NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA efficacy supplements
Application Number(s)	207318/S-016 and 210793/S-014
Priority or Standard	Priority
Submit Date(s)	October 28, 2025
Received Date(s)	October 28, 2025
PDUFA Goal Date	April 28, 2026
Division/Office	Division of Psychiatry / Office of Neuroscience
Review Completion Date	April 27, 2026
Established/Proper Name	Pimavanserin
(Proposed) Trade Name	Nuplazid
Pharmacologic Class	Atypical antipsychotic
Code name	N/A
Applicant	Acadia Pharmaceuticals, Inc.
Dosage form	Oral capsules (34 mg) and tablets (10 mg)
Applicant proposed Dosing Regimen	34 mg once daily; 10 mg once daily when administered with strong CYP3A4 inhibitors
Applicant Proposed Indication(s)/Population(s)	No change to indication: Treatment of hallucinations and delusions associated with Parkinson's disease psychosis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	719717006 |Psychosis co-occurrent and due to Parkinson's disease (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	No change
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	No change
Recommended Dosing Regimen	No change

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jasmeet Kalsi
Nonclinical Reviewer	Darren Fegely
Nonclinical Team Leader	Amy Avila
Office of Clinical Pharmacology Reviewer(s)	Praveen Balimane / Jie Liu
Office of Clinical Pharmacology Team Leader(s)	Venkateswaran ChithambaramPillai / Atul Bhattaram
Clinical Reviewer	Paul Bossie
Clinical Team Leader	Martine Solages
Statistical Reviewer	Michelle Marcovitz
Statistical Team Leader	Peiling Yang
Cross-Disciplinary Team Leader	Martine Solages
Division Director (signatory authority)	Tiffany R. Farchione

Additional Reviewers of Application

OPDP	Rachael Oyewole / Taylor Burnett Mmagu
Other	DPMH: Charlotte Jones / Shetarra Walker

OPDP=Office of Prescription Drug Promotion
DPMH=Division of Pediatrics and Maternal Health

Glossary

ABC-I	Aberrant Behavior Checklist-Irritability
AE	adverse event
ASD	autism spectrum disorder
BMI	body mass index
CFB	change from baseline
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
ECG	electrocardiogram
E-R	exposure-response
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
ICE	intercurrent event
IND	Investigational New Drug
LAR	legally acceptable representative
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
NDA	new drug application
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	potentially clinically important
PDP	Parkinson's disease psychosis
PI	prescribing information
PK	pharmacokinetics
POC	proof of concept
PPSR	Proposed Pediatric Study Request
PRO	patient reported outcome
RBS-R	Repetitive Behavior Scale-Revised
SAE	serious adverse event
SAP	statistical analysis plan
SGA	second generation antipsychotic
SI/B	suicidal ideation and behavior
SMQ	standardized MedDRA query
USPI	United States Prescribing Information
VABS	Vineland Adaptive Behavior Scales
WR	Written Request

1 Executive Summary

1.1. Product Introduction

Nuplazid (pimavanserin), an atypical antipsychotic, was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis on April 29, 2016 (NDA 207318), with a recommended dosage of 34 mg (as two 17-mg oral tablets) once daily. The 34-mg oral capsule (for once daily use) was approved on June 28, 2018 (NDA 210793), with an NDA 207318 supplement for a 10-mg oral tablet for once daily coadministration with strong CYP3A4 inhibitors (the 17-mg tablet has subsequently been discontinued). The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unclear. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and to a lesser extent at serotonin 5-HT2C receptors.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for pimavanserin in the treatment of irritability associated with autism spectrum disorders. These supplemental NDAs are intended to support an update to labeling Section 8.4 with clinical data (i.e., not to support a new indication) from a phase 2, proof-of-concept study to investigate the efficacy and safety of pimavanserin in pediatric patients ages 5 to 17 years with irritability associated with autism spectrum disorder (Study ACP-103-069) and its open-label safety extension (Study ACP-103-070). These studies were submitted in response to a Pediatric Written Request.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Autism spectrum disorder (ASD) is a neurodevelopmental disorder whose symptoms, including associated irritability, can profoundly impair functioning and cause substantial individual and family burden. Additional effective treatments are needed, including with improved safety profiles; however, the negative results of Study ACP-103-069 (Study 69), a phase 2, proof-of-concept, dose-finding, safety and efficacy study of pimavanserin in 237 pediatric subjects ages 5 to 17 years with irritability associated with ASD, do not support a new indication for use. Because these studies were conducted in response to a Pediatric Written Request, relevant pediatric safety and efficacy information (including from the open-label extension Study ACP-103-070 (Study 70)) will be included in labeling Section 8.4.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ASD is a neurodevelopmental disorder characterized by impairments in social communication and interaction, and by restricted, repetitive patterns of behavior, interests, or activities. • Many secondary neurobehavioral features are commonly associated with ASD, such as irritability or disruptive/challenging behaviors, self-injury, hyper- or hyporeactivity to sensory stimuli, intellectual or language impairment, executive dysfunction, and motor deficits. • ASD symptoms can profoundly impair functioning and cause substantial individual and family burden. • Symptoms, which can vary widely, are present from early childhood, often recognized in children as young as 2 years of age.	• ASD is a neurodevelopmental disorder with symptoms present in early childhood. • ASD is heterogenous in presentation and outcome. Secondary behavioral features such as irritability can cause significant impairment.
Current Treatment Options	• In terms of pharmacological therapy, there are currently no medications approved for the treatment of the core features of ASD. • Two second-generation antipsychotics are indicated for the treatment of irritability associated with autistic disorder in pediatric patients, aripiprazole and risperidone.	• Risperidone and aripiprazole improve irritability associated with ASD. • Second-generation antipsychotics carry various risks. • More treatment options are needed for the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Important risks of second-generation antipsychotics can include: ○ An increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis ○ Extrapyramidal symptoms (e.g., dystonia, parkinsonism, akathisia) ○ Tardive dyskinesia ○ Weight gain and metabolic effects (e.g., hyperglycemia, diabetes mellitus, dyslipidemia) ○ QT interval prolongation ○ Orthostatic hypotension, syncope, and falls ○ Neuroleptic malignant syndrome ○ Leukopenia, neutropenia, and agranulocytosis ○ Hyperprolactinemia ○ Dysphagia ○ Seizures ○ Potential for cognitive and motor impairment ○ Body temperature dysregulation ○ Drug reaction with eosinophilia and systemic symptoms ○ Pathological gambling and other compulsive behaviors	treatment of irritability associated with ASD in the pediatric population ages 5 to 17 years.
Benefit	• To meet the terms of a Pediatric Written Request, the Applicant submitted the results of Study ACP-103-069 (Study 69), a phase 2, proof-of-concept, dose-finding, safety and efficacy study of pimavanserin in 237 pediatric subjects ages 5 to 17 years with irritability associated with ASD. • The statistical reviewer confirmed that for the primary endpoint of change from baseline to Week 6 in the Aberrant Behavior Checklist-Irritability subscale score, high dose pimavanserin did not separate from placebo, after which formal testing stopped; in descriptive	• Study 69 appears to be an adequate and well-controlled trial that does not provide substantial evidence of effectiveness of pimavanserin for the treatment of irritability associated with ASD in pediatric patients 5 to 17 years of age. • The Applicant is not seeking a new indication. Labeling Section 8.4 will be updated with pediatric safety information.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	results, the low dose also did not separate from placebo. • Similarly, in descriptive results on the key secondary efficacy endpoint of change from baseline to Week 6 for the Clinical Global Impression-Severity-Irritability score, neither dose separated from placebo.	
Risk and Risk Management	• The safety data supporting this application are based primarily on Study 69 for randomized, double-blind, placebo-controlled comparison. Open-label extension Study 70 adds long-term safety information. • In Study 69, 158 subjects were exposed to pimavanserin, and 209 were exposed in Study 70. • There were no deaths in either study, no other serious adverse events in Study 69, and few in Study 70. Overall, there were low frequencies of discontinuations for adverse events (AEs) in the studies. • In Study 69, the most common treatment-emergent AEs (i.e., reported in ≥5% of subjects at a rate greater than placebo for pimavanserin overall) included upper respiratory tract infection (8% pimavanserin versus 5% placebo) and headache (6% versus 5%). In Study 70, the most common AEs (i.e., reported in ≥5% of subjects) included upper respiratory tract infection (10%), vomiting (7.2%), headache (6.7%), nasopharyngitis (6.2%), and pyrexia (5.3%). See Table 11 for AEs reported in ≥3% of subjects. • Other safety findings (e.g., clinical laboratory assessments, vital signs, electrocardiograms, assessments of extrapyramidal symptoms and suicidal ideation and behavior) did not suggest a new or worsened safety signal in the study populations.	• The Applicant submitted sufficient information to adequately assess safety in the pediatric irritability associated with ASD clinical trials population. • As expected given the notable differences in populations (e.g., related to age, treatment indication, comorbidities, concomitant medications) between the approved indication of adults with Parkinson's disease psychosis and the pediatric population with irritability associated with ASD in the clinical trials, the reported AEs also included some differences. • Otherwise, no new or worsened safety signal was apparent from the data. • Section 8.4 will report the most common adverse events in Study 69 and 70.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Sections 1 and 8
		□	Patient reported outcome (PRO)	
		X	Observer reported outcome (ObsRO)	Sections 1 and 8
		X	Clinician reported outcome (ClinRO)	Sections 1 and 8
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and interaction, and by restricted, repetitive patterns of behavior, interests, or activities. Many secondary neurobehavioral features are commonly associated with ASD, such as irritability or disruptive/challenging behaviors, self-injury, hyper- or hyporeactivity to sensory stimuli, intellectual or language impairment, executive dysfunction, and motor deficits. ASD symptoms can profoundly impair functioning and cause substantial individual and family burden. The U.S. Centers for Disease Control and Prevention estimates that about 1 in 31 children aged 8 years in the United States has been identified with ASD.[1] ASD is over three times more common in males than females. Symptoms are present from early childhood, often recognized in children as young as 2 years of age. Individuals with ASD vary substantially in terms of symptom presentation and outcome, requiring different levels of support. Diagnosis is made clinically, based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria (Table 1).

