PHARMACOKINETICS AND EXPOSURE-RESPONSE RELATIONSHIPS OF DASOTRALINE IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS

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ABSTRACT

Objectives: To characterize the pharmacokinetic and pharmacodynamic data to explore the time course and exposure response relationships in Phase 2 to define dasotraline benefit to risk relationship in adult Attention Deficit Hyperactivity Disorder (ADHD) subjects. Simulations were performed to support Phase 3 study design and dose selection.
Methods: Dasotraline population PK were analyzed using data from 395 subjects after single/multiple doses from 0.2 to 36 mg (3 Phase 1 and Phase 2 studies). PK/PD models related individual dasotraline exposures to norepinephrine metabolite DHPG concentrations. ADHD RS-IV total scores, and time to study dropout using data from 330 ADHD subjects. Final models were validated using VPCs. Clinical trial simulation scenarios examined a range of doses and durations to predict: minimal effective dose, no effect dose, and optimal duration of treatment for the planned efficacy study and determine the likelihood of a positive trial outcome (statistically significant ADHD RS-IV response comparing dasotraline to placebo with clinically meaningful effect size).
Results: A one-compartment model with dual (linear plus nonlinear) elimination described dasotraline PK. In an ADHD population administered 4 or 8 mg/day, dasotraline was characterized by a mean apparent half-life of 47 hours and steady-state by 10 days of dosing. The exposure response model for DHPG was a power function of predicted concentrations indicating clinically significant NET inhibition. Dasotraline average concentrations (C_{av}) reduced ADHD RS-IV according to a sigmoid E_{max} time-course model. A Cox proportional hazard model related time-varying C_{av} to the log of the survival function for dropout. Clinical trial simulations predicted 4 mg/day minimum effective dose, 2 mg/day no effect dose, and a sufficient likelihood of success for 8 week trials with 200 subjects per group (Figure 1).
Conclusions: Modeling and simulations successfully related dasotraline PK to pharmacological activity via DHPG and ADHD RS-IV scores supporting the concept that maintaining constant, steady-state inhibition of both dopamine and norepinephrine transporters is a novel pharmacological approach to the management of ADHD symptoms.

ClinicalTrials.gov identifier: NCT01692782.

BACKGROUND

- ADHD (Attention-Deficit/Hyperactivity Disorder) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity and impulsivity associated with clinically significant impairment in functioning
- Dopamine and norepinephrine are associated with the pathophysiology of ADHD, and drugs that facilitate synaptic concentrations of dopamine and norepinephrine are clinically useful in the pharmacological management of ADHD symptoms
- Dasotraline [(1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine] is a novel compound in clinical development for the treatment of ADHD
- Dasotraline is a potent inhibitor of human DA transporters (DAT; dopamine uptake IC_{50} 3 nM) and NE transporters (NET; norepinephrine uptake IC_{50} 4 nM), and a weaker inhibitor of human serotonin transporters (SERT; serotonin uptake IC_{50} 15 nM) (Sunovion data on file)
- The dasotraline pharmacokinetic profile of slow absorption/elimination is unique among current stimulant and nonstimulant medications indicated for ADHD, and can support relatively stable plasma concentrations over a 24-hour daily dosing interval
- A Phase 2 clinical trial with dasotraline demonstrated statistically and clinically meaningful effects in adults with ADHD

OBJECTIVE

- The objective of these pharmacokinetic (PK) and pharmacodynamic (PD) analyses was to define dasotraline benefit-risk relationships by characterizing the time-course and exposure-response relationships between dasotraline, its norepinephrine (NE) metabolite (3,4-dihydroxyphenylglycol [DHPG]), and improvement in severity of ADHD symptoms as measured by the ADHD RS-IV, using Phase 2 data

METHODS

Population PK
- A dasotraline population PK model was developed based on 4,570 dasotraline measurements in 395 subjects after single or multiple administrations of dasotraline in doses ranging from 0.2 to 36 mg
- Data from three intensely sampled Phase 1 studies and sparse samples from Phase 2 study in ADHA patients were pooled for population PK analysis
- In addition to body weight, which was included as part of the base PK model, additional demographic and clinical covariates were evaluated including age, total bilirubin, alanine aminotransferase (ALT), gender, race, and ethnicity
- The final population PK model was validated using a simulation based, prediction-corrected visual predictive check (pcVPC) methodology

