex, liver and kidney function, and fasted/fed status—were not found to have a clinically relevant effect on steady-state ACP-204 exposures

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Author Disclosures

MD, **BD**, **AY**, and **SP** are employees of Acadia Pharmaceuticals, Inc., and may own stock and/or stock options. **NL**, **DJ**, and **KM** are employees of Simulations Plus, Inc., and may own stock and/or stock options.

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