Table 1. Autism Spectrum Disorder Diagnostic Criteria

A.	Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive): 1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions. 2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication. 3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
B.	Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive): 1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

[1] CDC, 2025, Data and Statistics on Autism Spectrum Disorder, accessed March 30, 2026, https://www.cdc.gov/autism/data-research/index.html

	2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day). 3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest). 4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
C.	Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life).
D.	Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E.	These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Source: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision[2]

2.2. Analysis of Current Treatment Options

There are currently no medications approved for the treatment of the core features of ASD. Two second-generation antipsychotics (SGAs) are indicated for the treatment of irritability associated with autistic disorder: aripiprazole (Abilify, NDA 021436-s027, in patients 6 to 17 years of age) and risperidone (Risperdal, NDA 020272-s036, in patients 5 to 17 years of age). Subjects in the clinical studies supporting these approvals met criteria for ASD and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Important risks of SGAs can include:

- An increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Extrapyramidal symptoms (EPS; e.g., dystonia, parkinsonism, akathisia)
- Tardive dyskinesia
- Weight gain and metabolic effects (e.g., hyperglycemia, diabetes mellitus, dyslipidemia)

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed., Text Revision. Washington, DC: American Psychiatric Publishing, 2022. doi: 10.1176/appi.books.978089042578

- QT interval prolongation
- Orthostatic hypotension, syncope, and falls
- Neuroleptic malignant syndrome
- Leukopenia, neutropenia, and agranulocytosis
- Hyperprolactinemia
- Dysphagia
- Seizures
- Potential for cognitive and motor impairment
- Body temperature dysregulation
- Drug reaction with eosinophilia and systemic symptoms
- Pathological gambling and other compulsive behaviors (in aripiprazole USPI)

Although there are two medications approved for use for irritability associated with ASD, individual patient response cannot be predicted. For an individual patient, trials of different products may be required before an effective and tolerable treatment can be identified. Thus, having additional pharmacological treatment options (and with potential fewer risks) would be valuable.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nuplazid (pimavanserin) was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) on April 29, 2016 (NDA 207318), with a recommended dosage of 34 mg (as two 17-mg tablets) once daily. The 34-mg capsule was approved on June 28, 2018 (NDA 210793).

3.2. Summary of Presubmission/Submission Regulatory Activity

- On August 20, 2018, the Applicant submitted a proposed pediatric study request (PPSR) including studies to investigate the treatment of pediatric patients aged 5 to 17 with irritability associated with ASD (along with studies in schizophrenia and bipolar I disorder).

- On December 13, 2018, the Agency issued a pediatric Written Request (WR). Relevant studies for this sNDA included a multiple-dose pharmacokinetic (PK), safety, and tolerability study in pediatric patients 5 to 12 years of age, two efficacy and safety studies for the treatment of irritability associated with ASD in pediatric patients ages 5 to 17 years, and a long-term safety study in pediatric patients with schizophrenia, bipolar I disorder, or ASD.

- On June 7, 2019, the Applicant submitted a WR response with a proposal to amend the WR (b) (4)

(b) (4)

- On October 3, 2019, the Agency issued an Inadequate Proposal to Amend the WR letter, noting that (b) (4) The Agency noted that the exact mechanism by which medications approved to treat irritability in autism exert their effects is unknown and that pimavanserin's effects on the serotonergic system could theoretically impact symptoms such as irritability in autism.

- In August 3, 2020, Type C guidance Written Responses, the Agency provided feedback on the Applicant's proposed amendment to the WR following completion of the repeat-dose toxicity study in the juvenile rat and a pediatric PK study in pediatric patients ages 13 to <18 years with schizophrenia, bipolar disorder, ASD, (b) (4) (b) (4) (Study ACP-103-050, conducted under (b) (4)). The Agency (b) (4) stated that the PK study, safety and efficacy, and long-term studies should be open to 5-year-old patients.

- In an August 20, 2020, follow-up teleconference, the Agency advised the Applicant that they could amend the WR with a gated approach, including a proof-of-concept (POC) ASD study to inform dosing and PK assessments, obviating the need for a separate PK study, and potentially providing pediatric data for labeling even if negative.

- In preliminary comments for a March 24, 2021, Type C guidance meeting to align with the Agency on the POC design and proposed WR amendments, the Agency agreed that the study design, objectives, endpoints, and selected doses appeared acceptable, but would be a matter of review. The Agency stated that the language regarding two adequate and well-controlled studies should be retained in the WR until the results of the POC study are available. The Applicant subsequently cancelled the meeting.

- Following the Applicant's May 4, 2021, request for changes to the WR, the Agency issued Written Request Amendment 1 on September 1, 2021, which:

    - Removed studies in schizophrenia and bipolar I disorder based on failed adult programs in schizophrenia and major depressive disorder.

    - Revised studies in ASD to allow a gated approach with an exploratory POC, dose-ranging study of the efficacy, safety, and PK of pimavanserin in pediatric patients aged 5 to 17 with irritability associated with ASD (Study 1; Study ACP-103-069 (Study 69)). If the results of Study 1 suggested benefit in the treatment of irritability associated with ASD, then two adequate and well-controlled pediatric safety and efficacy studies and a

pediatric long-term safety study (Study ACP-103-070 (Study 70)) in pediatric patients with ASD aged 5 to 17 years would be required.

- On November 9, 2021, under IND (b) (4), the Agency issued a Study May Proceed letter for Study 69 including non-hold biometrics comments on the IND-opening protocol (submitted on September 28, 2021), including regarding the estimand strategies to handle intercurrent events and provision of Case Report Form details, a detailed statistical analysis plan (SAP), and recommending a tipping point analysis. Previous non-hold clinical comments were conveyed to the Applicant during draft protocol review and review of the WR amendment.

- On February 2, 2022, the Agency provided non-hold clinical and biometrics comments regarding an amendment to Study 69 (submitted December 20, 2021), recommending consideration of further randomization stratification by country or region (if feasible) and development of age-specific blood pressure exclusion criteria, and requesting SAP details. The clinical reviewer had found the Applicant's amendment revisions in response to prior comments otherwise acceptable.

- On February 16, 2022, the Agency provided non-hold clinical comments regarding the protocol for Study 70 (submitted on December 21, 2021), reminding the Applicant of the WR required monitoring of relevant adverse events (AEs) and providing recommendations regarding electrocardiogram (ECG) timing and long-term safety data collection.

- On April 6, 2022, the Applicant submitted responses and amendments to the Agency's February 2022 comments on protocols 60 and 70. The Applicant incorporated recommendations and the clinical and biometrics reviewers had no comments for the Applicant.

- On July 14, 2023, the Agency provided clinical and clinical pharmacology comments regarding protocol 69 Amendment 4 (submitted December 23, 2022) and protocol 70. The Agency recommended continuing to exclude use of modafinil and armodafinil given CYP3A4 interactions; adding cardiac safety monitoring during the open-label period given potential pharmacodynamic interactions with stimulants; and considering stratification by use of stimulants as unequal distribution could impact efficacy results.

- On October 11, 2024, the Agency provided biometrics comments regarding the protocol 69 SAP (including regarding the tipping point analysis, estimand, and SAS code), following no comments on a prior protocol amendment (submitted December 23, 2022).

- On December 31, 2024, the Agency denied the Applicant's December 20, 2024, Type D meeting request to discuss amending the WR based on the reportedly negative results of Study 69. The Agency stated that the proposed changes and reasons should be submitted as a WR amendment.

- Following the Applicant's January 14, 2025, request for changes to the WR, the Agency issued Written Request Amendment 2 on May 13, 2025, which removed the two adequate and well-controlled pediatric safety and efficacy studies because the results of the POC study (Study 1; Study 69) were negative. A pediatric long-term safety study (Study 2; Study 70) was still required as the study had been conducted and may yield safety information.

- On March 10, 2026, following Pediatric Exclusivity Board review of the Applicant's submission to meet the terms of the WR, the Agency granted Pediatric Exclusivity for studies conducted on pimavanserin.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were conducted for this efficacy supplement.

4.2. Product Quality

No new product quality data were submitted.

4.3. Clinical Microbiology

No clinical microbiology data were included in this efficacy supplement.

4.4. Devices and Companion Diagnostic Issues

This application does not include data related to any devices or companion diagnostics.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted two sNDAs, 207318/S-016 and 210793/S-014, to update the Pediatric Use section of the Prescribing Information with details from nonclinical and clinical studies conducted to satisfy a pediatric written request, to study the effectiveness of pimavanserin for the treatment of irritability associated with ASD in pediatric patients 5 through 17 years of age.

To support the safety of pimavanserin for treatment of pediatric patients, the Applicant conducted one nonclinical study: A 13-week toxicity study in the juvenile rats with final study reports (study no. 1574-007) submitted to the NDAs on June 5, 2020. Data from this juvenile animal toxicity study, together with nonclinical data used to support approval of pimavanserin in adult patients, were considered adequate to support administration of pimavanserin in pediatric patients 5 through 17 years of age. For a detailed review of the study conducted in juvenile rats see the nonclinical review by Dr. Amy Avila signed into DARRTS on July 23, 2020 (NDAs 207318 and 210793). Refer to the nonclinical review by Dr. Avila under NDA 207318 for a detailed review of nonclinical studies conducted to support the original approval of pimavanserin in adult patients. The following is a summary of the clinically relevant findings from nonclinical pimavanserin studies, including the study conducted in juvenile rats.

Although the exact mechanism of action of pimavanserin in psychiatric disorders is not fully understood it is thought to be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

Adult toxicology studies were conducted in three species (mice, rats, and monkeys) up to 3-months, 6-months, and 12-months in duration, respectively following oral administration. A juvenile toxicology study was conducted in rats following oral administration for up to 13 weeks. In the 13-week toxicity study in juvenile rats, male and female rats were administered pimavanserin by oral gavage at doses of 15, 30, and 45 mg/kg/day from postnatal day (PND) 21 to PND 111. A subset of animals were maintained for a 4-week recovery period and breeding. In addition to the standard toxicity endpoints, the following endpoints were also evaluated: functional observational battery (FOB) evaluations, motor activity, auditory startle habituation, learning and memory assessment (Morris water maze), and bone growth from the main study and recovery groups, and sexual maturation, reproductive parameters (mating, fertility, and fecundity), sperm analysis, and uterine examinations from the recovery and breeding groups. Five animals, across all dose groups and in both sexes, were found dead or euthanized moribund during the course of the study; however, a definitive cause of death was not determined for most animals, and it is unclear if the finding was drug-related. A decrease in mean body weight and body weight gain, up to 14% compared to controls, was observed in males and females at all dose levels, but not in a dose-related manner. The effect

on body weight was partially reversible and only correlated with an effect on food consumption for males indicating body weight effects were unlikely to be due solely to reduced food intake.