Population PK/PD
- Plasma DHPG concentrations from a Phase 2 study (NCT01692782)[1] in ADHD patients was collected at Screening, and on Day 1 (baseline), and Weeks 1-6
- Stationary covariates evaluated were age, race, gender, baseline weight, baseline body mass index, ethnicity, and baseline DHPG
- The final DHPG model was validated using a simulation-based, pcVPC methodology

Pharmacodynamic ADHD RS-IV Responses
- Data from a Phase 2 study (NCT01692782)[1] were used for PK/PD analyses of ADHD RS-IV total scores (assessed at each study visit)
- A total of 1847 measurements from 330 patients were included in the PK/PD analysis of the effect of dasotraline plasma concentrations on change in ADHD RS-IV total scores
- Stationary covariates evaluated were age, race, gender, baseline weight, baseline body mass index, ethnicity, baseline DHPG, baseline ADHD RS IV with adult prompts, and baseline insomnia severity index
- The final DHPG model was validated using a simulation-based, pcVPC methodology

Time to Study Dropout
- Data from a Phase 2 study (NCT01692782)[1] in ADHD patients was used to develop the model for time to study dropout
- A PK/PD model was developed to describe the relationship between the time to study dropout and dasotraline exposure using a semi parametric Cox proportional hazard model
- Stationary covariates evaluated were age, baseline weight, baseline BMI, baseline ADHD RS-IV with adult prompts total score, baseline DHPG, baseline heart rate (standing and supine), baseline insomnia severity index, gender, race, and ethnicity. Insomnia severity index values collected at multiple times throughout the study were also evaluated as a time varying covariate
- The final model for time to study dropout was validated using a simulation-based visual predictive check (VPC) methodology

Dasotraline Exposure Measures
- The population PK model was used to generate empiric Bayesian PK parameter estimates for each individual in the analysis datasets
- The individual measures of dasotraline exposure (eg, average steady-state concentration [C_{av}], area under the concentration time curve from time 0 to 24 hours [AUC_{0-24h}]), minimum drug concentration [C_{min}], and maximum drug concentration [C_{max}]) were calculated by numerical integration using the developed population PK model for dasotraline and the associated individual specific parameter estimates with NONMEM, Version 7, Level 1.2[2]
- The model predicted exposure measures obtained for each subject at each week were utilized in the development of the PK/PD models to describe theexposure response relationships for plasma DHPG concentrations, ADHD RS-IV with adult prompts total scores, and time to study dropout
- Exposure measures were set to 0 for placebo subjects

Population Model Development
- The key steps of the population PK analysis were: 1) exploratory data analysis, 2) application of the previously developed population PK model, 3) base structural model development, 4) evaluation of covariate effects, 5) model refinement, and 6) model evaluation
- The overall procedures followed for the development of the PK/PD models were: 1) generation of individual estimates of exposure based on the population PK model; 2) exploratory data analysis; 3) base structural model development incorporating drug exposure; 4) evaluation of covariate effects; 5) final model refinement; and 6) model evaluation
- All exploratory data analyses and presentations of data were performed using SAS Version 9.2 and KIWI Version 1.1. Population modeling was performed using the computer program NONMEM, Version 7, Level 1.2[2-4]

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RESULTS

Population PK Model
- A one compartment population PK model with sequential zero order followed by first order absorption and dual (nonlinear and linear) elimination described dasotraline PK in these subjects (**Table 1**)
- Linear apparent clearance was found to be time dependent following the inclusion Phase 2 data. This allowed the linear portion of CL/F to increase over time with multiple dose administration
- The CL/F term was estimated to increase from values ranging from 4.95 L/h to 8.16 L/h in the Phase 1 clinical pharmacology studies and to 15.0 L/h in the multiple dose efficacy study
- The nonlinear CL/F represented a saturable elimination pathway operating at approximately 50% of its capacity based on the estimate of the Michaelis Menten constant at lower dasotraline concentrations of around 1.7 ng/mL
- As concentrations increased above 3.0 ng/mL, the nonlinear component contributed less to total elimination
- The following covariate were not found to be associated with variability in the population PK model: age, total bilirubin, ALT, gender, race, or ethnicity
- The results of the pcVPC indicate no apparent biases in the overall model fit. Figure 1 shows the observed mean and model-predicted concentrations over time for the Phase 2 study

