Relationship Between Pimavanserin Exposure and Psychosis Relapse in Patients With Dementia-related Psychosis: Clinical Results and Modeling Analysis From the Phase 3 HARMONY Study

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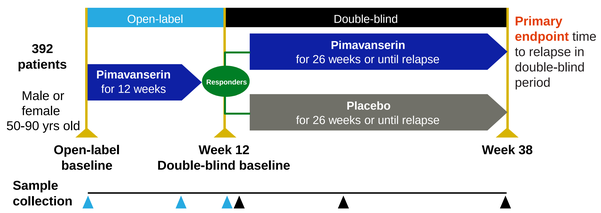
INTRODUCTION

- Dementia-related psychosis impacts more than 2.4 million patients;[1-5] however, there are no US FDA-approved therapies.[6]
- Pimavanserin is being investigated for the treatment of hallucinations and delusions associated with dementia-related psychosis.
- Exposure–response (E–R) analyses to assess the relationship between drug exposure and efficacy and/or safety are increasingly considered an integral part of clinical drug development.[7]

METHODS

- HARMONY (NCT03325556) was an international, placebo-controlled, phase 3 randomized withdrawal study of the efficacy and safety of pimavanserin for treating hallucinations and delusions associated with dementia-related psychosis (**Figure 1**).
- Eligible patients received open-label pimavanserin for 12 weeks. Patients with sustained response at weeks 8 and 12 were randomized in the double-blind period where they continued pimavanserin (at their final open-label dose) or switched to placebo.

Figure 1. Study Design



- A previously developed population pharmacokinetic model was used to obtain estimates of pimavanserin average daily exposure measures from patients during the double-blind period.
- Semi-parametric Cox proportional hazards models were used to evaluate the effect of pimavanserin daily exposure measures on the time to relapse (exposure–response efficacy relationship); the final exposure–response efficacy model was validated by Visual Predictive Check (VPC).
- The association between exposure and incidence of urinary tract infection (UTI) was examined using average daily pimavanserin exposure during the double-blind period and exposure on the day of the event (exposure–response safety relationship).
- UTI was preselected based on incidence rate at the time of analysis plan development.

DISCLOSURES

HARMONY was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA)

MD, EPF, MF, and SS are employees of Acadia Pharmaceuticals Inc.

JP, DJ, and JO are employees of Cognigen Corporation (Buffalo, NY, USA).

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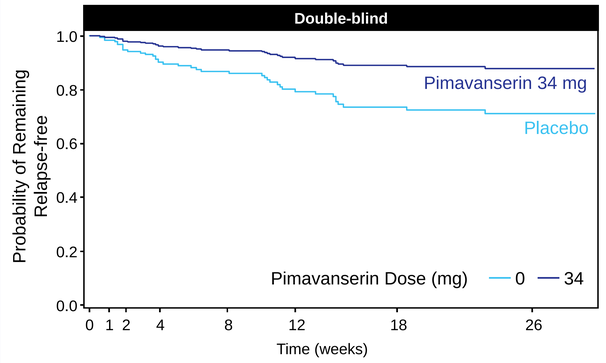
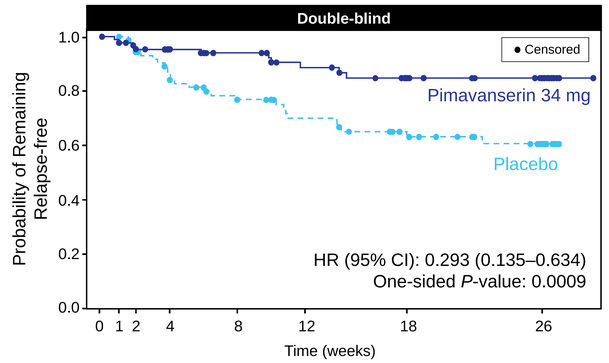
These results have been previously presented (Darwish M, et al. Relationship between pimavanserin exposure and psychosis relapse in patients with dementia-related psychosis: clinical results and modeling analysis from the phase 3 HARMONY study. Presented at CTAD; November 4–7, 2020. OC17.)

Pimavanserin is associated with significant reductions in the risk of relapse of symptoms of dementia-related psychosis

A. Risk of Relapse by Exposure for Pimavanserin 34 mg (median AUC) and Placebo in the HARMONY Double-blind Period



B. Risk of Relapse by Dose in Pimavanserin 34 mg and Placebo Patients in the HARMONY Double-blind Period



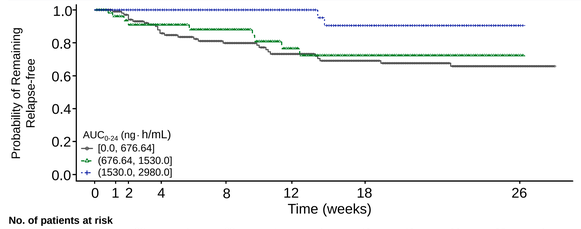
CI, confidence interval; HR, hazard ratio.

