# Relationship Between Pimavanserin Exposure and QTc Interval in Patients with Schizophrenia: Modelling Analysis from Randomized, Double-Blind, Placebo-Controlled Studies

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## INTRODUCTION

- Patients with schizophrenia who are receiving more than one antipsychotic may be at higher risk for QT interval prolongation.[1,2]
- Pimavanserin, a serotonin receptor-modulating agent with inverse agonist/antagonist activity at 5-$HT_{2A}$ receptors and to a lesser extent 5-$HT_{2C}$ receptors[3], is being investigated for treatment of negative symptoms of schizophrenia.
- Pimavanserin prolongs the QT interval, with mean increases in corrected QT (QTc) interval of approximately 5–8 ms.[4]
- Two studies, ADVANCE and ENHANCE, investigated the efficacy and safety of pimavanserin in patients with schizophrenia when added to background antipsychotic treatment.[5,6] Exposure–response (ER) analyses of data collected in these studies can help assess the potential for effects on the QTc interval in patients with schizophrenia receiving repeated clinical doses of pimavanserin in the presence of background antipsychotics.

## OBJECTIVE

- Characterize, with an ER model, the impact of pimavanserin exposure on QT interval in the presence of selected antipsychotics.

## METHODS

### Study Design and Analysis Population

- Data were pooled from 2 randomized, double-blind, placebo-controlled studies.
  - ADVANCE (NCT02970305) was a 26-week phase 2 clinical trial in patients with schizophrenia who had predominant negative symptoms while on treatment with an antipsychotic.[5]
  - ENHANCE (NCT02970292) was a 6-week phase 3 clinical trial in patients with schizophrenia that had an inadequate response to antipsychotic treatment.[6]
- Patients were adults aged 18 to 55 years, diagnosed with schizophrenia ≥1 year prior to randomization, medically stable for >12 weeks before screening, and assessed as having a score ≥4 at screening and baseline on either the Clinical Global Impression-Severity scale (CGI-S, ENHANCE) or the Clinical Global Impression of Schizophrenia Scale-Severity scale (CGI-SCH-S, ADVANCE).
- Patients were treated with one of the following: risperidone (short acting), risperidone consta (long acting), olanzapine, aripiprazole (short acting), aripiprazole (long acting), asenapine, brexpiprazole, cariprazine, or lurasidone.
  - Oral antipsychotic dose was stable 4 weeks prior to screening, long-acting antipsychotic dose was stable 16 weeks prior to screening, and antipsychotic dose remained stable throughout the double-blind period.
- Patients were randomized 1:1 to receive placebo or pimavanserin 20 mg once daily at baseline in the presence of background antipsychotic.
- The flexible dosing design allowed the starting dose to be adjusted to 34 mg or 10 mg daily until week 3 (ENHANCE) or week 8 (ADVANCE).

### Outcome and Exposure Measures

- Blood samples for pharmacokinetic (PK) analysis were collected at screening and baseline (both studies), weeks 1, 3, and 6 (ENHANCE), and weeks 2, 8, 14, and 26 (ADVANCE).
- NONMEM® (ICON plc) was used to generate individual measures of predicted pimavanserin concentrations based on the population PK model and individual empiric Bayesian PK parameter estimates.
- Twelve-lead electrocardiograms were collected at baseline (both studies), weeks 4 and 6 (ENHANCE), and weeks 14 and 26 (ADVANCE).
  - Electrocardiogram measurements were centrally evaluated.
  - QTc interval was calculated according to Fridericia's formula (QTcF).

### ER Analysis

- Individual plasma concentrations were predicted at time of QTcF measurement.
- An ER model was developed to describe the effect of time-matched pimavanserin concentrations on QTcF and the change in QTcF from baseline (ΔQTcF) at each week.
- Covariate analysis was performed to assess the influence of age, sex, baseline weight, race, and background antipsychotic medication.
- Model validation used prediction-corrected visual predictive check methodology.

## RESULTS

### Population Characteristics

- The dataset included 2080 records from 737 patients (359 pimavanserin, 378 placebo) collected from randomization to 28 weeks (**Table 1**).

**Table 1. Demographic Characteristics, by Treatment, for the Concentration-QTcF Analysis**

| | Pimavanserin (n=359) | Placebo (n=378) | Overall (N=737) |
|---|---|---|---|
| Age, mean (SD), y | 37.4 (9.5) | 37.0 (9.2) | 37.2 (9.3) |
| Male, n (%) | 230 (64.1) | 242 (64.0) | 472 (64.0) |
| Weight, mean (SD), kg | 81.6 (15.2) | 81.3 (15.4) | 81.4 (15.3) |
| QTcF, mean (SD) | 399.91 (18.27) | 398.64 (19.01) | 399.26 (18.66) |
| Background antipsychotic, n (%) | | | |
| Risperidone (short acting) | 118 (32.9) | 115 (30.4) | 233 (31.6) |
| Olanzapine | 109 (30.4) | 126 (33.3) | 235 (31.9) |
| Aripiprazole (short acting) | 82 (22.8) | 81 (21.4) | 163 (22.1) |
| Risperidone consta (long acting) | 28 (7.8) | 27 (7.1) | 55 (7.5) |
| Aripiprazole (long acting) | 12 (3.3) | 24 (6.3) | 36 (4.9) |
| Other | 10 (2.8) | 5 (1.3) | 15 (2.0) |