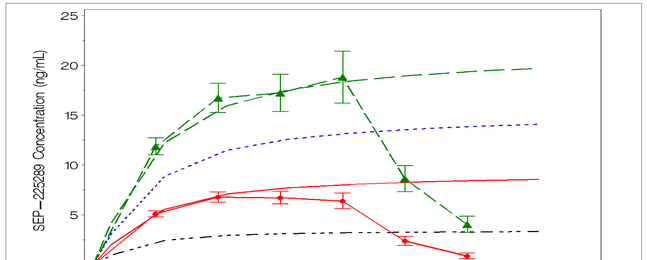
Table 1: Parameter Estimates and Standard Errors From the Final Population Pharmacokinetic Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
K_a: Rate of absorption (1/h)	1.43	7.95	87.7 %CV	16.2
D1: Duration of zero-order absorption (h)	6.38	3.09	32.4 %CV	16.2
V/F: Apparent volume of distribution (L)	2800	1.33	18.1 %CV	10.9
V_{max}: Maximum elimination rate (mg/h)	0.0495	4.02	0 %CV	FIXED
K_m: Michaelis-Menten constant (mg)	4.74	5.42	41.6 %CV	16.2
CLind1: Induced apparent oral clearance Phase 1 (L/h)	8.16	12.4	NE	NE
Ratio of additive/proportional component of RV Phase 1	0.0218	5.97	NE	NE
Ratio of additive/proportional component of RV Phase 2	0.194	9.50	NE	NE
Power of weight on V	0.777	7.89	NE	NE
Power of weight on CLind	1.18	13.4	NE	NE
Power of weight on CLint	1.64	33.8	NE	NE
CLint: Apparent oral clearance intercept (L/h)	4.95	13.1	NE	NE
Rate of induction (1/h)	0.00644	34.2	NE	NE
CLind2: Induced apparent oral clearance Study 306 201 (L/h)	15.0	7.54	NE	NE
IIV on CL	NA	NA	69.6 %CV	6.11
Proportional RV PH1	0.0244	1.55	69.9 - 15.6 %CV F [0.0050 - 25]	NA
Proportional RV PH2	0.0714	3.59	1040 - 26.7 %CV F [0.0050 - 25]	NA
Minimum value of the objective function = -4709.279				

- The following parameter estimates were found to be highly correlated ($r^2 \geq 0.810$): (power of weight on Cl_{int} and V_{max}; Maximum Elimination Rate (mg/h))
- The residual variability (%CV) for Phase 1 was calculated using the following equation: (SQRT(0.0244 x (power(F,2) + power(0.0218,2)))/F) x 100
- The residual variability (%CV) for Phase 2 was calculated using the following equation: (SQRT(0.0714 x (power(F,2) + power(0.194,2)))/F) x 100

%SEM=standard error of the mean expressed as a percentage; %CV=coefficient of variation expressed as a percentage; RV=residual variability; NE=not estimated; NA=not applicable; PH1=Phase1; PH2=Phase 2

Figure 1: Observed Mean (±95% Confidence Interval) and Model Predicted Dasotraline Concentrations From the Final Population Pharmacokinetic Model Using Data From Phase 2 Study



- Figure 1 shows dasotraline concentrations observed for PK population subjects in Study SEP360 201 (symbols, mean ± 95 %CI) compared with model predicted (lines) mean concentrations for a virtual population of 500 subjects over 8 weeks of DASOTRALINE administered at 2, 4, 6, or 8 mg/day

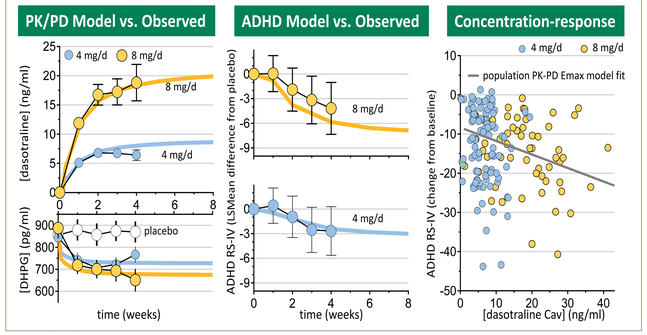
Population Pharmacokinetic/Pharmacodynamic Plasma DHPG Concentrations
- The exposure response model for DHPG concentration was a power function of the time matched, model predicted dasotraline concentrations (**Table 2**)
- Levels of DHPG decreased as dasotraline plasma concentrations increased, indicating that treatment with dasotraline was associated with NET inhibition (**Figure 2**)
- In an analysis of the influence of covariate effects on DHPG exposure response, the following covariates were not significant: age, baseline weight, baseline BMI, baseline DHPG, gender, race, or ethnicity as predictors of variability in the parameters of the DHPG model
- The pcVPC results indicated that the final DHPG model adequately characterized the data. The observed values for DHPG in Study SEP360 201 matched well with model predictions for DHPG changes and were consistent with clinically significant levels of norepinephrine transporter (NET) inhibition by dasotraline within the first days of dosing