Target organs of toxicity identified in both adult and juvenile animals include the central nervous system (CNS), lungs, and heart. Effects characteristic of CNS depression (CNS-related clinical signs, decreased motor activity, and effects on various functional observation battery assessments) consistent with the known pharmacology of pimavanserin were observed in both adult and juvenile rats. In the heart, administration of pimavanserin was associated with cardiomyopathy (myofiber degeneration) observed during microscopic evaluation in both adult and juvenile rats.

Pimavanserin is characterized as a cationic amphiphilic drug (CAD), which are drugs known to cause phospholipidosis (PLD)—the excessive accumulation of phospholipids in cells in animals and humans. In the adult toxicology studies, pimavanserin caused dose- and duration-dependent widespread, multi-organ, systemic PLD in mice, rats, and monkeys after both sub-chronic and chronic administration, occurring as early as 2-weeks of daily dosing in rats. Although microscopic findings consistent with PLD (foamy macrophages and/or cytoplasmic vacuolation) were observed in over 30 tissues/organs in rats; the lungs and kidneys were the most severely affected tissues. Similar findings of widespread PLD were not observed following 13 weeks of dosing in juvenile rats; however, the findings in the lungs (alveolar macrophage aggregation) of juvenile male and female rats and spleen (vacuolated macrophages) of juvenile female rats may be evidence of PLD. These findings had no impact on viability in adult or juvenile animals; however, it was accompanied by inflammation in the lungs of adult rats. Signs of chronic inflammation were not observed in the lungs of juvenile rats.

In general, the findings in the adult and juvenile rat toxicology studies were similar and juvenile rats do not appear to be significantly more sensitive to pimavanserin-related toxicity. However, there are several endpoints that are not measured, or cannot be measured, in general toxicity studies with adult animals, which were evaluated in the 13-week juvenile rat study. In juvenile rats, administration of pimavanserin was associated with a delay in the onset of sexual maturation for males and a small decrease in bone lengths for males and females, which correlated with a decrease in body weight. Administration of pimavanserin to juvenile rats through sexual maturity was not associated with persistent effects on fertility or reproductive capacity when assessed following dose-cessation; however, the number of implantation sites and viable embryos were decreased and there was an increase in post-implantation loss observed in pregnant dams on gestation day 13.

Conclusion
Based on the reproductive effects observed in females at all dose levels in the 13-week juvenile rat toxicology study, a NOAEL was not identified for female reproductive effects.

Based on the increased incidence of cardiomyopathy at 45 mg/kg/day, the NOAEL for general toxicity following oral administration of pimavanserin to juvenile rats for 13-weeks is 30 mg/kg/day.

Following oral administration or pimavanserin to juvenile rats for 13-weeks, the toxicities observed were generally in-line with those observed in adult animals. The clinically relevant findings from the 13-week juvenile rat study will be included in the Prescribing Information under section 8.4.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted final clinical study reports for two pediatric studies (ACP-103-069 and ACP-103-070) evaluating pimavanserin for irritability associated with autism spectrum disorder (ASD) in subjects aged 5 to 17 years, along with population pharmacokinetic (popPK) and exposure-response (E-R) analyses.

Study 069 was a 6-week, randomized, double-blind, placebo-controlled study (N=237) that did not demonstrate efficacy for the primary endpoint (change in ABC-Irritability score).

Study 070 was a 52-week open-label extension safety study (N=209) with 123 subjects exposed for ≥6 months, meeting the WR requirement of at least 100 subjects exposed for ≥6 months. The Applicant conducted popPK modeling using pooled data from 21 studies (10,855 concentrations from 1,538 subjects), including 150 pediatric subjects with ASD, to justify dose selection and characterize pimavanserin PK in the pediatric population as required by the WR. Sparse PK samples were collected from Study 069 at baseline, Week 1, Week 3, and Week 6 to characterize the plasma concentration-time profiles of pimavanserin and its major active metabolite (AC-279). The popPK analysis estimated all required PK parameters including area under the plasma concentration-time curve (AUC), half-life, peak plasma concentration (Cmax), time to reach Cmax (Tmax), apparent oral clearance, and apparent volume of distribution at steady state. The Applicant reported that target exposures (equivalent to the effective adult dose of 34 mg) were achieved in adolescents (13 to 17 years) receiving 34 mg and in children (5 to 12 years) receiving 20 mg for Cmax,ss. E-R analyses were conducted to characterize the PK/pharmacodynamic (PD) relationship as required. The Applicant reported no clear E-R relationship between pimavanserin exposure and efficacy or safety endpoints, except for QTcF, consistent with prior findings in adults with schizophrenia from Study ACP-103-038..

The Applicant has fulfilled the PK and PD requirements of the Written Request. From a clinical pharmacology perspective, this submission supports pediatric exclusivity determination.

Additionally, no new clinical pharmacology studies were submitted with this supplemental NDA application. The clinical pharmacology studies were extensively reviewed when the original NDA 207318 was submitted to support the approval of pimavanserin (17 mg tablet) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Refer to the Clinical Pharmacology and Biopharmaceutics review for NDA 207318 (17 mg tablet) archived on February 8, 2016, and the multidisciplinary review for supplemental NDA 207318 (S-003 for 10 mg tablet) and NDA 210793 (34 mg capsule) archived on June 28, 2018, for additional information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant has submitted data from the POC safety and efficacy Study 69 and its long-term open-label extension (OLE), Study 70. Also relevant to this population is Study ACP-103-050 (Study 50), a previously submitted completed, phase 1, pediatric PK study in subjects ages 13 to <18 years with mixed diagnoses. See Table 2 for an overview of the studies.

Table 2. Listing of Clinical Trials Relevant to Supplemental NDAs 207318-016 and 210793-014

Trial no.	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
ACP-103-069	05523895	Multicenter, randomized, double-blind, placebo-controlled, dose-finding study to evaluate safety, efficacy, and PK	Pimavanserin high dose (34 mg for 13 to 17 years, 20 mg for 5 to 12 years); or pimavanserin low dose (20 mg for 13 to 17 years, 10 mg for 5 to 12 years); or placebo, once daily, orally	Primary: CFB at Week 6 in caregiver-rated ABC-I subscale score Key Secondary: CFB at Week 6 in CGI-S-irritability score Other Secondary: Including CFB at Week 6 in: other caregiver-rated ABC-I subscale scores (stereotypic behavior, lethargy, hyperactivity, inappropriate speech); CGI-I-irritability score; RBS-R scores; VABS-Socialization subscale score	6 weeks with 30-day safety follow-up for premature withdrawal or not enrolling in rollover Study ACP-103-070	237 (78 in placebo and low dose, 81 in high dose)	Pediatric subjects ages 5 to 17 with ASD and irritability	47 sites in eight countries (17 USA and 30 rest of world (Australia, France, Hungary, Italy, Poland, Serbia, Spain)
		Studies to Support Safety						
ACP-103-070	05555615	Multicenter, open-label extension study	Pimavanserin high dose (34 mg for 13 to 17 years, 20 mg for 5 to 12 years); or pimavanserin low dose (20 mg for 13 to 17 years, 10 mg for 5 to 12 years), adjusted at investigator discretion, once daily, orally	Primary: Treatment-emergent adverse events; analyses of vital signs, weight and BMI, 12-lead ECGs, physical examination results, clinical laboratory tests and hormonal assessments, C-SSRS, ESRS-A Secondary: Proportion of subjects with ≥25% reduction from antecedent study Baseline in ABC-I subscale score AND CGI-I-irritability score of 1 or 2 compared to antecedent study Baseline at Week 52	52 weeks with 30-day safety follow-up	209	Subjects who had completed Study ACP-103-069 and had shown no significant worsening of symptoms on the CGI-I-irritability	46 sites in eight countries (see above)

		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
ACP-103-050	None	Multicenter, phase 1, open-label, multiple ascending dose study to assess PK, safety, and tolerability	Pimavanserin 10, 20, or 34 mg once daily orally	Primary: PK and safety endpoints	20 days with Day 28 and Day 50 safety follow-ups	34	Pediatric subjects ages 13 to <18 years with one of several psychiatric diagnoses, including ASD	Seven sites in three countries (USA, Bulgaria, Russia)

Source: Clinical reviewer-created from clinical study reports
Abbreviations: ABC-I, Aberrant Behavior Checklist-Irritability; ASD, autism spectrum disorder; BMI, body mass index; CFB, change from baseline; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ESRS-A, Extrapyramidal Symptom Rating Scale-Abbreviated; NCT, National Clinical Trial; no, number; PK, pharmacokinetics; RBS-R, Repetitive Behavior Scale-Revised; VABS, Vineland Adaptive Behavior Scales

7.2. Review Strategy

The efficacy review focused on the single randomized, double-blind, placebo-controlled Study 69. Agency statistician Michelle Marcovitz, PhD, reviewed the Applicant's statistical analysis. The safety review focuses on data from Study 69 and its OLE Study 70, supplemented by data from the phase 1 PK Study 50.

8 Statistical and Clinical Evaluation of Efficacy Trial and Review of Safety

8.1. Study ACP-103-069

8.1.1. Trial Design

Study Design

Study 69 was a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel group study of the safety and efficacy of pimavanserin (high dose and low dose) compared to placebo in the treatment of pediatric subjects aged 5 to 17 years (inclusive) with ASD with irritability. The study was conducted at 47 sites in eight countries, including 17 sites in the United States.

The study consisted of a 4-week screening period, a 6-week treatment period, and a 30-day safety follow-up period for subjects who discontinued prematurely or did not enroll in the 52-week, OLE Study 70. The study planned to enroll 456 subjects to randomize 228 (76 subjects per treatment arm) on Day 1 (Visit 2) in a 1:1:1 ratio to pimavanserin low dose, pimavanserin high dose, or placebo, stratified by age group (5 through 12 years old versus 13 through 17 years old) and region (United States versus rest of the world). The total sample size was planned to target a minimum of 35% of subjects in the younger age group. Of note, during the review of protocol amendment 1 (dated September 23, 2021), FDA sent a comment to the Applicant citing that "the proportion of younger age group is relatively small. Should this study be used to support an efficacy indication, be mindful of the sample size needed for each age group to fulfill [pediatric] WR."

