Effects of Adjunctive Pimavanserin and Current Antipsychotic Treatment on QT Interval Prolongation in Patients with Schizophrenia

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INTRODUCTION

- In clinical practice, augmentation with a second antipsychotic (AP) agent is a common strategy for treating patients with schizophrenia.[1]
- Treatment with multiple antipsychotic agents of similar mechanism of action has been associated with increased burden of adverse events.[1]
- QT interval prolongation may be a concern among patients who are receiving polypharmacy treatment for schizophrenia.[2,3]
- Pimavanserin, a selective 5-HT_{2A} receptor inverse agonist/antagonist, is approved by the United States Food and Drug Administration for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis[4] and is being actively investigated for its potential to treat the negative symptoms of schizophrenia.[5]
  - Increase in QT interval prolongation is included as a warning in the prescribing information along with a precaution to avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval.[4]
- Three studies (2 completed; 1 ongoing) investigated the efficacy of pimavanserin in schizophrenia when added to antipsychotic treatment, allowing the assessment of QT interval prolongation in patients receiving an antipsychotic and adjunctive pimavanserin.

OBJECTIVE

- To assess the QT interval prolongation in 3 large studies investigating once daily pimavanserin as adjunctive to current antipsychotic treatment in patients with schizophrenia.

METHODS

- Data from 3 studies were analyzed to determine the effects of pimavanserin on QT interval prolongation in patients with schizophrenia (**Table 1**).
  - ENHANCE (NCT02970292) was a 6-week, randomized, double-blind, placebo controlled phase 3 study in patients with schizophrenia and inadequate response to their current antipsychotic treatment.[6]
  - ADVANCE (NCT02970305) was a 26-week, randomized, double-blind, placebo-controlled phase 2 study in patients with schizophrenia and predominant negative symptoms while on treatment with an antipsychotic medication.[7]
  - Study 035 (ACP-103-035; NCT03121586) is an ongoing 52-week, open-label extension study of patients from ENHANCE and ADVANCE (database extraction date: April 28, 2020).[8]

Table 1. Included Studies

Study	Study Design	Treatment	Population	N	Time of QTcF Assessments
ENHANCE (ACP-103-034; NCT02970292)[6]	Phase 3, randomized, double-blind, placebo-controlled study	Pimavanserin or placebo (1:1) for 6 weeks	Adults ≥50 years of age with schizophrenia and an inadequate response to current antipsychotic treatment	396 • 198 pimavanserin • 198 placebo	Screening, baseline, week 4, and week 6 (EOS/ET)
ADVANCE (ACP-103-038; NCT02970305)[10]	Phase 2, randomized, double-blind, placebo-controlled study	Pimavanserin or placebo (1:1) for 26 weeks	Adults ≥50 years of age with negative symptoms of schizophrenia	400 • 201 pimavanserin • 199 placebo	Screening, baseline, week 14, and week 26 (EOS/ET)
Study 035 (ACP-103-035; NCT03121586)[11]	Ongoing open-label extension study	Pimavanserin for 52 weeks	Patients rollover from ENHANCE and ADVANCE	638[a] pimavanserin	OL baseline, weeks 2, 28, and 52

[a]Interim analysis as of April 28, 2020 data cutoff date.
EOS, end of study; ET, early termination; OL, open-label; QTcF, QT interval using Fridericia's correction method.

- In all 3 studies, patients had to be treated or must have been on the following APs: aripiprazole (including long-acting injectable [LAI]), asenapine, brexpiprazole, cariprazine, lurasidone, olanzapine, risperidone (including LAI).
  - No dose change of oral AP was permitted within 4 weeks prior to screening; no dose change of LAI AP was permitted within 16 weeks prior to screening.
  - The 3 most frequently used APs were aripiprazole (including LAI), risperidone (including LAI), and olanzapine.
  - A *no risperidone* subgroup was also analyzed to understand the effects of APs with low or moderate risk of QTc prolongation. This group included patients who were treated with either aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, or olanzapine.
- Electrocardiograms were unblinded from completed trials in which pimavanserin or placebo were added to main APs over 6 weeks (ENHANCE), 26 weeks (ADVANCE), and up to 78 weeks (ongoing 52-week, open-label rollover Study 035) of treatment.
- In a post hoc analysis, QT intervals of patients treated with aripiprazole, risperidone, or olanzapine were corrected (QTc) using Fridericia's method with elevated risk defined as either postbaseline value maximum of >500 ms or change from baseline to postbaseline maximum of >60 ms.

