Acadia Pharmaceuticals Inc. is providing this letter in response to your unsolicited request for medical information. It is for scientific-exchange and individual educational purposes only, and should not be copied or distributed. Information included in this letter may not be consistent with the US FDA-approved Prescribing Information for NUPLAZID® (pimavanserin) or may be related to unapproved uses of NUPLAZID. This letter is not intended to advocate any unapproved or approved use, indication, dosage, or other treatment-related decision. Acadia strives to provide current, accurate, and fair-balanced information in compliance with current industry information dissemination guidelines.

For further information regarding Indication, **Boxed WARNING** and other Important Safety Information for NUPLAZID, please click here: Prescribing Information.

12830 El Camino Real · Suite 400 · San Diego, California 92130 · USA · Tel. 858.558.2871 · Fax 858.558.2872 · acadia.com

NUPLAZID® (pimavanserin): Effect on QT Interval

This letter is provided in response to your specific request for information on the effect of pimavanserin on QT interval.

Relevant Label Information[1]

- NUPLAZID prolongs the QT interval (~5–8 milliseconds). NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval.
- NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.

Summary

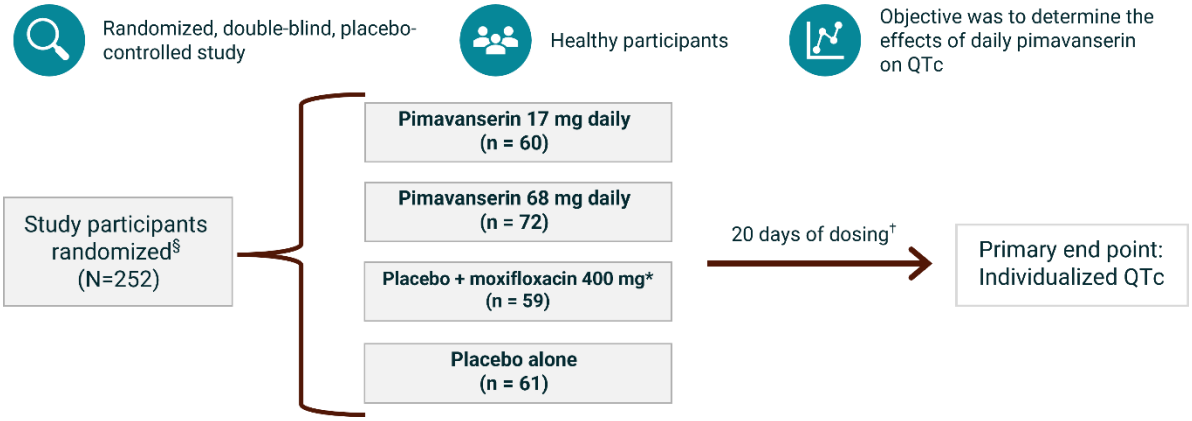
- Investigation of the electrocardiographic effects of pimavanserin resulted in no meaningful effects on heart rate, pulse rate, or QRS intervals in **ACP-103-018 (Thorough QT [TQT] study)** or **placebo-controlled Phase 2b/3 studies** in Parkinson's disease psychosis (PDP).[2,3]
- Pimavanserin has a mild-to-moderate propensity to increase the corrected QT interval (QTc) and may thus have a proarrhythmic risk.[3]
    - Pooled analysis from Phase 2b/3 studies (N=157) indicates a **mean increase** in QTc using Fridericia's formula (QTcF) of 6.9 milliseconds (upper 90% confidence interval [CI] of 10.0 milliseconds) with pimavanserin 34 mg once daily.[3]

TQT Study

Background

The study design for the **TQT Study** is shown in **Figure 1**.[2] Electrocardiograms (ECGs) and concurrent pharmacokinetic (PK) samples were analyzed in a blinded fashion by a core ECG laboratory (eRT, Inc).

Figure 1. Study Design for TQT Study[2]



§Equal numbers of males (n=126) and females (n=126) were randomized.
**moxifloxacin provided on Day 20 only.*
†ECGs and PK samples were collected in triplicate on Day -1 and 20 at regular intervals between 1–23.5 hours post-dose.
Abbreviations: ECG=electrocardiograms; PK=pharmacokinetic; QTc=corrected QT interval; TQT=Thorough QT.