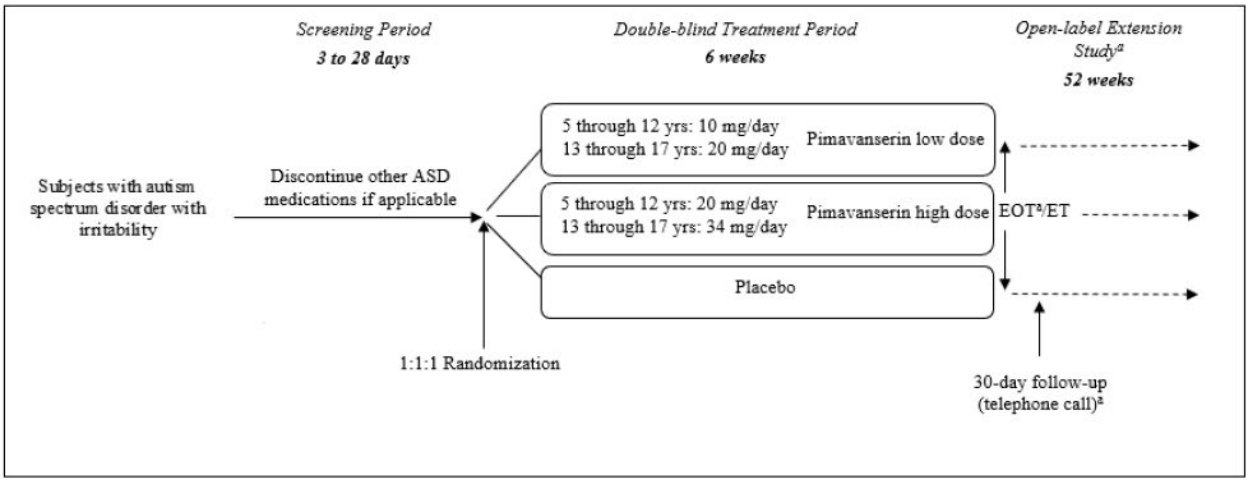
Subjects randomized to pimavanserin aged 5 through 12 received pimavanserin 10 mg/day (low dose group) or 20 mg/day (high dose group). Subjects randomized to pimavanserin aged 13 through 17 received pimavanserin 20 mg/day (low dose group) or 34 mg/day (high dose group). Per the Applicant, dose selection of the pimavanserin high dose was based on achieving the same systemic exposure (Cmax and AUC) in adults with pimavanserin 34 mg once daily that "consistently demonstrated efficacy and safety" in the adult population in several psychiatric conditions. According to the Applicant, in population PK modeling Study ACP-103-MS-010, stochastic simulations using actual (from Study 50) and virtual adolescent (13 through 17 years) and adult (18 through 49 years) populations (from 13 phase 1, 2b and 3 studies) were undertaken to help guide pimavanserin dose selection in pediatric subjects within the age range of 5 through 17 years that were likely to achieve the target exposure. Per the Applicant:

> However, steady state Cmax, following 34 mg dosing, was progressively higher with decreasing age, as well as with decreasing body weight. A 20 mg dose produced Cmax exposures in children 5 through 9 years of age that were comparable to the 34 mg dose in the adolescents and adults. Because body weight-adjusted PK for children 12 years

and younger is usually different from adolescents and adults for similar doses, a conservative approach was adopted, and the older children (10 through 12 years) were grouped with the younger children (5 through 9 years) to receive the lower doses.

See Figure 1 for the Applicant's study schema.

Figure 1. Study ACP-103-069 Schema



Source: Study ACP-103-069 clinical study report
Abbreviations: ASD, autism spectrum disorder; EOT, end of treatment; ET, early termination; yrs, years
[a] Subjects who completed the 6-week Treatment Period may have been eligible to enroll in a 52-week, open label extension study (Study ACP-103-070). Subjects entering ACP-103-070 did not complete a follow-up telephone call as they were immediately enrolled in ACP-103-070.

The study included male and female subjects, aged 5 to 17 years of age, with a DSM-5 primary diagnosis of ASD, confirmed by the Autism Diagnostic Interview-Revised and with irritability symptoms defined as: Aberrant Behavior Checklist-Irritability (ABC-I) subscale score ≥18 at screening and baseline (with <20% decrease in ABC-I subscale score between screening and baseline) and Clinical Global Impression-Severity (CGI-S)-Irritability score ≥4 at screening and baseline. Subjects were eligible for the study based on a number of other psychiatric, treatment-related, and other medical criteria (e.g., related to seizures, blood pressure, QT and other ECG findings, clinical laboratory results) Some notable eligibility criteria were:

- No current comorbid psychiatric disorder (other than attention-deficit hyperactivity disorder (ADHD) or anxiety disorder, as long as ADHD or anxiety were not primary, and were stable and adequately treated).

- Must be drug-naïve to antipsychotic treatment (or <2 weeks of antipsychotic treatment for any reason) or prior lack of tolerability to adequate dose of any duration of antipsychotic.

- Not at significant risk of suicide (based on all sources of information including Columbia-Suicide Severity Rating Scale (C-SSRS), violent behavior, or danger to self or others.

- No confirmed genetic disorder associated with ASD and no cognitive and/or behavioral disturbance or profound intellectual disability (intelligence quotient ≤50).

- Able to discontinue all prohibited concomitant medications, such as those targeting irritability (including off-label use of clonidine, guanfacine, propranolol, lithium, valproate; however, see Protocol Amendment #4 regarding a change for stimulant and non-stimulant (e.g., atomoxetine) medications), medications that prolong the QT interval, and strong CYP3A4 inhibitors and inducers. Antidepressants, anticonvulsants, and mood stabilizers were prohibited. Anticholinergics were prohibited other than benztropine for movement disorders and oral diphenhydramine for acute EPS. Benzodiazepines were permitted exceptionally for electrocardiograms (ECGs), blood draws, and acute anxiety (not within 12 hours prior to assessments). Lorazepam (or other specified available) as-needed was allowed for a maximum of 7 consecutive days. Certain hypnotics and sleep aids were permitted (e.g., melatonin, ramelteon, zaleplon; but not within 12 hours prior to assessments) and others were prohibited (e.g., eszopiclone, zolpidem, zopiclone). Stimulants, wake-promoting agents, and non-stimulant ADHD medications were permitted if stable for 12 weeks prior to screening and expected to remain stable (see Protocol Amendment #4 below regarding a change).

Study Endpoints

The primary efficacy endpoint was the change from baseline (CFB) to Week 6 in the ABC-I subscale score. The key secondary endpoint was CFB to Week 6 in the CGI-S-Irritability. The Agency considers the primary endpoint acceptable; it was previously accepted by the Agency for this condition.

Other secondary endpoints included CFB at Week 6 in other caregiver-rated ABC-I subscale scores (stereotypic behavior, lethargy, hyperactivity, inappropriate speech); CGI-I-irritability score; Repetitive Behavior Scale-Revised (RBS-R) scores; Vineland Adaptive Behavior Scales (VABS)-Socialization subscale score.

Statistical Analysis Plan

<u>Analysis Populations</u>

- Randomized Analysis Set: included all unique subjects who were randomized. Subjects were analyzed based on their randomized treatment.

- Safety Analysis Set: included all randomized subjects who received at least one dose of study drug (pimavanserin or placebo).

- Full Analysis Set: included all randomized subjects who received at least one dose of study drug and who had both a baseline value and at least one postbaseline value for the ABC-I subscale score.

The primary endpoint was analyzed based on the full analysis set.

Intercurrent Events

The primary clinical question of interest for the primary objective was considered to be: what is the difference in mean changes from Baseline at Week 6 in the ABC-I subscale score comparing pimavanserin high dose versus placebo and pimavanserin low dose versus placebo, in subjects with ASD with irritability, agitation, or self-injurious behaviors, assuming all subjects complete 6 weeks of treatment without extended use of rescue medication or use of prohibited medications? The estimand is the pharmacological effect seen had no study treatment discontinuation occurred. For subjects who discontinued prematurely, the last collected efficacy assessment was done at the early termination visit. Missing data due to premature treatment discontinuation was considered missing at random (MAR). The primary reason for the ICE of treatment discontinuation was further used to classify ICEs: Subjects who discontinue treatment prematurely due to COVID-19 or for other reasons were addressed by the hypothetical strategy, assuming that subjects with these ICEs evolve in the same way after ICE occurrence as the subjects in the treatment group who complete the treatment. Subjects whose use of rescue medications beyond the maximum allowed period or whose use of prohibited medications led to treatment discontinuation were handled in analyses according to the strategy for treatment discontinuation. The intercurrent event of “remote assessments” was handled by treatment policy (i.e., utilizing measurements of the primary efficacy endpoint regardless of the occurrence of this ICE).

Primary Efficacy Analysis

The primary efficacy outcomes were evaluated using a Mixed-Effect Model for Repeated Measures (MMRM) approach. The dependent variable was the change from baseline in the ABC-I subscale score. The independent variables in the model included the following: age group (5 through 12 years old, or 13 through 17 years old), region (United States or rest of the world), treatment group (pimavanserin high dose, pimavanserin low dose, or placebo), visit (Week 1, Week 2, Week 3, Week 4, Week 5, or Week 6), treatment-by-visit interaction, and the baseline ABC-I score. The parameter calculations assumed that missing data occurred at random (MAR).

To account for correlations between repeated measurements within individual subjects, an unstructured variance-covariance matrix was implemented. The Kenward-Roger method was applied to calculate the appropriate denominator degrees of freedom. If the model failed to converge when using the unstructured covariance matrix structure, the following alterative covariance structures were modeled in the order of heterogenous Toeplitz, heterogeneous compound symmetry, heterogenous autogressive (1), Toeplitz, compound symmetry, autoregressive (1), variance components. The first alternative covariance structure that allowed for convergence would be selected as the final model, and the sandwich estimator (Diggle et al. 1994) was used to estate the standard errors of the fixed effect parameters.

Multiplicity

To account for the multiplicity introduced by two treatment comparisons (pimavanserin high dose versus placebo and pimavanserin low dose versus placebo) for the primary endpoint and key secondary endpoint of CGI-S-Irritability, the study used a hierarchical testing procedure within which hypotheses were to be tested in the following sequential order:

1. Pimavanserin high dose versus placebo for CFB to Week 6 ABC-I subscale score
2. Pimavanserin low dose versus placebo for CFB to Week 6 ABC-I subscale score
3. Pimavanserin high dose versus placebo for CFB to Week 6 CGI-S-Irritability score
4. Pimavanserin low dose versus placebo for CFB to Week 6 CGI-S-Irritability score

Only if success was demonstrated for the primary endpoint of change from baseline to Week 6 for the ABC-I subscale score for pimavanserin high dose versus placebo, would testing proceed through the sequence. This procedure controls the studywise error rate at 2-sided alpha of 0.05.

