Pimavanserin for the treatment of irritability associated with autism spectrum disorder in children and adolescents: a randomised, double-blind, placebo-controlled study

PS01-0167

Dragana Bugarski-Kirola,[1] Robert K. Hofbauer,[2] Snjezana Sameljak,[1] Elysa Marco,[3,4] Anita Sumiła,[5,6] Mona Darwish,[2] Sharon Ortiz,[2] I-Yuan Liu,[7] Rene Nunez,[2] Peter Zhang,[2] Celso Arango[8,9]

[1]Acadia Pharmaceuticals GmbH, Basel, Switzerland; [2]Acadia Pharmaceuticals Inc., Princeton, NJ, USA; [3]Cortica Healthcare Inc., San Diego, CA, USA; [4]Lifetime in Neurodevelopmental Care, Encino, CA, USA; [5]Centrum Badan Klinicznych PI-House, Gdansk, Poland; [6]Instytut Psychologii, Wyższa Szkoła Kształcenia Zawodowego, Wrocław, Poland; [7]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [8]Department of Child and Adolescent Psychiatry, Hospital Universitario La Paz, IdiPaz, School of Medicine, Universidad Autónoma de Madrid, Spain; [9]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

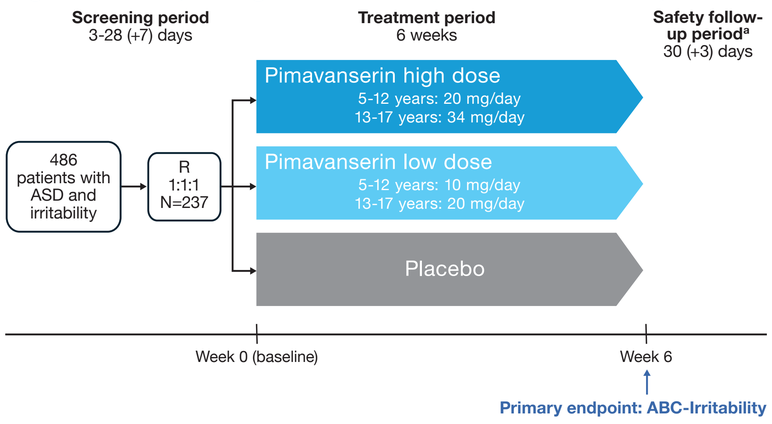
INTRODUCTION

- Irritability is common in autism spectrum disorder (ASD) and represents a substantial burden for patients and caregivers[1]
- Currently approved treatments for ASD-related irritability in the US include antipsychotics, such as risperidone and aripiprazole, which have activity at dopamine type 2 and/or serotonin 2A (5-HT_{2A}) receptors[2,3]
- Adverse effects associated with these therapies include sedation, weight gain, increased risk of developing metabolic disorders, and extrapyramidal symptoms including tremor, dyskinesia, and rigidity[3,4]
- Due to the considerable burden ASD-related irritability presents and the adverse events associated with currently approved treatments, effective management is a key unmet need in ASD
- Pimavanserin is a selective inverse agonist and antagonist of the 5-HT_{2A} (and, less so, 5-HT_{2C}) receptor[5]
- In this study, we evaluate the efficacy and safety of pimavanserin in children and adolescents with irritability associated with ASD

METHODS

- This was a phase 2, randomised, double-blind study (NCT05523895) in children and adolescents (aged 5-17 years) with ASD and irritability, agitation, or self-injurious behaviours
- Participants were randomised 1:1:1 as follows:
  - Pimavanserin high dose (5-12 years, 20 mg/day; 13-17 years, 34 mg/day)
  - Pimavanserin low dose (5-12 years, 10 mg/day; 13-17 years, 20 mg/day)
  - Placebo
- The 6-week double-blind treatment period was followed by a 30-day safety follow-up period (**Figure 1**)

Figure 1. Study Design Schematic (Randomised Analysis Set)



ABC, Aberrant Behaviour Checklist; ASD, autism spectrum disorder; R, randomised.
[a]Follow-up telephone call. Patients who completed the 6-week treatment period may have been eligible to enrol immediately in a 52-week open-label extension study (NCT05555615) in lieu of a follow-up telephone call.