Table 2: Parameter Estimates (%SEM) From the Final PK/PD DHPG Concentration Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
BL: Baseline DHPG (pg/mL)	863	1.84	173 SD	11.8
POW: Power Term	0.335	26.7	34.0 %CV	102
SLP: Slope for the median time-matched dasotraline concentration of 2.27 ng/mL (pg/mL/ng/mL)	-92.4	15.5	0 &CV	FIXED
RV	11900	9.62	109 SD	109 SD
Minimum value of the objective function = 8384.605				

%SEM=standard error of the mean expressed as a percentage; DHPG=3,4-dihydroxyphenylglycol; %CV=coefficient of variation expressed as a percentage; RV=residual variability; NA=not applicable

Figure 2. PK/PD Models: Relationship Between Dasotraline and DHPG Values; and ADHD RS-IV Values



Pharmacodynamic ADHD RS-IV Responses
- The model for ADHD RS-IV scores was a sigmoid E_{max} time course (**Table 3**). A linear function described the relationship between E_{max} and the predicted dasotraline C_{av}
- In Phase 2, randomized, double-blind, placebo controlled proof-of-concept study in adults with ADHD, LS mean improvement at Week 4 in ADHD RS-IV total scores were significantly greater for dasotraline 8 mg/d versus placebo (-13.9 vs -9.7; P=.0.019); and not significantly greater for 4 mg/d (-12.4; P=.0.076)
- The relationship between model predicted and observed ADHD RS-IV with adult prompts total scores was evaluated to confirm that the population PK/PD ADHD RS-IV model was appropriate for clinical trial simulation (**Figure 2**). The pcVPC results indicated that the final model adequately characterized the data
- Although the influence of age, baseline weight, baseline BMI, baseline ADHD RS-IV with adult prompts total score, baseline DHPG, baseline insomnia severity index, gender, race, and ethnicity was evaluated in the model, none of the covariates was found to be a statistically significant predictor

Table 3: Parameter Estimates (%SEM) From the Final PK/PD ADHD RS-IV Total Score Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
BL: Baseline ADHD RS-IV with adult prompts total score	36.8	0.991	5.98 SD	8.08
E_{max}: Maximum reduction in ADHD RS-IV with adult prompts total score due to time	-10.2	8.90	9.23 SD	10.3
T50: Time producing 50% of E_{max} for placebo (weeks)	0.762	10.9	43.2 %CV1	18.6
T50A: Time producing 50% of E_{max} for 4 and 8 mg (weeks)	1.08	7.79		
SLP: Slope for C_{av} on E_{max}	-0.422	26.2	NE	NE
S: Hill coefficient	1.14	11.3	114 %CV	28.1
cov(IIV on S, IIV on E_{max})	-6.24	19.1	NA	NA
Residual variability	15.9	8.87	3.98 SD	NA
Minimum value of the objective function = 8585.916				

- The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.351 for cov(IIV on S, IIV on E_{max})

%SEM=standard error of the mean expressed as a percentage; C_{av}=average steady-state concentration; ADHD RS-IV=Attention Deficit Hyperactivity Disorder Rating Scale Version IV with adult prompts NE=not estimated; SD=standard deviation; IIV=interindividual variability; E_{max}=maximum reduction in ADHD score; %CV=coefficient of variation expressed as a percentage; NA=not applicable

