Development of ACP-711, a Selective Modulator of $GABA_A$ Receptor α_3, for Essential Tremor: Use of First-in-Human Phase 1 Pharmacokinetics and Pharmacodynamics to Identify Target Dose/Exposure

Poster No. 007
Neighborhood 16
Abstract No. 1687

Mona Darwish,[1] Nancy Lin,[2] Pierandrea Muglia,[3] Janus Larsen,[3] Caroline Neuray,[4] Massimo Bani,[3] Kelly Maxwell,[2] Robert K. Hofbauer,[1] Sanjeev Pathak[1]

[1]Acadia Pharmaceuticals Inc., Princeton, New Jersey, USA; [2]Simulations Plus, Inc., Research Triangle, North Carolina, USA; [3]Saniona A/C, Glostrup, Denmark; [4]Neurai Consulting LTD, London, UK. **Presenting author**: Mona Darwish <mdarwish@ACADIA-Pharm.com>

INTRODUCTION

- Essential tremor is one of the most common neurological diseases and movement disorders,[1,2] and dysfunctional GABA signaling may play a role in its etiology[3,4]
- Many GABAergic medications, such as primidone and benzodiazepines, are associated with significant AEs when used for the treatment of essential tremor[4,5]
- ACP-711, a $GABA_AR$ α_3-selective positive allosteric modulator, is under development for the treatment of essential tremor
- This analysis aims to define a target exposure and support fixed capsule dose selection by integrating nonclinical and Phase 1 PK, PD, and safety data to inform covariate assessment and dose prediction through modeling and simulations

METHODS

Nonclinical Data Informing Dose Selection and Target Exposure

- Nonclinical effective concentration was defined using the rat harmaline-induced tremor model of essential tremor
- Upper limit of exposure was based on a safety margin from the NOAEL found in a 90-day toxicology study in the most sensitive species (dog), using AUC as the exposure parameter

Clinical PK PD Assessments

- $GABA_AR$ occupancy assessed from a Phase 1 clinical trial was evaluated by ^{11}C-flumazenil via PET at 1.16-2.25 mg/kg over 48 hours
- A popPK model was developed using data from three Phase 1 studies (001, 002, and 003) in healthy young adult and elderly participants (n=110) receiving oral ACP-711 (0.1-2.25 mg/kg) as a solution or capsule following single and multiple dosing
  - PopPK modeling was conducted using NONMEM
  - Covariate effects evaluated included age, body weight, BMI, race, sex, food (fed vs fasted status), and formulation (solution vs capsule)
  - Model performance was assessed using pcVPCs
  - Clinical relevance of significant covariate effects was assessed using forest plots based on $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$ following BID capsule dosing
  - Effects on ACP-711 exposure were summarized using GMRs and 90% CIs relative to the reference group (relevance bounds=0.8-1.25)

Simulations for Fixed Doses Associated With Target Exposure

- Deterministic simulations using post hoc Bayesian parameter estimates from studies 001, 002, and 003 were performed at steady state following the highest tested, well-tolerated dose (1.6 mg/kg BID) of the oral solution to define the target exposure range for $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$
- Stochastic simulations were performed using a virtual NHANES population (n=1484) to evaluate fixed oral capsule doses (50-160 mg, BID) and to identify dose regimens achieving the selected target exposure

Safety Assessments

- ACP-711 safety and tolerability were summarized across Phase 1 studies involving oral solutions and capsules in young adults and elderly individuals

RESULTS

Nonclinical Data Informing Dose Selection and Target Exposure

- Nonclinical effective concentration ≈ 1210 ng/mL
  - ACP-711 at 3 mg/kg (1210 ng/mL) reduced harmaline elicited tremor in rats, with a dose and exposure related increase in magnitude and consistency of effect at higher doses (10-30 mg/kg)
- Upper limit of exposure: AUC at NOAEL ≈ 60,665 ng×h/mL; C_{max} at NOAEL ≈ 11,520 ng/mL
  - The NOAEL following ACP-711 at 45 mg/kg/day in dogs was set as the upper limit of exposure