- Primary endpoint: Change from baseline at week 6 in the following:
  - Caregiver-rated Aberrant Behaviour Checklist (ABC)-Irritability subscale
- Key secondary endpoints: Change from baseline at week 6 in the following:
  - Clinical Global Impression-Severity (CGI-S) irritability
  - Clinical Global Impression-Improvement (CGI-I) irritability
  - Additional ABC subscales, including stereotypic behaviour, lethargy, hyperactivity, and inappropriate speech
  - Repetitive Behaviour Scale-Revised (RBS-R)
  - Vineland Adaptive Behaviour Scales (VABS)-Socialisation
  - Caregiver Strain Questionnaire (CGSQ)
- Safety and tolerability were evaluated by analysis of treatment-emergent adverse events (TEAEs)
- Assessments were conducted at baseline and weeks 1-6 or early termination

RESULTS

- A total of 232 randomised patients were included in the full analysis set (pimavanserin low dose, n=76; pimavanserin high dose, n=78; placebo, n=78), of whom 216 completed double-blind treatment (**Table 1**)

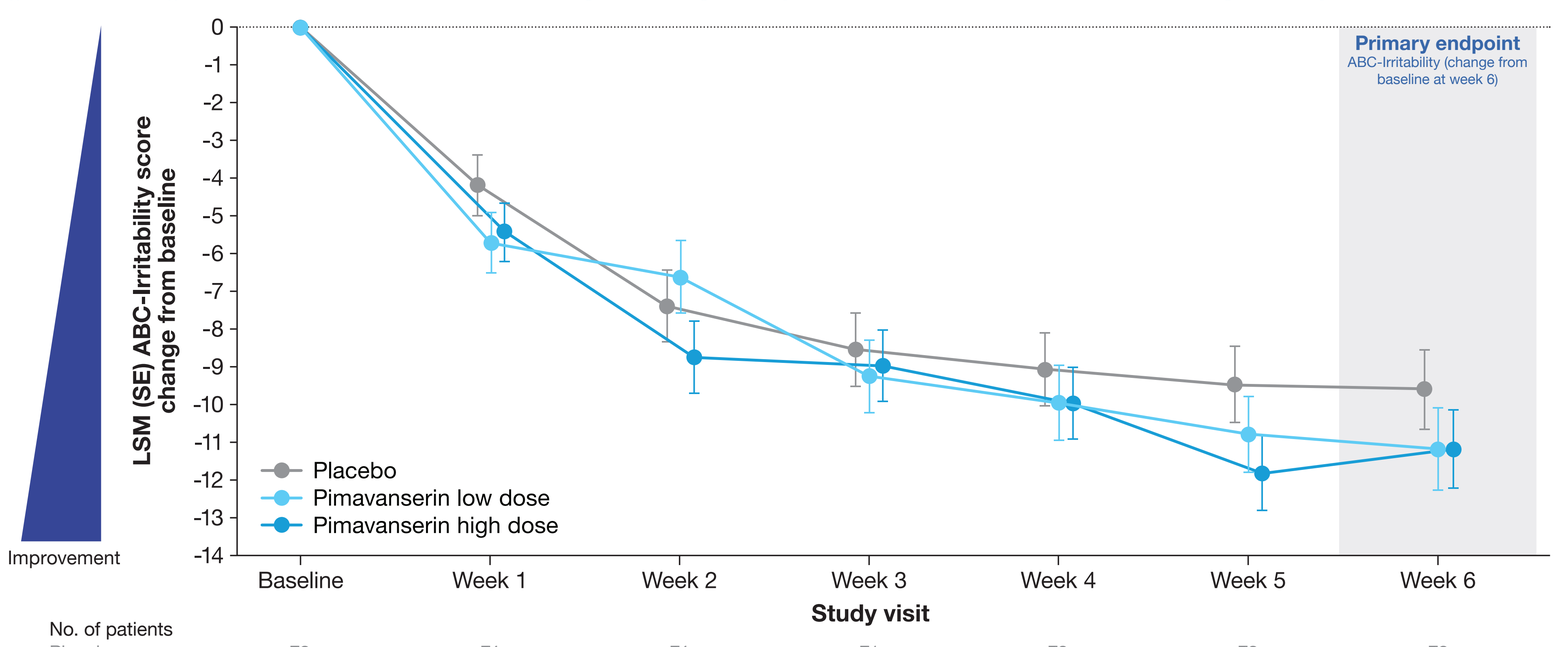
Table 1. Baseline Demographics and Characteristics (Full Analysis Set)