RESULTS

ENHANCE

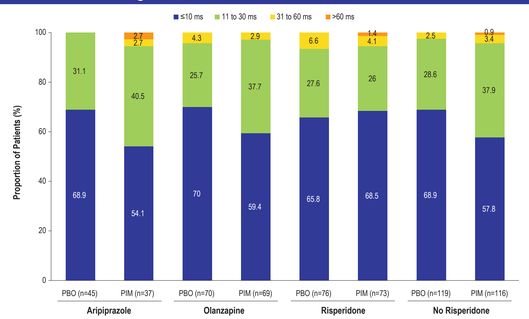
- In ENHANCE, no patients had corrected QT interval using Fridericia's correction method (QTcF) values >480 ms; change from baseline in QTcF >60 ms was reported in 2 patients (1.1%) in the pimavanserin group and none in the placebo group.[6]
- Of patients who were treated with adjunctive pimavanserin in ENHANCE (risperidone, n=73; aripiprazole, n=37; olanzapine, n=69), mean QTcF intervals at baseline were generally similar among APs (**Table 2**).
- There were no postbaseline QTc values >480 ms (**Table 2**); one patient in each of the risperidone and aripiprazole groups had change from baseline to postbaseline maximum >60 ms (**Figure 1**).
  - Among patients on risperidone, more patients had a change from baseline to postbaseline maximum ranging from 31 to 60 ms (n=5; 6.6%) with placebo than in the risperidone plus adjunctive pimavanserin group (n=3, 4.1%) (**Figure 1**).

Table 2. ENHANCE: QTcF at Baseline and On-Study

	Aripiprazole		Olanzapine		Risperidone		No Risperidone	
	PBO N=45	PIM N=38	PBO N=71	PIM N=71	PBO N=78	PIM N=78	PBO N=120	PIM N=120
Baseline QTcF (n)	45	38	71	71	78	78	120	120
Mean (SE), ms	389.5 (2.97)	398.2 (3.48)	399.5 (2.05)	401.0 (2.11)	401.3 (2.05)	400.2 (2.37)	395.1 (1.73)	399.8 (1.69)
Change from baseline to week 6 (n)	42	35	68	64	72	67	114	107
Mean (SE), ms	-0.8 (1.62)	0.1 (2.61)	-0.3 (1.85)	2.4 (1.89)	-1.1 (1.94)	0.1 (2.12)	-0.2 (1.26)	2.0 (1.50)
Overall postbaseline maximum (N)[a]	45	37	70	69	76	73	119	116
≤450 ms, n (%)	45 (100)	37 (100)	68 (97.1)	68 (98.6)	75 (98.7)	72 (98.6)	117 (98.3)	115 (99.1)
451 to 480 ms, n (%)	--	--	2 (2.9)	1 (1.4)	1 (1.3)	1 (1.4)	2 (1.7)	1 (0.9)
481 to 500 ms, n (%)	--	--	--	--	--	--	--	--
>500 ms, n (%)	--	--	--	--	--	--	--	--

[a]Subjects with a least one postbaseline value for the given treatment group.
N=subjects randomized to a given treatment; n=subjects with at least one postbaseline value for the given treatment group.
PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method; SE, standard error.

Figure 1. ENHANCE: Change in QTcF from Baseline to Overall Postbaseline Maximum



PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method.