Protocol Amendments

The original protocol was dated April 30, 2021. It was subsequently amended four times (three prior to enrollment):

- Amendment 1 was dated 23 September 2021. The significant protocol changes were as follows:
    - Increased the sample size from approximately (b) (4) subjects screened to randomize (b) (4) in each treatment arm) to approximately 380 subjects screened to randomize 228 (76 in each treatment arm) such that overall Type 1 error could be controlled at the one-sided 2.5% level. The number of sites was increased to 60 to accommodate the increased sample size.
    - Defined caregivers allowed to provide input for caregiver-facing scales, and indicated that caregivers were trained in accurate symptom reporting for the ABC, RBS-R.
- Amendment 2, dated December 3, 2021, added language to indicate that every attempt will be made to recruit equal numbers of subjects from both age groups.
- Amendment 3 was dated 25 March 2022. The amendment:
    - Added proactive assessment of adverse events (AEs) of syncope and somnolence at each visit
    - Added stratification by geographic region (United States versus rest of world)
    - Indicated that all known potential class side effects of antipsychotics would be

actively monitored.

- Amendment 4 was dated 21 December 2022 (after first subject enrollment on 16 May 2022). The primary rationale for the amendment was based on the data gathered in the preceding 6 months showing that a substantial number of prescreened subjects were not converted into screened subjects due to comorbid ADHD and treatment with stimulants/non-stimulants. To address this, the protocol was amended to improve the generalizability of study findings and to facilitate recruitment by allowing subjects who were on stable doses of stimulants and non-stimulants targeting irritability into the study.

  Clinical Reviewer's Comment: This permitted medication change appears acceptable for generalizability purposes. The Agency provided feedback as described in Section 3.2; the Applicant did not modify further based on Agency feedback. Study completion occurred on 27 September 2024, so Amendment 4 was implemented approximately 1/5 of the way into study conduction. Review can examine use and distribution of stimulants and related medications for potential impact on results.

8.1.2. Trial Results

Analysis results of Study 69 are presented in this section.

Compliance with Good Clinical Practices

The Applicant states that this study was performed in compliance with International Council for Harmonization guideline for Good Clinical Practice, including the archiving of essential documents.

Financial Disclosure

See Appendix 15.2.

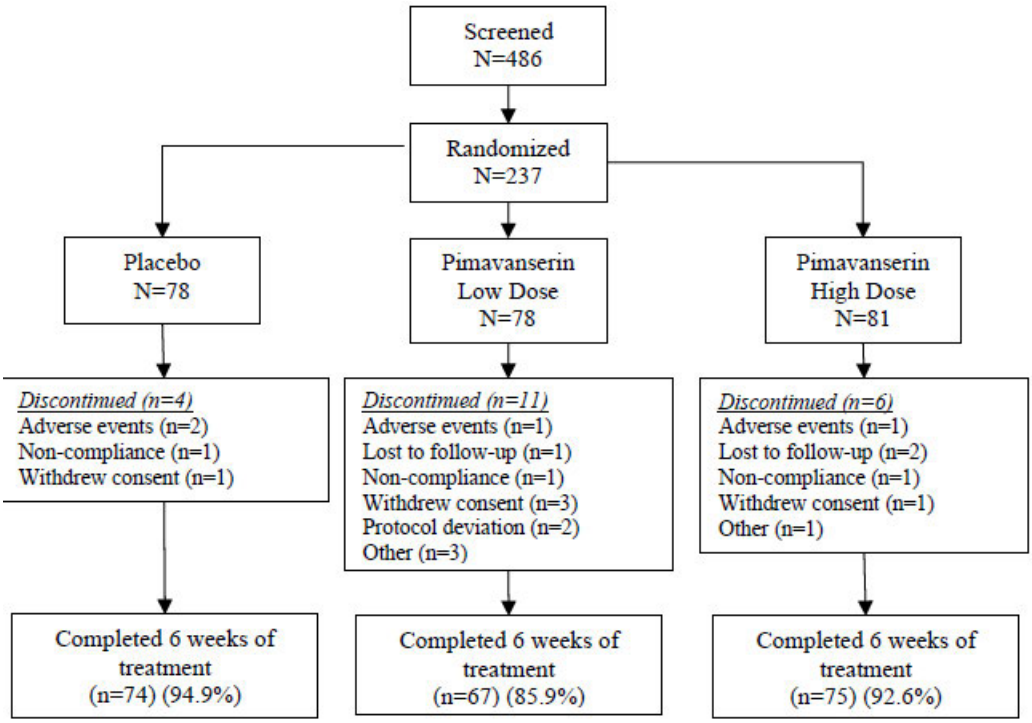
Subject Disposition

Per the Applicant, a total of 237 subjects were randomized (78 subjects in the placebo group, 78 subjects in the pimavanserin low dose group, and 81 subjects in the pimavanserin high dose group) across 47 study sites; 236 of the randomized subjects received at least one dose of study drug and were included in the Safety Analysis Set, and 232 of the randomized subjects who received at least one dose of study drug and had both a Baseline and at least one post-Baseline ABC-I subscale score were included in the Full Analysis Set. See Figure 2 for the Applicant's subject disposition figure and Table 3 for the Applicant's analysis sets.

Of the 237 enrolled subjects in the Randomized Analysis Set, 216 (91.1%) subjects completed the study (94.9% of subjects in the placebo group, 85.9% subjects in the pimavanserin low dose group, and 92.6% subjects in the pimavanserin high dose group), and 21 (8.9%) subjects

terminated the study early (5.1% subjects in the placebo group, 14.1% subjects in the pimavanserin low dose group, and 7.4% subjects in the pimavanserin high dose group) (Table 4). The most frequently reported reasons for early termination were withdrawal by subject or legally acceptable representative (LAR) (five (2.1%) subjects), AE (four (1.7%) subjects), other not related to COVID-19 (four (1.7%) subjects), lost to follow-up (three (1.3%) subjects), and non-compliance with study drug (three (1.3%) subjects).

Figure 2. Study ACP-103-069 Subject Disposition for All Randomized Subjects



Source: Study ACP-103-069 clinical study report

Table 3. Study ACP-103-069 Analysis Sets

Analysis Set	Placebo n (%)	Pimavanserin Low Dose n (%)	Pimavanserin High Dose n (%)	Total n (%)
Randomized Analysis Set[a]	78	78	81	237
Safety Analysis Set[b]	78 (100.0)	77 (98.7)	81 (100.0)	236 (99.6)
Full Analysis Set[c]	78 (100.0)	76 (97.4)	78 (96.3)	232 (97.9)
Pharmacokinetics Analysis Set[d]	- -	73 (93.6)	77 (95.1)	150 (63.3)

Source: Study ACP-103-069 clinical study report
Abbreviations: ABC-I, Aberrant Behavior Checklist-Irritability
[a] Randomized subjects used as the denominator for calculating percentages within each treatment group.
[b] Randomized and treated with at least one dose of study drug.
[c] Randomized and treated with at least one dose of study drug, and have both a Baseline and at least one postbaseline ABC-I subscale score.
[d] Safety Analysis Set subjects with at least one measurable pimavanserin plasma concentration.

Table 4. Study ACP-103-069 Summary of Subject Disposition (Randomized Analysis Set)

Subject Disposition	Placebo (N=78) n (%)	Pimavanserin Low Dose (N=78) n (%)	Pimavanserin High Dose (N=81) n (%)	Total (N=237) n (%)
Completed study	74 (94.9)	67 (85.9)	75 (92.6)	216 (91.1)
Early termination	4 (5.1)	11 (14.1)	6 (7.4)	21 (8.9)
Primary reason for early termination				
Adverse event	2 (2.6)	1 (1.3)	1 (1.2)	4 (1.7)
Death	--	--	--	--
Lack of efficacy	--	--	--	--
Lost to follow-up	--	1 (1.3)	2 (2.5)	3 (1.3)
Non-compliance with study drug	1 (1.3)	1 (1.3)	1 (1.2)	3 (1.3)
Physician's decision	--	--	--	--
Pregnancy	--	--	--	--
Protocol deviation	--	2 (2.6)	--	2 (0.8)
Study terminated by Sponsor	--	--	--	--
Use of prohibited medication	--	--	--	--
Withdrawal by subject or LAR	1 (1.3)	3 (3.8)	1 (1.2)	5 (2.1)
Other	--	3 (3.8)	1 (1.2)	4 (1.7)
Other: Related to COVID-19	--	--	--	--
Other: Not Related to COVID-19	--	3 (3.8)	1 (1.2)	4 (1.7)
Secondary reason for early termination [a]				
Adverse event	--	--	--	--
Death	--	--	--	--
Lack of efficacy	--	1 (1.3)	--	1 (0.4)
Lost to follow-up	1 (1.3)	--	--	1 (0.4)
Non-compliance with study drug	--	--	--	--
Physician's decision	--	--	--	--
Pregnancy	--	--	--	--
Protocol deviation	--	--	--	--
Study terminated by Sponsor	--	--	--	--
Use of prohibited medication	--	--	--	--
Withdrawal by subject or LAR	--	--	--	--
Other	--	1 (1.3)	--	1 (0.4)
Did subject enroll in ACP-103-070 study?				
Yes	73 (93.6)	63 (80.8)	73 (90.1)	209 (88.2)
No	1 (1.3)	4 (5.1)	2 (2.5)	7 (3.0)

Source: Study ACP-103-069 clinical study report
Abbreviations: LAR, legally acceptable representative

Protocol Violations/Deviations

According to the Applicant, overall, 16 (6.8%) subjects had a major protocol deviation. The most common categories of major protocol deviations were eligibility and entry criteria (eight (3.4%) subjects), investigational product (three (1.3%) subjects), and informed consent and study procedures criteria (two (0.8%]) subjects each) Table 5.