	Placebo (n=78)	Pimavanserin low dose (n=76)	Pimavanserin high dose (n=78)	Total (N=232)
Demographic parameters				
Age at randomisation, mean (SE), y	9.8 (0.33)	9.7 (0.41)	9.9 (0.35)	9.8 (0.21)
Sex, n (%), male	57 (73.1)	57 (75.0)	66 (84.6)	180 (77.6)
Race, n (%)				
American Indian or Alaska Native	1 (1.3)	1 (1.3)	- -	2 (0.9)
Asian	1 (1.3)	4 (5.3)	5 (6.4)	10 (4.3)
Black or African American	8 (10.3)	12 (15.8)	10 (12.8)	30 (12.9)
Native Hawaiian or Other Pacific Islander	1 (1.3)	- -	- -	1 (0.4)
White	61 (78.2)	55 (72.4)	57 (73.1)	173 (74.6)
Other	6 (7.7)	4 (5.3)	6 (7.7)	16 (6.9)
Ethnicity, n (%)				
Hispanic or Latino	10 (12.8)	12 (15.8)	11 (14.1)	33 (14.2)
Disease parameters				
ABC-Irritability, mean (SD)	29.1 (6.16)	29.1 (5.41)	30.3 (6.09)	29.5 (5.90)
CGI-S of Irritability score, mean (SD)	5.1 (0.73)	5.1 (0.64)	5.1 (0.69)	5.1 (0.68)

ABC, Aberrant Behaviour Checklist; CGI-S, Clinical Global Impression of Severity scale.

- Observed reductions in mean ABC-Irritability subscale scores were similar across treatment groups at week 6 (**Table 2**) and at each visit (**Figure 2**)
  - No significant treatment effect compared with placebo was observed for the primary endpoint at week 6, and the hierarchical efficacy analysis concluded at this point

Figure 2. Change From Baseline in ABC-Irritability Score by Visit (Observed Cases; MMRM[a]; Full Analysis Set)



No. of patients							
Placebo	78	74	74	71	70	73	72
Pimavanserin low dose	76	70	70	71	66	68	64
Pimavanserin high dose	78	76	72	71	71	75	74

ABC, Aberrant Behaviour Checklist; LSM, least squares mean; MMRM, mixed-effects model for repeated measures.
[a]LSM from MMRM with fixed effects of treatment group, age group, region, visit, treatment-by-visit interaction, and baseline ABC-Irritability score as a covariate.

Table 2. Primary Endpoint: Change From Baseline to Week 6 in ABC-Irritability Score (Observed Cases; MMRM; Full Analysis Set)

Parameter	Placebo (n=78)	Pimavanserin low dose (n=76)	Pimavanserin high dose (n=78)
n	72	64	74
MMRM LSM (SE)[a]	–9.6 (1.06)	–11.2 (1.09)	–11.2 (1.05)
95% CI	(–11.7, –7.5)	(–13.3, –9.0)	(–13.3, –9.1)
Difference in MMRM LSM (SE)[b]	--	–1.6 (1.52)	–1.6 (1.49)
95% CI of difference	--	(–4.6, 1.4)	(–4.5, 1.3)
MMRM *P* value[c]	--	0.2986	0.2859
Effect size (Cohen's *d*)	--	0.17	0.17

ABC, Aberrant Behaviour Checklist; LSM, least square mean; MMRM, mixed effects model for repeated measures.
[a]LSM from MMRM with fixed effects of treatment group, age group, region, visit, treatment-by-visit interaction, and baseline ABC-Irritability score as a covariate.
[b]Difference between LSM changes for pimavanserin high dose or pimavanserin low dose and placebo at the specified visit from MMRM analysis.
[c]Two-sided *P* value.

- Similar trends were observed for all secondary endpoints (**Table 3**)

Table 3. Secondary Endpoints: Change From Baseline to Week 6 (Observed Cases; MMRM; Full Analysis Set)

Endpoint, MMRM LSM (SE)[a]	Placebo (n=78)	Pimavanserin low dose (n=76)	Pimavanserin high dose (n=78)
CGI-S of Irritability	–1.1 (0.13)	–1.4 (0.14)	–1.2 (0.13)
Difference vs placebo		–0.3 (0.19); *P*=0.1088	–0.1 (0.19); *P*=0.4434
CGI-I of Irritability	3.1 (0.12)	2.8 (0.13)	2.9 (0.12)
Difference vs placebo		–0.3 (0.18); *P*=0.0988	–0.2 (0.17); *P*=0.1637
ABC-Lethargy	–6.7 (0.81)	–7.2 (0.83)	–6.0 (0.80)
Difference vs placebo		–0.5 (1.16); *P*=0.6821	0.6 (1.14); *P*=0.5765
ABC-Stereotypic behaviour	–3.1 (0.46)	–4.0 (0.47)	–3.4 (0.45)
Difference vs placebo		–0.9 (0.66); *P*=0.1705	–0.3 (0.64); *P*=0.6084
ABC-Hyperactivity	–8.4 (1.10)	–10.3 (1.13)	–8.7 (1.09)
Difference vs placebo		–1.9 (1.57); *P*=0.2179	–0.4 (1.55); *P*=0.8154
ABC-Inappropriate speech	–1.7 (0.31)	–2.0 (0.32)	–1.1 (0.31)
Difference vs placebo		–0.3 (0.45); *P*=0.5122	0.6 (0.44); *P*=0.1930
RBS-R score	–15.4 (1.75)	–11.8 (1.83)	–12.3 (1.73)
Difference vs placebo		3.7 (2.53); *P*=0.1462	3.2 (2.46); *P*=0.1969
VABS score	2.9 (1.42)	4.2 (1.48)	4.7 (1.39)
Difference vs placebo		1.3 (2.05); *P*=0.5301	1.8 (1.99); *P*=0.3554
CGSQ score	–1.47 (0.24)	–2.00 (0.25)	–1.25 (0.23)
Difference vs placebo		–0.53 (0.34); *P*=0.1250	0.22 (0.33); *P*=0.5019