ECG Results

During the TQT study, the maximum studied dose (68 mg) yielded a median observed plasma concentration (C_p) of 155 ng/mL, and a median maximum concentration (C_{max}) of 197 ng/mL, which is approximately 2.5-fold higher than the median C_{max} associated with pimavanserin 34 mg/day.[3] There was no meaningful effect on heart rate, pulse rate, or QRS intervals. The placebo-adjusted change from baseline individualized corrected-QT interval (QTcI) is shown in **Table 1**.

Table 1. Maximal Mean Placebo-adjusted Change from Baseline: Individual Corrected QT interval[3]

	Pimavanserin 17 mg/day (n=60)	Pimavanserin 68 mg/day (n=72)
Maximal Mean Δ-Δ QTcI mean (upper 90% CI)	4.7 ms (6.8 ms)	13.9 ms (15.9 ms)

Abbreviations: CI=confidence interval; ms=milliseconds; QTcI=individualized corrected QT interval.

There was no meaningful outlier effect. No participants receiving pimavanserin had an absolute QTcI >480 milliseconds or an increase from baseline >60 milliseconds.[3] One (1) participant receiving pimavanserin 68 mg/day had an increase from baseline in the QTcI of between 30 and 60 milliseconds.

Treatment-emergent Adverse Events of Proarrhythmic Potential

Syncope as a treatment-emergent adverse event (TEAE) was reported in 2 of 72 participants (2.8%) in the pimavanserin 68 mg group and 1 of 59 participants (1.7%) in the placebo/moxifloxacin group.[2] No additional TEAEs suggestive of proarrhythmic potential or clinically significant cardiovascular-related TEAEs were reported in any treatment group.

Exposure-response Analysis

Pimavanserin exposure-response (E-R) modeling was performed with data from the TQT study.[3] A mixed linear effects model was initially used to examine the PK/QTc relationship with

pimavanserin, but additional E-R modeling demonstrated that a 2-part regression was superior in properly representing the data. Ultimately, two "optimal" models were selected. Overall, the models suggest that an increase in QTc is minimal or absent following a rapid increase in the QTcI, above a threshold concentration (~86 ng/mL). Based on these models, with a daily dose of 34 mg (for which the expected Cp is ~70 ng/mL), the upper 90% CI of the increase in the QTcI is ~11 milliseconds.

Potential limitations of the E-R modeling include concentrations of pimavanserin metabolite AC-279 were not determined, and AC-279-specific electrophysiologic effects were not delineated.[3] However, the thorough QT E-R model for pimavanserin, although based on pimavanserin concentrations, would include effects of both parent and metabolite. This model was used to predict the QTcI values at the 17 mg/day and 68 mg/day doses (**Table 2**). Predicted values show an overall good correlation with the observed values in the TQT study, supporting the overall clinical relevance of the E-R modeling with pimavanserin.

Table 2. Observed Increase in QTcI at Steady State as a Result of the C_{max} Associated with Range of Doses[3]

Dose (mg)	Median C_{max} Values Obtained	Increase in QTcI (ms)		
		QTcI by eRT	Model 1C	Model 1D
17	43	4.7	4.6	4.9
68	197	13.9	12.0	10.5

Note: Values derived from TQT study and PK modeling.
Abbreviations: C_{max}=maximum concentration; eRT=eRT Inc; ms=millisecond; QTcI=individualized corrected QT interval; TQT=Thorough QT.

Placebo-controlled Phase 2b/3 Studies

Background

Safety data were pooled from 3 randomized, double-blind, placebo-controlled Phase 2b/3 and Phase 3 studies in PDP:[3]

- **Study 012**: Phase 2b/3 study (N=298) that evaluated the safety and efficacy of once daily pimavanserin 8.5 mg and 34 mg vs placebo for up to 6 weeks.
- **Study 014**: Phase 2b/3 study that evaluated the safety and efficacy of once daily pimavanserin 8.5 mg and 17 mg vs placebo in 123 participants (original planned sample size was 279) for up to 6 weeks.
- **Study 020**: Pivotal phase 3 study (N=199) that evaluated safety and efficacy of once daily pimavanserin 34 mg vs placebo for up to 6 weeks.

