Pharmacokinetic Profile of Pimavanserin in Patients with Dementia-Related Psychosis and Concomitant Acetylcholinesterase Inhibitor Use: Modeling Data from the Phase 3 HARMONY Study

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INTRODUCTION

- Pimavanserin is a selective serotonin-modulating agent with inverse agonist/antagonist activity at the $5HT_{2A}$ receptor, and to a lesser extent at the $5HT_{2C}$ receptor.[1]
- Pimavanserin's efficacy and safety were evaluated in patients with dementia-related psychosis in the phase 3 HARMONY study.[2]
- Polypharmacy is common in elderly patients[3] and many patients with neurodegenerative diseases receive acetylcholinesterase inhibitors (AChEIs).
- Although the clearance mechanisms of AChEIs do not indicate that a drug-drug interaction with pimavanserin is likely, any effects of AChEIs on pimavanserin's pharmacokinetic (PK) profile have not been previously explored.

OBJECTIVE

- This analysis evaluated the PK profile of pimavanserin in patients receiving concomitant AChEIs using data from the HARMONY study and the previously developed pimavanserin PK model in healthy subjects and patients with various psychiatric disorders.

METHODS

Study Design

- HARMONY (NCT03325556) was a randomized discontinuation study in patients with dementia-related psychosis.
  - The methodology and primary results of HARMONY have been previously presented.[4]
- Patients received open-label pimavanserin, 34 mg daily with the option to reduce to 20 mg (based on tolerability) during the first 4 weeks but remained stable on the final selected dose from week 4 to week 12 (N=31/392 on 20 mg and N=361/392 on 34 mg). Those defined as responders with a sustained response at weeks 8 and 12 were randomized into the 26-week double-blind period either to continue pimavanserin on their stable dose (N=105) or to switch to placebo (N=112).
  - Patients entering the study were permitted to be taking an AChEI, memantine, or both. The dose of the medication must have been stable for 12 weeks prior to visit 2 (open-label baseline) and remained stable throughout the duration of the study.
- PK samples were collected at baseline and at weeks 12, 13, 22, and 38 (or end of treatment).

Exposure Measures

- A population PK model to describe pimavanserin PK was previously developed using data from 1156 subjects in 18 clinical studies.
- Individual Bayesian estimates of pimavanserin apparent clearance (CL/F) and apparent volume of distribution (V/F) were obtained using the previously developed population PK model for patients in HARMONY with or without concomitant AChEIs.
- Steady state area under the plasma concentration-time curve within a dosing interval ($AUC_{0\text{-}24,ss}$) and maximum drug concentration ($C_{max,ss}$) were computed for pimavanserin doses normalized to 34 mg daily.

RESULTS

Patients

- Patients enrolled in the open-label period of HARMONY were a mean (standard error [SE]) 74.5 (0.42) years[4]; 58.4% were female and 96.6% were white. The mean (SE) Mini-Mental State Examination score was 16.7 (0.24).
- PK data were obtained for 337 patients in HARMONY; 158/337 (46.9%) patients had concomitant AChEI use (**Table 1**).

Table 1. Prevalence of AChEIs in HARMONY Patients

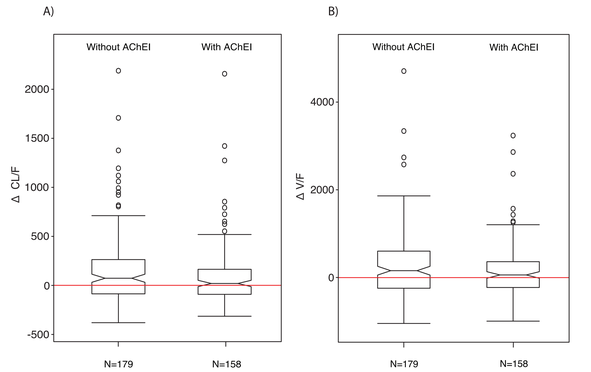
AChEI Drug	Patients Who Received a Concomitant Medication n (%)[a]
Donepezil/memantine combination	3 (0.9)
Galantamine	7 (2.1)
Rivastigmine	59 (17.5)
Donepezil	92 (27.3)

[a]Three patients received >1 AChEI drug.