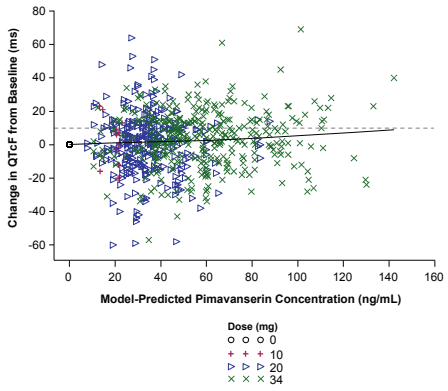
SD, standard deviation; QTcF, QT interval corrected by Fridericia's formula.

- Doses of 10, 20, and 34 mg were received by 7, 163, and 202 pimavanserin-treated patients, respectively.

### Exploratory Analyses of ΔQTcF

- As pimavanserin concentration increased, ΔQTcF increased in a linear manner (**Figure 1**).
- A ΔQTcF >60 ms occurred in 3 pimavanserin-treated patients.

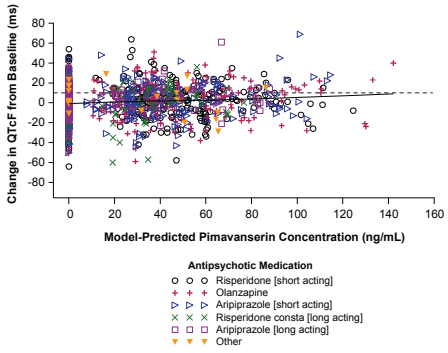
**Figure 1. ΔQTcF from Baseline Versus Pimavanserin concentrations, Stratified by Dose**




Scatterplot with a loess smooth line. The line represents a smoothing spline fit to the data.
ΔQTcF, change in QT interval corrected by Fridericia's formula.

- When analyzed by background antipsychotic medication, no apparent difference in the relationship between ΔQTcF and pimavanserin concentration was observed (**Figure 2**).

**Figure 2. ΔQTcF from Baseline Versus Pimavanserin Concentrations, Stratified by Main Antipsychotic Medication**

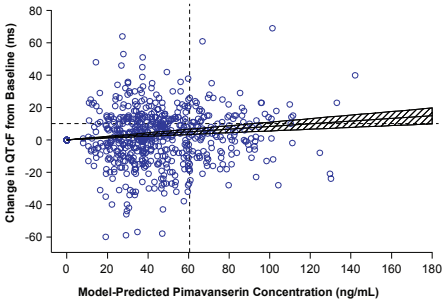



Scatterplot with a loess smooth line The line represents a smoothing spline fit to the data.
ΔQTcF, change in QT interval corrected by Fridericia's formula.

### Concentration-QTcF Model

- Observed data were best fit by a linear model (concentration–QTcF), including estimation of baseline QTcF interval, slope of pimavanserin concentration effect, week effect, and additive shift on baseline QTcF interval for female sex (**Figure 3**).
  - Sex was found to be a significant covariate that influenced baseline QTcF (11.7 ms longer baseline QTcF in females compared with males).
- At the average steady state maximum concentration of 60.4 ng/mL with a pimavanserin 34 mg once-daily regimen, the median predicted QTcF interval increase was 5.0 ms (90% prediction interval, 3.3 to 6.6 ms).

**Figure 3. Model-Predicted Median and 90% Prediction Interval of ΔQTcF from Baseline Versus Pimavanserin Concentrations Overlaid with Observed ΔQTcF Data**




The solid line and shaded area represent the median prediction and 90% prediction interval based on parameter estimate uncertainty, respectively. Horizontal dashed line indicates the 10 msec ΔQTcF threshold. Vertical dashed line shows the model–predicted median $C_{max,ss}$ following 34 mg pimavanserin dose.
ΔQTcF, change from baseline to QT interval corrected for heart rate according to Fridericia's formula; $C_{max,ss}$, maximum concentration at steady state.

- No pimavanserin exposure–related effect was apparent across QTcF categories (>450, >480, and >500 ms) or QTcF interval change (>30 and >60 ms).
- Observed dependence of QTcF on pimavanserin concentrations was independent of background antipsychotic medications.

## CONCLUSIONS

- **The modelled effect of pimavanserin exposure on QTcF interval in patients with schizophrenia showed no difference in impact of pimavanserin exposure on QTcF interval in the presence of selected concomitant antipsychotics.**
- **Observed dependence of QTcF on pimavanserin concentrations was independent of background antipsychotic medications.**
- **ENHANCE and ADVANCE were not designed or powered to thoroughly evaluate the relationship of pimavanserin exposure to QTc prolongation, and conclusions drawn from this analysis are based on modelling and simulation from the observed data.**
- **ER modelling results from ENHANCE and ADVANCE were consistent with previously reported QTcF interval increase (5 ms).[7]**

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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 supported by Acadia Pharmaceuticals Inc. MD, DBK, DD, and SS are employees of and may hold stock and/or stock options in Acadia Pharmaceuticals Inc. JP, KM, and JO are employees of Cognigen Corporation.