Standard 12-lead ECG tracings and PK samples were obtained at Screening, Day 1 (Baseline, prior to initial dosing), Week 1 (Studies 012 and 014 only; no PK sample), and Weeks 2, 4, and 6, generally at trough (note: the difference between C_{max} and trough is ~10%).[3] Initially the ECGs were machine-read, but after evaluating the results of the TQT study, the decision was made to have the ECGs analyzed by a core ECG laboratory. Most ECGs were available for this core laboratory review and an analysis demonstrated that there was no informative censoring.

ECG Results

Similar to the TQT study, there was no meaningful effect on heart rate, pulse rate, or QRS intervals.[3] The placebo-subtracted corrected QT interval using QTcF data showed no meaningful effect of pimavanserin on cardiac repolarization at the 8.5 mg/day dose and a mild degree of QTcF prolongation at 34 mg/day (**Table 3**).

Table 3. Maximal Mean Placebo-Adjusted Change from Baseline: QTcF[3]

	Pimavanserin 8.5 mg/day: Study 012 (n=66)	Pimavanserin 34 mg/day: Pooled data from Studies 012 and 020 (n=157)
Maximal Mean Δ-Δ QTcF mean (upper 90% CI)	1.4 ms (5.6 ms)	6.9 ms (10.0 ms*)

**At Day 8, ECGs were only available in Study 012, where the change from baseline in the QTcF was 6.1 milliseconds (upper 90% CI of 10.9 milliseconds)*

Abbreviations: CI=confidence interval; ms=milliseconds; QTcF=corrected QT interval using Fridericia's formula.

The QTcF outlier analyses demonstrated a lack of meaningful differences in outliers with a QTcF >480 milliseconds or an increase in QTcF >60 milliseconds (**Table 4**).[3] However, there was a higher incidence in the pimavanserin cohort in the QTc increase from baseline of 30–60 milliseconds in the pimavanserin 34 mg group. This likely represents the mild-moderate QTcF prolonging effect of pimavanserin.

Table 4. Core Lab Analysis – QTc Outlier Analysis[3]

n (%)	Pimavanserin		Placebo (n=150)
	8.5 mg/day (n=67)	34 mg/day (n=164)	
QTcF >480 ms (Baseline value ≤480 ms)	2 (3.0%)	4 (2.4%)	5 (3.3%)
QTcF >500 ms (Baseline value ≤500 ms)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Increase in QTcF 30–60 ms	5 (7.5%)	32 (19.5%)	11 (7.3%)
Increase in QTcF >60 ms	0 (0.0%)	0 (0.0%)	1 (0.7%)

Abbreviations: ms=milliseconds; QTcF=corrected QT interval using Fridericia's formula.

Potential Arrhythmic Adverse Events

The occurrence of potential arrhythmic events that might represent a ventricular arrhythmia such as sudden death, cardiac arrest, presyncope, and syncope were evaluated in the adverse event reporting database from the 3 pooled studies.[3] During the studies, there were no reported cardiac arrests or sudden deaths in participants receiving pimavanserin. One (1) participant died of a myocardial infarction and, since the participant was found dead in bed, this likely represented a cardiac arrest. One (1) participant in the placebo group had a cardiorespiratory arrest that, upon review, appears to have been a primary cardiac arrest. Two (2) participants receiving pimavanserin (1 each receiving 8.5 mg and 34 mg) had syncopal episodes. In 1 participant, the event was documented to be due to "asystole" and was treated with a pacemaker. One (1) participant in the placebo group had a presyncopal event. Thus, there were 2 potential tachyarrhythmic events in participants receiving pimavanserin (0.52%, 2/383) and 2 in participants receiving placebo (0.87%, 2/231).

Exposure-response Analysis

Pimavanserin E-R modeling was performed with data from the Phase 2b/3 studies using the optimal PK/PD model with a two-part regression approach, similar to TQT study.[3] The optimal PK/PD model demonstrated a relative plateau above a plasma concentration of ~40 ng/mL (the 34 mg dose is associated with a median C_{max} of ~71 ng/mL in participants). The model-predicted change in QTcF value from baseline for the pimavanserin 34 mg dose was the same as for the plateau. The upper bound of the 90% CI was approximately 10 milliseconds.

References

1. NUPLAZID® (pimavanserin) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. In. San Diego, CA.
3. Acadia Pharmaceutical Inc. NUPLAZID® Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee on 29 March 2016.