ABC, Aberrant Behaviour Checklist; CGI-I, clinical global impression of improvement; CGI-S, clinical global impression of severity scale; CGSQ, caregiver strain questionnaire; LSM, least-square mean; MMRM, mixed-effects model for repeated measures; RBS-R, repetitive behaviour scale-revised; VABS, Vineland adaptive behaviour scale.
[a]Change from baseline at week 6. Difference vs placebo indicates difference in MMRM LSM between pimavanserin group and placebo values. Fixed effects for treatment group, age group, region, visit, and treatment-by-visit interaction.

- TEAEs were similar across groups (**Table 4**)
  - No serious TEAEs or deaths occurred in either pimavanserin group

Table 4. Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

Participants, n (%)	Placebo (n=78)	Pimavanserin low dose (n=77)	Pimavanserin high dose (n=81)
Any TEAE	39 (50.0)	36 (46.8)	43 (53.1)
Any serious TEAE	1 (1.3)	--	--
Any related TEAE	10 (12.8)	9 (11.7)	14 (17.3)
Any related serious TEAE	1 (1.3)	--	--
Any TEAE leading to discontinuation of study drug or study termination	2 (2.6)	1 (1.3)	1 (1.2)
Any TEAE resulting in death	--	--	--
Most common TEAEs (≥5% in any treatment group)			
Nausea	1 (1.3)	4 (5.2)	1 (1.2)
Upper respiratory tract infection	4 (5.1)	7 (9.1)	5 (6.2)
Decreased appetite	--	4 (5.2)	2 (2.5)
Headache	4 (5.1)	5 (6.5)	5 (6.2)
Somnolence	4 (5.1)	2 (2.6)	4 (4.9)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Pimavanserin did not demonstrate statistically significant improvement versus placebo in primary or secondary efficacy endpoints for irritability in children or adolescents with ASD
- Pimavanserin was well tolerated in this population with no occurrences of serious TEAEs or deaths

Acknowledgment and Funding

Medical writing support was provided by Hala Addassi, PhD, from Citrus Health Group, Inc. (Chicago, Illinois), and was funded by Acadia Pharmaceuticals, Inc. (San Diego, California).

Author Disclosures

DBK, **RKH**, **MD**, **IL**, **RN**, **SS**, and **PZ** are employees of Acadia Pharmaceuticals Inc., and may own stock. **EM** is a site principal investigator for this Acadia clinical trial and does not own stock. **AS** has received honoraria from Acadia, SyneuRx International, Lundbeck, Emalex, Shire, Servier, and Bioproject. **SO** is a contingent worker on assignment for Acadia and does not own stock. **CA** has been a consultant to or has received honoraria or grants from Abbot, Acadia, Ambrosetti, Angelini, Biogen, BMS, Boehringer, Carnot, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Rovi, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda, and Teva.

References

1. Chua SY, et al. *Front Psychiatry*. 2023;14:1244164.
2. Blankenship K, et al. *Ped Health*. 2010;4(4):375-381.
3. Jiang CC, et al. *Signal Transduct Target Ther*. 2022;7(1):229.
4. McPheeters ML, et al. *Pediatrics*. 2011;127(5):e1312-1321.
5. Acadia Pharmaceuticals Inc. NUPLAZID® (pimavanserin) Prescribing Information. 2025. https://www.nuplazid.com/pdf/nuplazid-prescribing-information.pdf

Poster presented at the European College of Neuropsychopharmacology (ECNP) Annual Meeting 2025; 11-14 October 2025; Amsterdam, The Netherlands

ACADIA®