Clinical PK PD Assessments

$GABA_AR$ Occupancy

- In PET assessments (n=3), ACP-711 at 94-157 mg (1.16-2.25 mg/kg) indicated $GABA_AR$ occupancy ranging from 22% to 86% at plasma concentrations from 129 to 1420 ng/mL (EC_{50}, 301.1 ng/mL) (Figure 1)

PopPK Model

- ACP-711 PK following oral dosing was adequately described by a two-compartment model with first-order absorption (oral solution) and combined first-order and delayed zero-order absorption (capsule) (Figure 2; Table 1)
- ACP-711 systemic exposure increased in a dose-proportional manner, with power model slope estimates close to unity for both $AUC_{0\text{-}12}$ (exponent, 0.99; 95% CI, 0.89-1.08) and C_{max} (exponent, 0.92; 95% CI, 0.84-1.00)

Covariate Assessment

- The following covariate-parameter relationships were statistically significant (P<0.001) predictors of ACP-711 popPK:
  - Food intake with solution decreased K_A
  - RBA of capsule vs solution was ~70%
  - Sex was identified as a significant covariate on CL/F
  - Body weight significantly influenced CL/F, CLD/F, VC/F, and VP/F
- Sex and body weight were further assessed for clinically relevant impact on $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$ using model-based simulations
  - Female participants had significantly higher exposures vs male participants (Figure 3)
  - The effect of body weight was inconclusive in female and male participants (Figure 4)
- These findings may support a sex-based dosing strategy in future planned clinical studies

Simulations for Fixed Doses Associated With Target Exposure

- Deterministic simulations of 1.6 mg/kg BID oral solution doses established target exposure ranges, median (±20%):
  - $AUC_{0\text{-}12,ss}$: 11,424.5 (±2284.9) ng×h/mL
  - $C_{max,ss}$: 1276.9 (±255.4) ng/mL
- Previous nonclinical and clinical data informed model-simulated fixed doses of 100 mg for female participants and 160 mg for male participants, which resulted in similar exposure profiles across groups within the target exposure range (Figure 5)

Safety Assessments

- Multiple doses up to the highest tested (1.6 mg/kg BID, oral solution) were well tolerated
- AEs were mild to moderate and resolved during the study; no discontinuations, serious AEs, or dose-limiting AEs were observed

Figure 1. ACP-711 Clinical $GABA_AR$ Occupancy

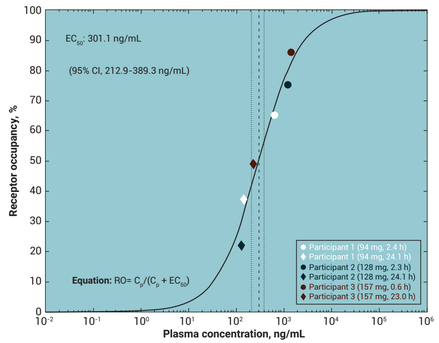
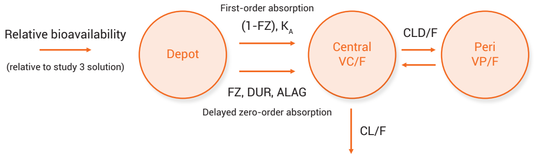


Figure 2. PopPK Model Schematic



Oral Solution: First-order absorption.
Capsule: First-order absorption + delayed zero-order absorption.
Disposition: 2-compartment linear elimination with allometric scaling.