ADVANCE

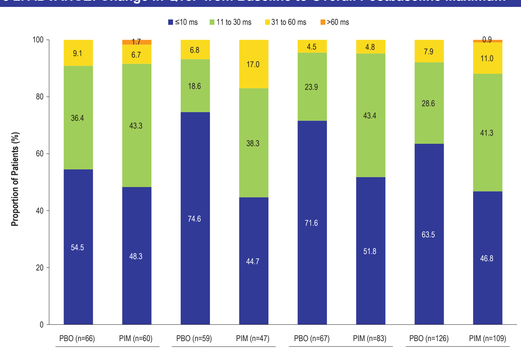
- In ADVANCE, no patients had QTcF values >500 ms; change from baseline in QTcF >60 ms was reported in 1 patient (0.5%) in the pimavanserin group and none in the placebo group.[7]
- In the pimavanserin group of ADVANCE (risperidone, n=83; aripiprazole, n=60; olanzapine, n=47), mean QTcF intervals at baseline were generally similar among antipsychotics (**Table 3**).
- One patient from the *no risperidone* subgroup had a postbaseline QTc value >480 ms (**Table 3**).
- More patients had change from baseline to postbaseline maximum between 31 to 60 ms in each of the groups treated with other APs (n=22, 9.4%) than in the group treated with risperidone (n=7, 4.7%) (**Figure 2**).
- One patient treated with aripiprazole and pimavanserin had a change from baseline to postbaseline maximum >60 ms (**Figure 2**).

Table 3. ADVANCE: QTcF at Baseline and On-Study

	Aripiprazole		Olanzapine		Risperidone		No Risperidone	
	PBO N=69	PIM N=63	PBO N=62	PIM N=50	PBO N=69	PIM N=86	PBO N=133	PIM N=115
Baseline QTcF (n)	69	63	62	50	69	86	133	115
Mean (SE), ms	396.0 (2.65)	397.3 (2.20)	399.5 (2.51)	398.6 (2.51)	401.8 (2.03)	400.3 (1.82)	398.0 (1.82)	398.0 (1.62)
Change from baseline to week 26 (n)	56	54	54	41	63	78	110	97
Mean (SE), ms	3.2 (2.27)	6.4 (2.46)	-1.4 (1.90)	5.1 (3.30)	-1.6 (2.08)	3.0 (1.79)	1.0 (1.49)	5.7 (1.99)
Overall postbaseline maximum (N)[a]	66	60	59	47	67	83	126	109
≤450 ms, n (%)	65 (98.5)	58 (96.7)	59 (100)	45 (95.7)	66 (98.5)	83 (100)	125 (99.2)	105 (96.3)
451 to 480 ms, n (%)	1 (1.5)	1 (1.7)	--	2 (4.3)	1 (1.5)	--	1 (0.8)	3 (2.8)
481 to 500 ms, n (%)	--	--	--	--	--	--	--	1 (0.9)
>500 ms, n (%)	--	--	--	--	--	--	--	--

[a]Subjects with a least one postbaseline value for the given treatment group.
N=subjects randomized to a given treatment; n=subjects with at least one postbaseline value for the given treatment group.
PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method; SE, standard error.

Figure 2. ADVANCE: Change in QTcF from Baseline to Overall Postbaseline Maximum



PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method.

Study 035

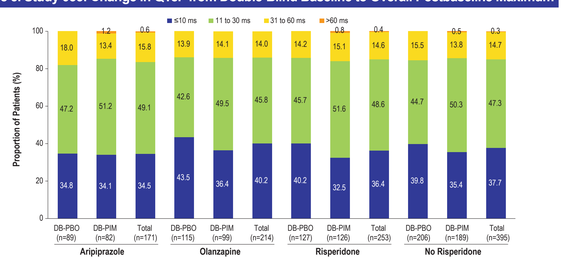
- During the double-blind period prior to enrollment in the open-label rollover study (aripiprazole n=171; olanzapine, n=214; risperidone, n=253 [all both arms in the double-blind period]), mean QTcF interval at the double-blind baseline were generally similar among AP subgroups (**Table 4**).
  - Of these patients who had reached week 52 at the time of the interim analysis, 80 patients were treated with aripiprazole, 125 with olanzapine, and 142 with risperidone.
- One patient treated with aripiprazole had postbaseline maximum of 481 to 500 ms, and one patient each treated with aripiprazole and risperidone had double-blind baseline to post double-blind baseline maximum of >60 ms (**Table 4**).
  - Similar proportions of patients had changes from double-blind baseline to post double-blind baseline maximum between 31 to 60 ms across treatments (**Figure 3**).