Table 5. Study ACP-103-069 Major Protocol Deviations

	Placebo (N=78) n (%)	Pimavanserin Low Dose (N=78) n (%)	Pimavanserin High Dose (N=81) n (%)	Total (N=237) n (%)
Number of subjects with major protocol deviations	3 (3.8)	8 (10.3)	5 (6.2)	16 (6.8)
Deviation category:				
Eligibility and entry	- -	7 (9.0)	1 (1.2)	8 (3.4)
Investigational product	2 (2.6)	- -	1 (1.2)	3 (1.3)
ICF	- -	1 (1.3)	1 (1.2)	2 (0.8)
Study procedures	1 (1.3)	- -	1 (1.2)	2 (0.8)
Source documentation	- -	- -	1 (1.2)	1 (0.4)

Source: Study ACP-103-069 clinical study report
Abbreviations: ICF, informed consent form

Demographic Characteristics

See (Table 6) for baseline demographics. Per the Applicant, there were more male subjects (overall 77.6%) than female (overall 22.4%), with a somewhat larger difference in the pimavanserin high dose group (84.0% versus 16.0%). The overall mean (SE) age was 9.8 (0.21) years, consistent across treatment groups, with overall 79.3% of subjects in the range 5 through 12 years and 20.7% in the range 13 through 17 years, consistent across treatment groups. Overall, subjects were predominantly White (73.8%) followed by Black or African American (13.1%), Asian (5.1%), American Indian or Alaska Native (0.8%), Native Hawaiian or Other Pacific Islander (0.4%), and Others (6.8%), generally consistent across treatment groups. Subjects were predominantly not Hispanic or Latino (84.8%) followed by Hispanic or Latino (13.9%), and the majority of subjects were male (77.6%), generally consistent across treatment groups. Approximately 50% of subjects were enrolled in the United States. These demographic characteristics appear consistent with the ASD population (i.e., sex distribution) and generally with the U.S. population (i.e., racial and ethnic demographics). The distribution by age groups appears acceptable.

Table 6. Study ACP-103-069 Baseline Demographic Characteristics, Randomized Analysis Set

Demographic Parameter Statistic	Placebo (N=78) n (%)	Pimavanserin Low Dose (N=78) n (%)	Pimavanserin High Dose (N=81) n (%)	Total (N=237) n (%)
Sex, n (%)[a]				
Female	21 (26.9)	19 (24.4)	13 (16.0)	53 (22.4)
Male	57 (73.1)	59 (75.6)	68 (84.0)	184 (77.6)
Age, years				
n	78	78	81	237
Mean (SE)	9.8 (0.33)	9.8 (0.40)	9.8 (0.35)	9.8 (0.21)
SD	2.88	3.54	3.11	3.18
Median	10.0	9.0	10.0	9.0
Min, max	5, 16	5, 17	5, 17	5, 17
Age at randomization categories, n (%)[a]				
5 to 12 years	63 (80.8)	61 (78.2)	64 (79.0)	188 (79.3)
13 to 17 years	15 (19.2)	17 (21.8)	17 (21.0)	49 (20.7)
Primary race, n (%)[a]				
White	61 (78.2)	56 (71.8)	58 (71.6)	175 (73.8)
Black or African American	8 (10.3)	12 (15.4)	11 (13.6)	31 (13.1)
Asian	1 (1.3)	5 (6.4)	6 (7.4)	12 (5.1)
American Indian or Alaska Native	1 (1.3)	1 (1.3)	- -	2 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.3)	- -	- -	1 (0.4)
Other	6 (7.7)	4 (5.1)	6 (7.4)	16 (6.8)
Not reported	- -	- -	- -	- -
Ethnicity, n (%)[a]				
Hispanic or Latino	10 (12.8)	12 (15.4)	11 (13.6)	33 (13.9)
Not Hispanic or Latino	67 (85.9)	65 (83.3)	69 (85.2)	201 (84.8)
Not Reported	1 (1.3)	1 (1.3)	- -	2 (0.8)
Unknown	- -	- -	1 (1.2)	1 (0.4)
Region, n (%)[a]				
United States	39 (50.0)	38 (48.7)	40 (49.4)	117 (49.4)
Rest of world	39 (50.0)	40 (51.3)	41 (50.6)	120 (50.6)

Source: Study ACP-103-069 clinical study report
Abbreviations: max, maximum; min, minimum; SD, standard deviation; SE, standard error
[a] Number of subjects with non-missing values in the given treatment group is used as the denominator for calculating percentages.

Baseline Disease Characteristics and Prior Medications

See Table 7 for a summary of baseline disease characteristics including ABC-I subscale score and CGI-S-irritability score. Baseline scores were relatively consistent across treatment groups, with the majority of subjects with baseline ABC-I subscale scores ≥25 and CGI-S-Irritability scores of 5 or 6 (markedly ill and severely ill, respectively).

Table 7. Study ACP-103-069 Other Baseline Disease Characteristics

Baseline Disease Parameter	Placebo (N=78)	Pimavanserin Low Dose (N=78)	Pimavanserin High Dose (N=81)	Total (N=237)
ABC-Irritability Subscale Score				
n	78	77	81	236
Mean (SE)	29.1 (0.70)	29.0 (0.62)	30.5 (0.69)	29.6 (0.39)
SD	6.16	5.46	6.18	5.96
Median	30.0	29.0	31.0	30.0
Min, max	18, 41	20, 43	18, 43	18, 43
ABC-Irritability Subscale Categories, n (%)[a]	78	77	81	236
<25	19 (24.4)	19 (24.7)	15 (18.5)	53 (22.5)
≥25	59 (75.6)	58 (75.3)	66 (81.5)	183 (77.5)
CGI-S of Irritability Score				
n	78	77	81	236
Mean (SE)	5.1 (0.08)	5.1 (0.07)	5.1 (0.08)	5.1 (0.04)
SD	0.73	0.65	0.69	0.69
Median	5.0	5.0	5.0	5.0
Min, max	4, 7	4, 6	4, 6	4, 7
CGI-S of Irritability Categories, n (%)[a]	78	77	81	236
4 Moderately Ill	17 (21.8)	13 (16.9)	16 (19.8)	46 (19.5)
5 Markedly Ill	40 (51.3)	44 (57.1)	43 (53.1)	127 (53.8)
6 Severely Ill	20 (25.6)	20 (26.0)	22 (27.2)	62 (26.3)
7 Among the Most Extremely Ill	1 (1.3)	- -	- -	1 (0.4)

Source: Study ACP-103-069 clinical study report
Abbreviations: ABC, Aberrant Behavior Checklist; CGI-S, Clinical Global Impression-Severity, max, maximum; min, minimum; SD, standard deviation; SE, standard error
[a] Number of subjects with non-missing values in the given treatment group is used as the denominator for calculating percentages.

According to the Applicant, 60 (25.4%) subjects overall used any prior medications. The most common prior medication were alprazolam (six (2.5%) subjects), melatonin and paracetamol (five (2.1%) subjects each). Psychostimulants, agents used for ADHD, and nootropics were reported overall for six (2.5%) subjects overall.

Concomitant Medications, Rescue Medication Use, and Treatment Compliance

Per the Applicant, 144 (61.0%) subjects used any concomitant medications.

- By class, hypnotics and sedatives were among the most common overall (43 (18.2%) subjects), which included the most common concomitant medication melatonin (40 (16.9%) subjects), generally similar across treatment groups. Besides melatonin, other hypnotics and sedatives (e.g., diphenhydramine) were infrequently used.

- Psychostimulants, agents used for ADHD, and nootropics were among the most commonly used concomitant medications as a class. The Applicant included both stimulant (i.e., methylphenidate and amphetamine-related products) and nonstimulant (e.g., clonidine, guanfacine, atomoxetine) ADHD medications in this grouping. These medications were used overall by 40 (16.9%) subjects, with greater use in the pimavanserin high dose arm (19 (23.5%) subjects) compared to low dose (11 (14.3%) subjects) or placebo (10 (12.8%) subjects). Use was distributed across multiple products. No modafinil or armodafinil use was reported.

- Anxiolytic use (i.e., alprazolam, lorazepam, hydroxyzine) was low (overall 15 (6.4%) subjects) and generally similar across treatment arms.

- No benztropine use was reported.

  <u>Clinical Reviewer's Comment:</u> Psychostimulant use was somewhat higher in the pimavanserin high dose group. The net effect of stimulants on irritability is unclear, as it can occur as an adverse reaction per labeling (or similar terms, such as agitation); however, as described previously regarding Amendment 4, the Applicant allowed use "targeting irritability," suggesting off-label use for a beneficial effect. Therefore, it is difficult to know how use may interact with pimavanserin and potential treatment effect.

According to the Applicant, overall treatment compliance to study drug (assessed by capsule count and based on the Safety Analysis Set) was similar for all treatment groups. Overall, 225 (95.3%) subjects in the Safety Analysis Set were ≥80% and ≤120% compliant with study drug.

Efficacy Results – Primary Endpoint

The statistical reviewer confirmed that study ACP-103-069 did not meet its primary objective. Statistical testing of the primary endpoint of change from baseline in ABC-I subscale score was performed, such that high dose pimavanserin versus placebo was tested first. This test did not reach statistical significance at the two-sided 0.05 level. The LS mean difference (SE) for high dose pimavanserin versus placebo was -1.6 (1.49) (95% CI: -4.5, 1.3; p = 0.2859). The test of low dose pimavanserin versus placebo can be reported descriptively—the LS mean difference (SE) was -1.6 (1.52) (95% CI: -4.6, 1.4; p = 0.2986). See Table 8.

Table 8. Study ACP-103-069 Results of Primary Efficacy Endpoint, Change from Baseline to Week 6 in ABC-I Subscale Score, Full Analysis Set

Statistics	Pimavanserin High Dose (N = 78)	Pimavanserin Low Dose (N = 76)	Placebo (N = 78)
Baseline, mean (SD)	30.3 (0.69)	29.1 (0.62)	29.1 (0.70)
Change from Baseline to Week 6	-11.1 (1.05)	-11.6 (1.20)	-9.6 (1.09)
n	74	64	72
LS mean (SE)	-11.2 (1.05)	-11.2 (1.05)	-9.6 (1.06)
LS mean difference (SE)	-1.6 (1.49)	-1.6(1.52)	
95% CI	(-4.5, 1.3)	(-4.6, 1.4)	
p-value	0.2859	0.2986	

Source: Study ACP-103-069 clinical study report, page 127, Table 14.2.1.1, verified by FDA statistical reviewer
Abbreviations: ABC-I, Aberrant Behavior Checklist–Irritability subscale; SD, standard deviation; N, number of subjects in the full analysis set population; n, number of subjects in the specific visit with non-missing observation; LS, Least Squares; SE, standard error of the least squares mean; LSMD, least squares mean difference; CI, confidence interval

Data Quality and Integrity

The reviewers found the data of sufficient quality and integrity for review.

Efficacy Results – Secondary and other relevant endpoints

The key secondary efficacy endpoint of CFB to Week 6 for the CGI-S-Irritability score endpoint could not be formally tested for either high dose pimavanserin versus placebo or low dose pimavanserin versus placebo because the test of the primary endpoint did not reach statistical significance for the high dose pimavanserin versus placebo comparison. The LS mean difference (SE) for high dose pimavanserin versus placebo was 0.1 (0.19)) (95% CI: -0.5, 0.2; p = 0.4434). The test of low dose pimavanserin versus placebo was verified by the statistical reviewer and can be reported descriptively, the LS mean difference (SE) was -0.3 (0.19)) (95% CI: -0.7, 0.1; p = 0.1088). See Table 9.