Table 1. Parameter Estimates From the Final PopPK Model

Parameter	Final parameter estimate		Magnitude of variability	
	Population mean	%RSE	Final estimate	%RSE
CL/F (L/h)	10.2	4.89	42.2 %CV	11.8
Exponent of (WTKG/77.6) for CL/F	0.750	FIXED		
Proportional shift in CL/F for SEXF=1	−0.333	20.3	NE	NA
VC/F (L)	68.0	5.49	27.0 %CV	29.0
Exponent of (WTKG/77.6) for VC/F	1.00	FIXED		
K_A (1/h)	1.11	7.62	76.4 %CV	27.7
Proportional shift in K_A for FED=1	−0.807	6.16		
Proportional shift in K_A for studies 1&2	1.79	28.1		
CLD/F (L/h)	13.9	6.20	NE	NA
Exponent of (WTKG/77.6) for CLD/F	0.750	FIXED		
VP/F (L)	68.4	4.41	22.5 %CV	25.0
Exponent of (WTKG/77.6) for VP/F	1.00	FIXED		
BIO (-)				
RBA for study 3 solution	1.00	FIXED		
RBA capsule	0.725	7.96	137 %CV	25.0
Studies 1&2 shift on bioavailability	0.784	3.57		
DUR (h)	3.01	3.75	NE	NA
FZ (-)	0.990	0.300	201 %CV	45.2
ALAG (h)	0.504	0.257	NE	NA
RV	0.0511	7.92	22.6 %CV[a]	NA
Minimum value of the objective function = 25,479.529				

[a]The magnitude of residual variability (%CV) was calculated using the following equation: [SQRT(0×F²+0.0511)/F]×100.

Figure 3. Estimated Sex Effects on ACP-711 Exposures, 100 mg BID Capsule (Analysis Population)

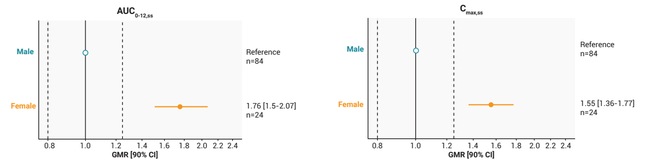
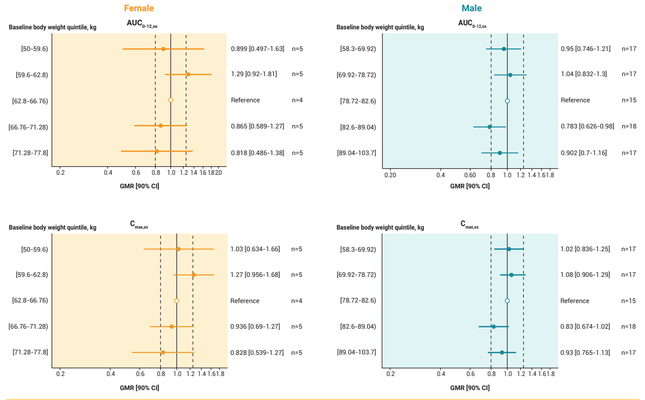
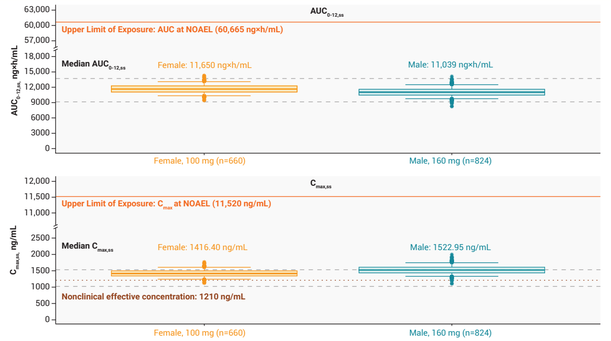


Figure 4. Estimated Body Weight Effects on ACP-711 Exposures by Sex, 100 mg BID Capsule (Analysis Population)



n is the number of individuals in each group; [or] indicates respective limit is included in the interval; (or) indicates respective limit is not included in the interval.

