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Population Pharmacokinetic Modeling and Stochastic Simulations to Support Pediatric Dose Selection of Pimavanserin

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INTRODUCTION

- Pimavanserin is a selective serotonin receptor-modulating agent with inverse agonist/antagonist activity at the $5HT_{2A}$ receptor, and to a lesser extent at the $5HT_{2C}$ receptor.[1]
- The safety and efficacy of pimavanserin 34 mg has been characterized in both placebo-controlled trials and open-label extension studies in adult patients with Parkinson's disease psychosis, as well as in development programs in adult patients with schizophrenia, major depressive disorder, and dementia-related psychosis.[2-5]
- Although pimavanserin pharmacokinetics (PK) and tolerability have been evaluated in adolescent patients with psychiatric disorders, its efficacy and safety have not been evaluated in adolescent or pediatric patients.
- PK data from varying adult populations (healthy subjects and patients) can be used to predict an appropriate dose for adolescent or pediatric patients. An ideal pediatric dose would achieve the same systemic pimavanserin exposure as pimavanserin 34 mg in adult patients.

OBJECTIVE

- The objective of this analysis was to perform model-based simulations of pimavanserin steady-state exposures to identify a dose in pediatric patients that results in exposure comparable to the target exposure achieved with the oral 34-mg once daily dose that has demonstrated safety and efficacy in different patient populations.

METHODS

Study Design

- A population pharmacokinetic (PK) model was generated using pooled plasma drug concentration data from 13 phase 1/2b/3 clinical studies of pimavanserin, including a phase 1 study of adolescent patients (aged 13–17 years).
  - The dataset used to generate the model included 22 adolescent patients with psychiatric disorders, healthy adult subjects, adults with Parkinson's disease (with or without psychosis), and adults with major depressive disorder.
  - The disposition of pimavanserin was well-described by a 1-compartment model with first-order absorption and linear elimination, including 3 covariate-parameter relationships that described the effect of age on apparent clearance (CL/F) and the effects of age and body weight on apparent volume of distribution (V/F).
- The final PK model was used to perform model-based stochastic simulations to explore the expected range of pimavanserin exposures in virtual pediatric patients (aged 5–17).

Stochastic Simulations

- The growth charts from the Centers for Disease Control and Prevention were used to sample virtual pediatric patients (aged 5–17 years) to create relevant simulation populations with the age ranges of interest and the appropriate body weight characteristics.
- Simulations were also performed using the adult patients (aged 18–49 years) from the actual population PK analysis population based on individual empiric Bayesian parameter estimates obtained from the final PK model. These data served as the reference groups for the target drug exposures associated with the oral pimavanserin 34-mg dose.
- Hypothetical doses of pimavanserin were orally administered once daily for a total of 10 weeks.
- Steady-state pimavanserin exposures, including the area under the plasma concentration-time curve within a dosing interval ($AUC_{0\text{-}24,ss}$) and maximum drug concentration levels (C_{max}) for 10-, 20-, and 34-mg once daily doses were simulated for virtual pediatric populations and for the 34-mg dose for the actual adult patients (aged <50 years).

RESULTS

Key Characteristics of Virtual and Actual Patients

- The younger pediatric population (5–9 years) was made up of 500 virtual patients with a mean (standard deviation [SD]) age of 7 (1.4); the older pediatric population (10–17 years) was made up of 800 virtual patients with a mean (SD) age of 13.5 (2.3). Additional demographic characteristics are presented in **Table 1**.
- 204 patients were included in the actual PK analysis population used for reference. (**Table 1**).

Table 1. Key Demographic Characteristics for the Virtual Population and Actual Population Used for Simulations

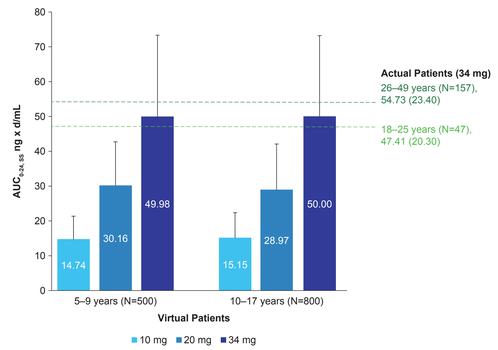
	Virtual Pediatric Population (CDC Growth Chart)		Actual Analysis Population: Patients Aged <50 Years	
	5–9 Years (n=500)	10–17 Years (n=800)	18–25 Years (n=47)	26–49 Years (n=157)
Age, mean (SD), years	7 (1.4)	13.5 (2.3)	21.89 (2.2)	37.04 (7.21)
Body weight, mean (SD), kg	23.9 (5.4)	48.8 (13.3)	75.97 (10.7)	77.95 (13.8)
Sex, n (%)				
Male	252 (50.4)	408 (51.0)	33 (70.2)	115 (73.2)
Female	248 (49.6)	392 (49.0)	14 (29.8)	42 (26.8)

CDC, Centers for Disease Control and Prevention; SD, standard deviation.

Simulated Pimavanserin Exposures

- Simulated steady-state $AUC_{0\text{-}24,ss}$ levels following 34-mg dosing were similar in virtual patients aged 5–9 or 10–17 years (**Figure 1**).
- Among adults aged 18–49 years, mean (SD) $AUC_{0\text{-}24,ss}$ ranged from 47.41 (20.30) to 54.73 (23.40) ng x d/mL following pimavanserin 34 mg.