- In the final exposure–response efficacy model at the median pimavanserin area under the curve (AUC) of 1330 ng·h/mL, **pimavanserin reduced risk of relapse by 62%** compared with placebo.
  - The HR (95% CI) was 0.9993 (0.9987–0.9998), indicating that the **risk of relapse was decreased 0.07% for every 1 ng·h/mL increase in daily pimavanserin AUC**.
- Cox proportional hazards models showed a **significant relationship between higher exposure and greater probability of remaining relapse-free** for all exposure measures tested (all *P*<0.05).
- The HARMONY interim analysis included 194 randomized patients, of whom 184 (94%) completed the open-label phase on pimavanserin 34 mg.
- At the pre-specified interim analysis, **the risk of relapse in the HARMONY double-blind period was significantly reduced by >2.8-fold in all pimavanserin patients**, meeting the primary endpoint.
- In a subgroup analysis of patients who received **pimavanserin 34 mg, the risk of relapse was significantly reduced by >3.4-fold compared with placebo.**

RESULTS

- A total of 18,640 daily records from 185 patients sampled in the HARMONY double-blind period were included in the exposure–response efficacy dataset.
- In exploratory exposure–response analyses, the probability of remaining relapse-free based on pimavanserin average daily AUC exposure demonstrated a lower likelihood of relapse in the highest exposure tertile (**Figure 2**).
  - Exploratory analyses using pimavanserin average or maximum concentration were similar.

Figure 2. Kaplan-Meier Estimated Probability of Remaining Relapse-Free Versus Days, Stratified by Tertiles of Pimavanserin Exposure ($AUC_{0–24}$)

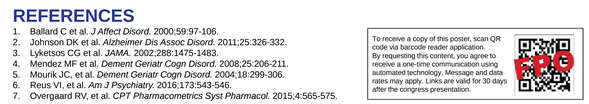


No. of patients at risk

[0.0, 676.64]	27	90	74	63	55	51	49	42	36	35	1
(676.64, 1530.0]	102	34	31	25	19	16	16	14	12	12	0
(1530.0, 2980.0]	56	30	26	23	21	20	18	16	15	15	0

- Visual predictive check plots showed good concordance between the final AUC model-based prediction and the observed data-based Kaplan-Meier estimates of time to relapse for each pimavanserin AUC exposure tertile (**Figure 3**).

Figure 3. VPC Plots of Exposure–Response Efficacy Model-Predicted and Observed Kaplan-Meier Estimated Relapse-Free Probabilities, by Pimavanserin Average Daily AUC Tertiles



- UTI was experienced by 5.1% of patients in the open-label period, and by 6.7% and 3.6% of pimavanserin and placebo patients, respectively, during the double-blind period.
- In the final E–R safety model, the probability of first occurrence of a UTI was not associated with daily average pimavanserin AUC, average concentration, or maximum concentration (all *P*>0.2) (**Table 1**).
  - Other exposure measures, including pimavanserin AUC on the day of adverse event occurrence, also were not associated with the probability of UTI.

Table 1. E–R Safety Modeling of Probability of First Occurrence of UTI During the HARMONY Double-Blind Period

	Overall (N=204)		
Parameter	Estimate (SE)	Odds Ratio (95% CI)	*P* value
Average daily pimavanserin AUC (ng·h/mL)	0.0004 (0.0004)	1.000 (1.000–1.001)	0.2866
Average daily pimavanserin C_{max} (ng/mL)	0.0106 (0.0098)	1.011 (0.991–1.030)	0.2806
Average daily pimavanserin C_{av} (ng/mL)	0.0108 (0.0101)	1.011 (0.991–1.031)	0.2852

C_{max}, maximum observed plasma concentration; C_{avg}, average plasma concentration; SE, standard error.

CONCLUSIONS AND DISCUSSION

- The exposure-efficacy analyses predict that higher pimavanserin exposure is associated with greater reduction in risk of relapse in patients with hallucinations and delusions associated with dementia-related psychosis, and provide an exposure-response foundation for the clinical observations in HARMONY.
- Pimavanserin exposure was not associated with the incidence of UTI, although the small number of UTI events does not allow for rigorous assessment of the exposure-adverse event relationship.
- These subgroup and modeling analyses support the efficacy of pimavanserin 34 mg in patients with hallucinations and delusions associated with dementia-related psychosis.

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