Table 9. Study ACP-103-069 Results of Key Secondary Efficacy Endpoint, Change from Baseline to Week 6 for the CGI-S, Full Analysis Set

Statistics	Pimavanserin high dose (N = 78)	Pimavanserin low dose (N = 76)	Placebo (N = 78)
Baseline, mean (SD)	5.1 (0.08)	5.1 (0.07)	5.1 (0.08)
Change from Baseline to Week 6	-1.2(0.13)	-1.5(0.16)	-1.1(0.13)
n	74	64	72
LS mean (SE)	-1.2 (0.13)	-1.4 (0.14)	-1.1 (0.13)
LS mean difference (SE)	-0.1 (0.19)	-0.3 (0.19)	
95% CI	(-0.5, 0.2)	(-0.7, 0.1)	
p-value	0.4434	0.1088	

Source: Study ACP-103-069 clinical study report, page 127, Table 14.2.2.2.1, verified by FDA statistical reviewer
Abbreviations: CGI-S, Clinical Global Impression-Severity-Irritability; N, number of subjects in the full analysis set population; SD, standard deviation; n, number of subjects in the specific visit with non-missing observation; LS, Least Squares; SE, standard error of the least squares mean; CI, confidence interval

Dose/Dose Response, Durability of Response, and Persistence of Effect

As above, neither pimavanserin dose separated from placebo on the primary endpoint (formally tested for high dose, descriptive for low dose) or key secondary endpoints (descriptive for both doses). The Applicant conducted additional popPK modeling adding sparse PK data from Study 69 (Study ACP-103-MS-023) and completed a modeling characterization of PK exposure-response analyses (Study ACP-103-MS-024). According to the Applicant, exposure-response analyses for efficacy confirmed the clinical results, showing no clear relationship between caregiver ABC-I scores and pimavanserin exposure measures. Furthermore, E-R modeling indicated no statistically significant effect of pimavanserin exposure on the caregiver ABC irritability scores (ACP-103-MS-024).

Efficacy Results – Secondary or exploratory endpoints

The Applicant stated that the results of their other secondary endpoint analyses are consistent with the primary analysis.

Additional Analyses Conducted on the Individual Trial

The Applicant stated that the results of their sensitivity analyses are consistent with the primary analysis.

Subpopulations

The Applicant stated that their subgroup analyses by age, sex, race, intelligence quotient, region, severity, and ABC-I subscale score and CFB by visit with stimulant use during the

treatment period were consistent with the primary analysis.

8.1.3. Integrated Assessment of Effectiveness

Study 69 was a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel group study of the safety and efficacy of pimavanserin (high dose and low dose) compared to placebo in the treatment of pediatric subjects aged 5 to 17 years (inclusive) with ASD with irritability. The statistical reviewer confirmed that for the primary endpoint of CFB to Week 6 in ABC-I subscale score, high dose pimavanserin did not separate from placebo, after which formal testing stopped; in descriptive results, the low dose also did not separate from placebo. Similarly, in descriptive results on the key secondary efficacy endpoint of CFB to Week 6 for the CGI-S-Irritability score, neither dose separated from placebo. Per the Applicant, results were consistent across their sensitivity and subgroup analyses. Therefore, the results do not support the use of pimavanserin for the treatment of irritability associated with ASD in pediatric patients ages 5 to 17 years.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety data supporting this application are based primarily on Study 69 for randomized, double-blind, placebo-controlled comparison. Study 70 adds long-term OLE safety information. The Applicant did not include an Integrated Summary of Safety given the differences in Study 69 and Study 70 designs. (Study 50, the multiple ascending dose pediatric PK study submitted previously, serves as a supplementary source of open-label safety data.) The results of the studies appear sufficiently generalizable for the purpose of the safety assessment in the ASD population.

8.2.2. Review of the Safety Database

Overall Exposure

According to the Applicant, overall, the mean duration of exposure to pimavanserin was 42 days in Study 69 (similar across treatment groups) and 236 days in OLE Study 70. The majority of subjects in Study 50 completed the 20-day treatment exposure. The demographic characteristics of Study 69 were previously discussed (Table 6), which were generally similar for the OLE Study 70. Comparatively, Study 50 included a smaller difference between sexes (58.8% male and 41.2% female),

Adequacy of the safety database:

The safety population included all subjects who received at least one dose of study medication.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data were of sufficient integrity and quality for review. OSI inspections were waived given the nature of the submission as a negative trial without obvious issues upon filing review.

Categorization of Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 for Studies 69 and 70, and version 21.0 for Study 50. The Applicant's serious AE (SAE) and AE definitions, monitoring, and severity determinations appear appropriate. The Applicant's verbatim-to-PT mapping appeared generally reasonable upon examination and did not require any recoding. Grouping for abdominal discomfort and abdominal pain upper into abdominal pain; initial, middle, and terminal insomnia into insomnia; rash macular into rash; sinus tachycardia into tachycardia; and tension headache into headache did not produce notable changes to the Applicant's results.

Routine Clinical Tests

Safety outcomes in all clinical protocols included routine safety assessments collected at baseline and appropriate follow-up times. The Applicant provided appropriate thresholds for potentially clinically important (PCI) clinical laboratory results and vital signs. The Applicant monitored for suicidal ideation and behavior (SI/B) with the C-SSRS and assessed related AEs with a standardized MedDRA query (SMQ) for depression and suicide-self-injury. The Applicant monitored for EPS with the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A) and assessed related AEs with an SMQ for EPS.

8.2.4. Safety Results

Deaths

No deaths occurred in any of the studies.

Serious Adverse Events

In Study 69, one subject on placebo reported an SAE of hypersensitivity. No SAEs were reported for subjects on pimavanserin.

In Study 70, five subjects reported one SAE each (0.5%), including:

- Hypersensitivity, in a 10-year-old male subject receiving pimavanserin 10 mg, on Day 44, which was considered related to a concomitant antibiotic for urinary infection. The subject was treated with an antibiotic for a non-serious AE of cystitis that began on Day 37, after which the subject discontinued study drug for the cystitis AE and withdrawal by

LAR.

- Pneumonia respiratory syncytial viral, in a 14-year-old female subject receiving pimavanserin 34 mg, on Day 149. Study drug was unchanged.

- Heart rate irregular, in a 12-year-old male subject receiving pimavanserin 20 mg and concomitant methylphenidate 7.5 mg twice daily, on Day 119. The subject reportedly had had an argument with a family member and was upset, after which he reportedly had chest pain, high blood pressure (>240 systolic), pale face, and rapid heartbeat. He was admitted to the cardiology unit and the event was considered resolved the next day with study drug unchanged (and continued for approximately 6 further months until the study was terminated by the Applicant). ECGs on-study were considered normal or abnormal, not clinically significant.

- Febrile convulsion, in a 5-year-old male subject receiving pimavanserin 20 mg, on Day 152, which was considered related to a fever treated as acute laryngitis and study drug was unchanged.

- Aggression, which also led to discontinuation (though classified as a secondary reason with primary reason noncompliance with study drug), in a 17-year-old male subject receiving pimavanserin 34 mg, on Day 90 (study drug was discontinued the same day). The investigator reported that the drug had appeared to be effective for some time (he also received pimavanserin low dose during Study 69) but then irritability increased and his mother called an ambulance for aggression toward her. He was admitted, discharged, and readmitted to a psychiatric unit, and treated with clonazepam, olanzapine, haloperidol, hydroxyzine, alprazolam, and risperidone. The event did not resolve after study drug discontinuation until Day 127.

No SAEs were reported in Study 50.

Clinical Reviewer's Comment: The limited open-label Study 70 SAEs do not suggest a safety signal, and appear likely unrelated to pimavanserin. Although QT prolongation is a labeled risk, the SAE of heart rate irregular had a prolonged time-to-onset, occurred following a stressor, and did not recur with study drug unchanged with prolonged further exposure. The SAE of aggression had a prolonged time-to-onset (although the dose was increased in the OLE) and is confounded by the underlying condition.

Dropouts and/or Discontinuations Due to Adverse Effects

In Study 69, four subjects discontinued for six AEs:

- Hypersensitivity and depressed mood, in one subject each receiving placebo.

- Anxiety, irritability, and middle insomnia, in a 7-year-old male subject receiving pimavanserin low dose and concomitant melatonin 1 mg daily, which began on Day 16. The subject had discontinued prior risperidone 0.5 mg daily for study enrollment (Day -35). Study drug was discontinued on Day 22, and the event resolved on Day 34. Risperidone was resumed on Day 25.

- Abdominal pain in an 8-year-old male subject receiving pimavanserin high dose, which began on Day 28. Study drug was discontinued the same day, and the event resolved Day 39.

  Clinical Reviewer's Comment: The limited Study 69 discontinuations for AEs do not suggest a safety signal. The anxiety, irritability, and middle insomnia are confounded by discontinuation of prior risperidone and underlying condition.

In Study 70, nine subjects discontinued for 11 AEs; in addition to the cystitis AE and aggression AE discussed previously, including:

- Anxiety, with a concurrent AE of psychomotor hyperactivity, in a 6-year-old male receiving pimavanserin 10 mg, which began on Day 8. Pimavanserin was titrated to 20 mg daily on Day 17. The AE of psychomotor hyperactivity was considered resolved on Day 57 and the AE of anxiety on Day 64. Study drug was discontinued on Day 64.

- Tachycardia, in a 12-year-old male subject receiving pimavanserin 20 mg, which began on Day 254 (with study drug discontinuation the same day). The subject discontinued concomitant lisdexamfetamine 60 mg daily on Day 233 and resumed it on Day 252, and took one cannabinoid not-otherwise-specified gummy on Day 252. ECG baseline heart rate was 108 bpm, with subsequently lower readings until Day 209 of 116 bpm and Day 215 (unscheduled) of 129 bpm, followed by 90 bpm on Day 251 and 107 bpm on Day 254. The event resolved on Day 286.

- Major depression, in a 12-year-old female subject receiving pimavanserin 20 mg, with a history of major depressive disorder, which began on Day 156. Study drug was discontinued on Day 159 and the subject withdrew on Day 196. The subject began mirtazapine 15 mg daily on Day 197. The event was considered not resolved.

- Irritability, in a 17-year-old male subject receiving pimavanserin 34 mg, which began on Day 78 (with study drug discontinuation the same day). The event resolved the same day.