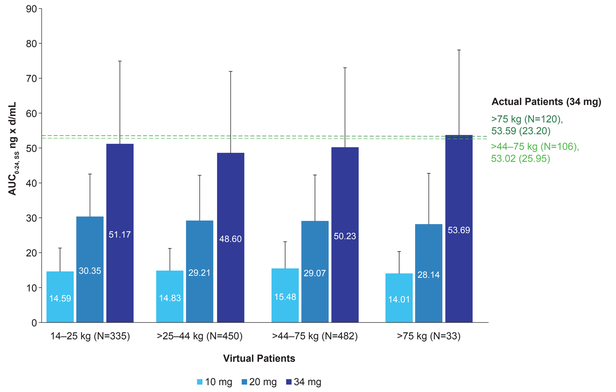
Figure 1. Simulated Steady-State $AUC_{0\text{-}24,ss}$ Stratified by Age Group



Data presented are mean (SD).
Dashed lines represent mean (SD) $AUC_{0\text{-}24,ss}$ for the actual analysis population.
$AUC_{0\text{-}24,ss}$, area under the curve with a dosing interval at steady state; SD, standard deviation.

- Simulated steady-state $AUC_{0\text{-}24,ss}$ levels with the 34-mg dose were similar in virtual patients across body weight groups (**Figure 2**).
- Among adults, mean (SD) $AUC_{0\text{-}24,ss}$ was approximately 54 ng x d/mL following pimavanserin 34 mg in patients with a body weight >44 kg.

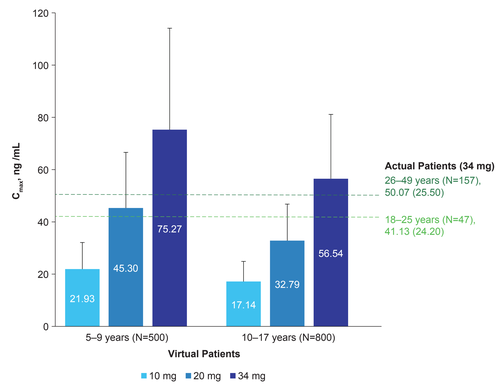
Figure 2. Simulated Steady-State $AUC_{0\text{-}24,ss}$ Stratified by Weight Group



Data presented are mean (SD).
Dashed lines represent mean (SD) $AUC_{0\text{-}24,ss}$ for the actual analysis population.
$AUC_{0\text{-}24,ss}$, area under the curve with a dosing interval at steady state; SD, standard deviation.

- In the adult population (aged 18–49 years), mean (SD) C_{max} ranged from 41.13 (24.20) to 50.07 (25.50) ng/mL following pimavanserin 34 mg. Comparable distributions of C_{max} were predicted following pimavanserin 20 mg in the young pediatric population (aged 5–9 years; mean [SD], 45.30 [21.31]) and following pimavanserin 34 mg in the older pediatric population (aged 10–17 years; mean [SD], 56.54 [24.58] ng/mL) (**Figure 3**).

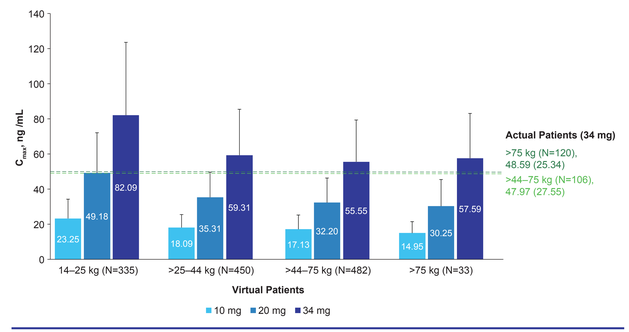
Figure 3. Simulated Steady-State C_{max} Stratified by Age Group



Data presented are mean (SD).
Dashed lines represent mean (SD) C_{max} for the actual analysis population.
C_{max}, maximum drug concentration; SD, standard deviation.

- Simulated C_{max} also appeared higher in the group with the lowest body weight (14–25 kg) compared with groups weighing >25–44 kg, >44–75 kg, or >75 kg (**Figure 4**).
- In actual patients, mean (SD) C_{max} was approximately 48 ng/mL following pimavanserin 34 mg.

Figure 4. Simulated Steady-State C_{max} Stratified by Weight Group



Data presented are mean (SD).
Dashed lines represent mean (SD) C_{max} for the actual analysis population.
C_{max}, maximum drug concentration; SD, standard deviation.

CONCLUSIONS

- **Model-based stochastic simulations exploring 10-mg, 20-mg, and 34-mg dose levels of pimavanserin indicate that pimavanserin 20 mg may be most appropriate in a young pediatric population (aged 5–9 years) and pimavanserin 34 mg may be most appropriate in an older pediatric population (aged 10–17 years) to yield steady-state pimavanserin exposures similar to a daily pimavanserin 34-mg oral dose in adults (aged 18–49 years).**
- **These results can be used to inform dose selection for clinical trials in young patients.**

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DISCLOSURES

This poster includes information from clinical trials investigating uses that have not been approved by the US Food and Drug Administration. This study was funded by Acadia Pharmaceuticals Inc. MD, DB, AB, DD, and SS are employees of Acadia Pharmaceuticals Inc. DJ and JO are employees of Cognigen Corporation.

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