Figure 5. Model-Predicted ACP-711 Exposures Following Fixed Capsule Doses by Sex (Full Virtual Population, Fasted State)



Mean (SD) $T_{max,ss}$ was 3.51 (0.00) h for female and male participant groups.
Boxes are 25th, 50th, and 75th percentiles; **whiskers** are 5th to 95th percentiles; **asterisks** show data points outside this range; split linear scaling is shown on y-axes.
Dashed gray lines: Median (±20%) target ranges following 1.6 mg/kg BID dosing; for AUC: 11,424.5 (±2284.9) ng×h/mL; for C_{max}: 1276.9 (±255.38) ng/mL.
Solid red lines: NOAEL in dogs following 45 mg/kg/day BID dosing from 90-day toxicology study; AUC: 60,665 ng×h/mL; C_{max}: 11,520 ng/mL.
Dotted orange line: Nonclinical effective concentration (1210 ng/mL) for 3 mg/kg from rat harmaline-induced model of essential tremor study.

CONCLUSIONS

- ACP-711 showed good oral bioavailability to brain $GABA_ARs$, with a dose-dependent relationship between exposure and receptor occupancy
- Model-based simulations of both sex and body weight identified sex as the primary determinant of exposure, with female participants exhibiting higher exposures than male participants
  - Sex-based dosing (100 mg BID for female participants and 160 mg BID for male participants) yielded the most participants within the target range across weight ranges
  - Therefore, dose adjustment based on sex rather than body weight is selected for the next Phase 1 study to assess the appropriateness of the selected dose
- ACP-711 was safe and tolerable at concentrations reaching the desired target occupancy
- These data will be evaluated in healthy elderly individuals in Phase 1 studies prior to target dose recommendations for a proof-of-concept clinical trial in patients with essential tremor

ABBREVIATIONS

AE, adverse event; ALAG, zero-order lag time; $AUC_{0\text{-}12,ss}$, area under the concentration-time curve from time 0 to 12 hours at steady state; BID, twice daily; BIO, bioavailability; BMI, body mass index; CI, confidence interval; CLD/F, apparent distribution clearance; CL/F, apparent clearance; $C_{max,ss}$, maximum observed drug concentration at steady state; C_p, plasma drug concentration; %CV, coefficient of variation expressed as a percent; DUR, zero-order absorption duration; EC_{50}, plasma concentration corresponding to 50% occupancy; F, model prediction; FED, fed state; FZ, fraction of dose absorbed via zero-order input; GABA, γ-aminobutyric acid; $GABA_AR$, γ-aminobutyric acid type A receptor; GMR, geometric mean ratio; K_A, first-order absorption rate constant (1/h); NE, not estimated; NHANES, National Health and Nutrition Examination Survey; NOAEL, no-observed-adverse-effect level; NONMEM, nonlinear mixed-effects modeling; pcVPC, prediction-corrected visual predictive check; PD, pharmacodynamic(s); PET, positron emission tomography; PK, pharmacokinetic(s); popPK, population pharmacokinetic(s); RBA, relative bioavailability; RO, receptor occupancy; %RSE, relative standard error expressed as a percent; RV, proportional error; SEXF, female sex; $T_{max,ss}$, time of the maximum drug concentration at steady state; VC/F, apparent central volume of distribution; VP/F, apparent peripheral volume of distribution; WTKG, body weight (kg).

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DISCLOSURES

MD, RKH, and **SP** are employees of Acadia Pharmaceuticals Inc. and may own stock. **NL** and **KM** are employees of Simulations Plus, Inc. and may own stock and/or stock options. **PM, JL, CN,** and **MB** are employees or consultants of Saniona A/C and may own stock.

ACKNOWLEDGMENTS

Medical writing support was provided by Citrus Health Group, Inc. (Chicago, Illinois) and was funded by Acadia Pharmaceuticals Inc. (San Diego, California).

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Poster presented at the American Academy of Neurology (AAN) 2026 Annual Meeting; April 18-22, 2026; Chicago, Illinois, USA