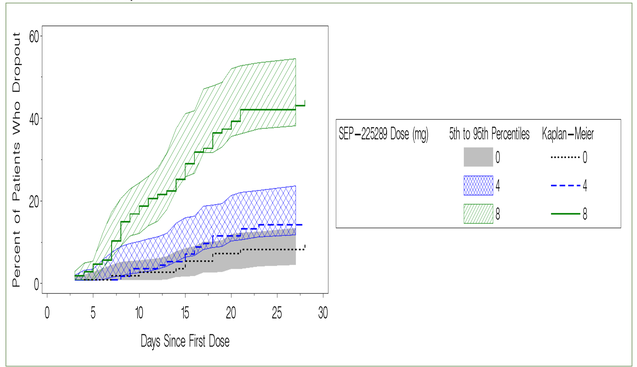
Time to Study Dropout
- Overall, 9% of placebo subjects and 15% and 45% of subjects administered 4 mg and 8 mg dasotraline dropped out of the study. The remaining 91%, 85%, and 55% of placebo, 4 mg, and 8 mg subjects were censored (completed the study)
- Higher dasotraline C_{av} was statistically significantly associated with a higher risk of study dropout (**Table 4**). The risk of study dropout is reduced by approximately 8 fold when comparing the hazard ratio for 8 mg to 4 mg assuming the median C_{av} for each dose
- The interaction between time and dasotraline C_{av} was necessary to include in the Cox proportional hazard model to properly account for time-varying exposure.
- The VPC results indicate no apparent bias and illustrate good concordance between the model based simulations and the data based estimates of survival for each dose and corresponding range of dasotraline C_{av} values observed throughout the study (**Figure 3**)
- No statistically significant influence of age, baseline weight, baseline BMI, baseline ADHD RS-IV with adult prompts total score, baseline DHPG, baseline heart rate (standing and supine), insomnia severity index (baseline and time varying), gender, race, or ethnicity was found for time to study dropout

Table 4: Parameter Estimate for the Final Pharmacokinetic/Pharmacodynamic Time to Study Dropout Model

Parameter	N	Final Parameter Estimate		Hazard Ratio (95% CI)	P	Global Pro Chi-Square	DF
		Typical Value	Standard Error (%SEM)				
Dasotraline C_{av} (ng/mL)	8228	0.2112	0.0484 (22.9226)	1.235 (1.123, 1.358)	<.0001	<.0001	2
Interaction between C_{av} and time		-0.0063	0.0027 (42.7126)	0.994 (0.988, 0.999)	0.0192		
-2 Log Likelihood = 784.020							

N=number of subjects; CI=confidence interval; P=p-value; DF=degrees of freedom; %SEM=standard error of the mean expressed as a percentage; C_{av}=average steady-state concentration

Figure 3: Simulated Percentiles of Subjects Who Dropped Out of the Study Versus Days With Kaplan-Meier Estimates of the Observed Data by Dasotraline Dose



Clinical Trial Simulations
- The probability of success of a 4 mg/day treatment regimen of dasotraline was above 80% by 8 weeks of treatment with 200 subjects per arm. Therefore, simulations predicted 4 mg/day as the minimum effective dose
- At the 2 mg/day dose level, further increasing sample size to 300 subjects per arm was still insufficient to demonstrate positive efficacy, thus predicting 2 mg/day as the no effect dose
- Increasing the length of the clinical trials from 8 to 12 weeks resulted in only a small increase in the percentage of successful trials, thus predicting optimal trial duration of 8 weeks
- These clinical trial simulations (**Figure 3**), based on understanding of the exposure response relationship for dasotraline in adults with ADHD, predicted a sufficient likelihood of success for trials with 8 weeks of treatment, doses of 4 mg/day or 6 mg/day, and sample size of 200 subjects per arm

CONCLUSIONS

- Individual measures of dasotraline exposure were well-described by the dasotraline population PK model
- Population PK/PD modeling successfully related dasotraline PK to pharmacological activity via DHPG and ADHD RS-IV scores supporting the concept that maintaining constant, steady-state inhibition of both dopamine and norepinephrine transporters is a novel pharmacological approach to the management of ADHD symptoms
- This model-based strategy provided an enhanced understanding of the benefit risk ratio for dasotraline, and allowed for the evaluation of potential Phase 3 study designs and dose regimens in terms of probability of success

REFERENCES

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DISCLOSURES

Drs. Hopkins, Sunkaraneni, Skende, Loebel, and Koblan are employees of Sunovion Pharmaceuticals Inc.
Drs. Passarell and Hing are employees of Cognigen Corp., which performed the PK/PD analyses under a contract with Sunovion.