Table 4. Study 035: QTcF at Double-Blind Baseline and On-Study

	Aripiprazole			Olanzapine			Risperidone			No Risperidone		
	DB PBO OL PIM N=89	DB PIM OL PIM N=82	Total N=171	DB PBO OL PIM N=115	DB PIM OL PIM N=99	Total N=214	DB PBO OL PIM N=127	DB PIM OL PIM N=126	Total N=253	DB PBO OL PIM N=206	DB PIM OL PIM N=189	Total N=395
DB Baseline QTcF (n)	89	82	171	115	99	214	127	126	253	206	189	395
Mean (SE), ms	393.7 (2.11)	398.6 (2.02)	396.0 (1.47)	399.0 (1.78)	402.0 (1.72)	400.4 (1.24)	400.8 (1.53)	399.9 (1.75)	400.4 (1.16)	396.5 (1.36)	400.3 (1.27)	398.3 (0.94)
Change from DB baseline to OL week 52 (n)	44	36	80	64	61	125	72	70	142	109	102	211
Mean (SE), ms	5.2 (2.38)	1.9 (3.48)	3.7 (2.04)	3.6 (2.09)	3.2 (2.11)	3.4 (1.48)	4.7 (1.86)	4.0 (2.01)	4.4 (1.36)	4.3 (1.56)	2.6 (1.75)	3.5 (1.17)
Overall OL postbaseline maximum (N)[a]	89	82	171	115	99	214	127	126	253	206	189	395
≤450 ms, n (%)	87 (97.8)	79 (96.3)	166 (97.1)	112 (97.4)	96 (97.0)	208 (97.2)	124 (97.6)	124 (98.4)	248 (98.0)	201 (97.6)	183 (96.8)	384 (97.2)
451 to 480 ms, n (%)	2 (2.2)	2 (2.4)	4 (2.3)	3 (2.6)	3 (3.0)	6 (2.8)	3 (2.4)	2 (1.6)	5 (2.0)	5 (2.4)	5 (2.6)	10 (2.5)
481 to 500 ms, n (%)	--	1 (1.2)	1 (0.6)	--	--	--	--	--	--	--	1 (0.5)	1 (0.3)
>500 ms, n (%)	--	--	--	--	--	--	--	--	--	--	--	--

[a]Subjects with a least one postbaseline value for the given cohort.
N=OL subjects for the given cohort; n=OL subjects with at least one change from DB baseline value for the given cohort.
DB, double blind; OL, open label; PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method; SE, standard error.

Figure 3. Study 035: Change in QTcF from Double-Blind Baseline to Overall Postbaseline Maximum



DB, double-blind; PBO, placebo; PIM, pimavanserin; QTcF, QT interval using Fridericia's correction method.

- No adverse events associated with an increase in the QTc interval were reported in either treatment group.

CONCLUSIONS

- **Across 3 large studies of patients with schizophrenia who received pimavanserin along with another AP, mean changes in QTc prolongation were minimal and were similar to the placebo treatment arms.**
- **Adjunctive pimavanserin with AP treatment (ie, aripiprazole, olanzapine, risperidone) showed no evidence of QTc prolongation >500 ms post baseline.**
- **No safety concerns related to an increase in the QTc interval were reported.**

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ACKNOWLEDGMENTS

Medical writing support for the development of this poster, under the direction of the authors, was provided by Alison Adams, PhD, and Dena McWain of Ashfield MedComms, an Ashfield Health company, and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

This study was funded by Acadia Pharmaceuticals Inc. All authors are employees of Acadia Pharmaceuticals Inc.

Supported by funding from Acadia Pharmaceuticals Inc.

Poster presented at the 61st Annual meeting of the American College of Neuropsychopharmacology. December 4–7, 2022, Phoenix, AZ, USA | Previously presented at APA 2021

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