Population-Based Covariate Analysis of CL/F and V/F

- In patients with/without AChEI use, CL/F and V/F showed no apparent differences between groups (**Figure 1**).
- Covariate testing found no statistically significant effect (α = 0.05) of AChEI use on CL/F or V/F.

Figure 1. Delta Plots of CL/F (A) and V/F (B) in the HARMONY Analysis Population for AChEI Status

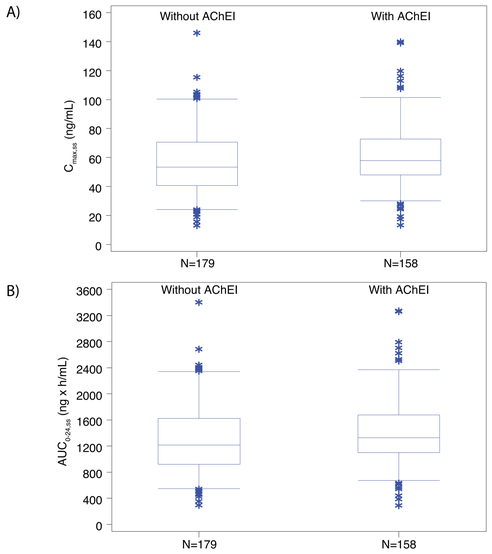


Boxes represent the 25th and 75th percentiles and lines represent the median. Notches provide an approximate 95% confidence interval about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values outside this range are marked with open circles.
AChEI, acetylcholinesterase inhibitors; CL/F, apparent clearance; V/F, apparent volume of distribution.

Model-Predicted Pimavanserin Exposures

- Minimal differences in steady-state pimavanserin exposures were predicted between patients with concomitant AChEI use versus those without (**Figure 2**).

Figure 2. Boxplots of C_{max} (A) and AUC (B) in HARMONY Patients by AChEI Status



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range.
AChEI, acetylcholinesterase inhibitors; AUC, area under the plasma concentration-time curve at steady state; C_{max}, maximum drug concentration at steady state.

- The median C_{max} was 8.4% higher in patients taking concomitant AChEIs (57.9 ng/mL) relative to those not taking concomitant AChEIs (53.4 ng/mL) (**Table 2**).
- The median AUC was 9.2% higher in patients taking concomitant AChEIs (1328.9 ng × h/mL) relative to those not taking concomitant AChEIs (1216.5 ng × h/mL) (**Table 2**).

Table 2. Summary Statistics of C_{max} and AUC in HARMONY Patients by Concomitant AChEI Status

Statistic	$C_{max,ss}$ (ng/mL)		$AUC_{0\text{-}24,ss}$ (ng × h/mL)	
	Without AChEI (n=179)	With AChEI (n=158)	Without AChEI (n=179)	With AChEI (n=158)
Mean (SD)	57.0 (22.3)	62.0 (21.9)	1309.8 (522.5)	1425.7 (514.6)
Median	53.4	57.9	1216.5	1328.9
5th percentile, 95th percentile	24.1, 100.4	30.0, 101.5	545.6, 2341.1	674.2, 2368.6

AChEI, acetylcholinesterase inhibitor; AUC, area under the plasma concentration-time curve at steady state; C_{max}, maximum drug concentration at steady state; SD, standard deviation.

CONCLUSIONS

- **Concomitant AChEIs had no effect on the PK parameters (AUC or C_{max}) of pimavanserin.**
- **Differences in predicted exposure measures at steady state (C_{max} and AUC) between groups were negligible (<10%).**
- **These modeling results suggest that concomitant AChEI use does not have a meaningful impact on the PK profile of pimavanserin.**
- **Interpretation of these results is limited in that AChEI treatment was not randomized.**

REFERENCES

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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, TB, DD, and SS are employees of and may hold stock and/or stock options in Acadia Pharmaceuticals Inc.

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