- Somnolence and encopresis, in a 7-year-old female subject receiving pimavanserin 10 mg, which began on Days 14 and 15, respectively. The subject had received pimavanserin high dose (i.e., 20 mg) in Study 69. Study drug was discontinued on Day 26. Encopresis was considered resolved on Day 15 and somnolence resolved on Day 17.

- Nausea, in a 9-year-old male receiving pimavanserin 10 mg, which began on Day 1. Study drug was discontinued on Day 15 and the subject withdrew on Day 16, with the AE ongoing. The subject had received pimavanserin high dose (i.e., 20 mg) in Study 69.

- Headache, in a 7-year-old female receiving pimavanserin 10 mg and concomitant atomoxetine 18 mg daily, which began on Day 42. Study drug was discontinued on Day 52 and the event resolved the same day.

The Applicant also provided a narrative for a 9-year-old female subject whose primary reason for discontinuation was withdrawal by LAR (but without a secondary reason for AE), who experienced an AE of anxiety that apparently technically occurred after completion of Study 69 (during which she received pimavanserin high dose (i.e., 20 mg)), but "pre-treatment" for Study 70 (i.e., on Day -1). In Study 70, the subject received pimavanserin 10 mg. Study drug was discontinued on Day 12 of Study 70 and the subject withdrew from the study on Day 43, with the AE ongoing.

> *Clinical Reviewer's Comment: The limited open-label Study 70 AEs leading to discontinuation do not suggest a safety signal, as they appear likely unrelated to pimavanserin, with delayed time to onset and/or confounding by concomitant medications and/or underlying conditions. The tachycardia AE appears potentially related to, or at least confounded by, concomitant lisdexamfetamine.*

No discontinuations for AEs were reported in Study 50.

Significant Adverse Events

In Study 69, severe AEs were reported in two (2.6%) subjects who received placebo (hypersensitivity and depressed mood) and in one (1.2%) subject who received pimavanserin high dose (eosinophilia). In Study 70, severe AEs were reported in five (2.4%) subjects and included aggression (two (1.0%) subjects), pyrexia, gastroenteritis viral, and irritability (one (0.5%) subject each). (See previous narratives.) No severe AEs were reported in Study 50.

Treatment Emergent Adverse Events and Adverse Reactions

In Study 69, the most common AEs (i.e., reported in ≥5% of subjects at a rate greater than placebo for pimavanserin overall) included upper respiratory tract infection (8% pimavanserin versus 5% placebo) and headache (6% versus 5%). See Table 10 for AEs reported in ≥2% of subjects at a rate greater than placebo for pimavanserin overall.

Table 10. Study ACP-103-069 Treatment-Emergent Adverse Events in ≥2% of Subjects Treated With Pimavanserin Overall at a Rate Greater Than Placebo, Safety Analysis Set

MedDRA Preferred Term	Pimavanserin Overall (N=158) n (%)	Pimavanserin High Dose (N=81) n (%)	Pimavanserin Low Dose (N=77) n (%)	Placebo (N=78) n (%)
Upper respiratory tract infection	12 (7.6%)	5 (6.2%)	7 (9.1%)	4 (5.1%)
Headache[a]	10 (6.3%)	5 (6.2%)	5 (6.5%)	4 (5.1%)
Insomnia[b]	7 (4.4%)	1 (1.2%)	6 (7.8%)	1 (1.3%)
Abdominal pain[c]	6 (3.8%)	5 (6.2%)	1 (1.3%)	1 (1.3%)
Nausea	5 (3.2%)	1 (1.2%)	4 (5.2%)	1 (1.3%)
Decreased appetite	6 (3.8%)	2 (2.5%)	4 (5.2%)	--
Rash[d]	6 (3.8%)	3 (3.7%)	3 (3.9%)	--
Dizziness	4 (2.5%)	4 (4.9%)	--	1 (1.3%)
Increased appetite	4 (2.5%)	2 (2.5%)	2 (2.6%)	1 (1.3%)
Tachycardia[e]	4 (2.5%)	3 (3.7%)	1 (1.3%)	--

Source: Clinical reviewer-created from Study ACP-103-069 ADAE dataset
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities
Note: Subjects are counted once for each grouped preferred term.
[a] Grouping includes headache, tension headache
[b] Grouping includes insomnia, initial insomnia, middle insomnia, terminal insomnia
[c] Grouping includes abdominal discomfort, abdominal pain, abdominal pain upper
[d] Grouping includes rash, rash macular
[e] Grouping includes tachycardia, sinus tachycardia

No AE occurred at ≥5% with pimavanserin overall and greater than twice the rate with placebo. The most common AE rates are generally low, and some without a clear plausible mechanistic relationship (e.g., upper respiratory tract infection). Of the AEs listed, nausea is included in the current pimavanserin label premarketing adverse reactions and rash is included in postmarketing experience for the adult PDP population.

In Study 70, the most common AEs (i.e., reported in ≥5% of subjects) included upper respiratory tract infection (10%), vomiting (7.2%), headache (6.7%), nasopharyngitis (6.2%), and pyrexia (5.3%). See Table 11 for AEs reported in ≥3% of subjects.

Table 11. Study ACP-103-070 Treatment-Emergent Adverse Events in ≥3% of Subjects, Safety Analysis Set

MedDRA Preferred Term	Pimavanserin (N=209) n (%)
Upper respiratory tract infection	21 (10.0%)
Vomiting	15 (7.2%)
Headache	14 (6.7%)
Nasopharyngitis	13 (6.2%)
Pyrexia	11 (5.3%)
Rhinitis	9 (4.3%)
Diarrhea	7 (3.3%)
Gastroenteritis	7 (3.3%)
Somnolence	7 (3.3%)
Irritability	7 (3.3%)

Source: Clinical reviewer-created from Study ACP-103-070 ADAE dataset
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities
Note: Subjects are counted once for each grouped preferred term.

The open-label Study 70 common AEs occurred at generally low frequencies and do not suggest a safety signal. Of note, some occurred more frequently with placebo in Study 69 (e.g., somnolence, whether overall or by high/low dose groups).

In Study 50, AEs reported in more than two subjects (including all dosing groups of 10, 20, and 34 mg) included headache (six (17.6%) subjects), sedation (five (14.7%) subjects), somnolence (three (8.8%) subjects, and upper respiratory tract infection (two (5.9%) subjects). Only somnolence demonstrated a positive dose-response relationship, while others demonstrated a lack or negative relationship.

Laboratory Findings

In Study 69, as described by the Applicant, changes in chemistry (including liver function tests, glucose, cholesterol, triglycerides, and prolactin), hematology, and urinalysis results were generally minimal. The majority of subjects demonstrated no shifts from normal to abnormal, and no pattern of shifts from normal to abnormal was apparent. All AEs that were considered related to abnormal laboratory results were single or dual events, were assessed as mild or moderate, and no SAEs related to abnormal laboratory results were reported. AEs that were considered related to abnormal laboratory results included blood creatine phosphokinase increased in the placebo-treated group (one subject), blood bilirubin increased and neutrophil count decreased in the pimavanserin low dose group (one subject with each), and eosinophilia (two subjects) and blood creatine phosphokinase increased (one subject) in the pimavanserin high dose group.

Of the two subjects with PCI liver function tests (both on low dose pimavanserin), the one

elevated alanine aminotransferase at Week 3 was minimally above 3x the upper reference range and resolved by Week 6, and the elevated bilirubin (also an AE) was highest at baseline (after within-range screening), and lower at Weeks 1 and 6, if still above the upper reference range (it did return to within range between Weeks 1 and 6). Of other clinical laboratory postbaseline PCI changes, overall frequencies were low, and/or not significantly different between groups (including some more frequent with placebo), and only isolated occurrences were considered clinically significant.

In Study 70, the Applicant reported similar and generally minimal changes in clinical laboratory values, with baseline shifts above or below range occurring sporadically. A high maximum postbaseline value for prolactin was reported in five (2.6%) subjects; two (1.0%) subjects had an AE of blood prolactin increased. As in Study 69, all AEs related to abnormal laboratory results were single or dual events, were assessed as mild or moderate, and no SAEs related to abnormal laboratory results were reported. Among postbaseline PCI values, as in Study 69, overall frequencies were low, and most were not considered clinically significant, with isolated cases for individual parameters.

Overall, Study 69 and OLE Study 70 clinical laboratory results do not suggest a safety signal. For Study 69 PCI elevated glucose values, which had a higher frequency on pimavanserin (9.9%) versus placebo (4.4%), only one subject (of 13) among the pimavanserin cases was considered clinically significant.

Vital Signs

In Study 69, as described by the Applicant, mean changes from baseline at each visit for sitting or supine blood pressures, temperature, respiratory rate, weight, and BMI were generally minimal. Mean changes in pulse rate were lower in subjects who received placebo than those who received pimavanserin overall, with slightly higher mean changes for those who received pimavanserin low dose. Overall PCI abnormal postbaseline vital signs frequencies (including those meeting orthostatic hypotension) were low, and/or not significantly different between groups (including some more frequent with placebo), with no apparent dose-response, and for weight generally not considered clinically significant. Blood pressure increased was reported as an AE (occurring twice) in one subject on pimavanserin low dose, considered mild, recovered, and not related to study drug. Weight increased was reported as an AE in very low numbers and similar between placebo (2.6%) and pimavanserin high dose (2.5%).

In Study 70, the Applicant reported similarly generally minimal changes in vital sign values, with low frequencies of PCI vital sign changes overall and the majority considered not clinically significant. (A high frequency (49%) of weight increases ≥7% from baseline were considered in accordance with age.) One AE of heart rate irregular was reported as previously described. Weight increased was reported as an AE in six (2.9%) subjects, all considered mild or moderate. Overweight was reported as an AE in one (0.5%) subject, considered mild. Weight decreased was reported as an AE in two (1.0%) subjects, considered mild or moderate.

Electrocardiograms and QT

In Study 69, as described by the Applicant, small mean changes in heart rate, PR interval, RR interval, and QRS duration from baseline to each visit were recorded. No subjects had a postbaseline maximum QTcF >450 ms or change to postbaseline maximum QTcF >60 ms. One subject on pimavanserin overall (0.7%) had a postbaseline change between 31 to 60 ms versus none on placebo. More subjects on pimavanserin overall (41.4%) had a postbaseline change between 11 to 30 ms than placebo (24.7%), with a degree of dose-response (i.e., high dose (44.9%) versus low dose (37.8%)). No subjects on pimavanserin had a postbaseline abnormal ECG that was considered clinically significant. There were few ECG-related AEs. AEs using the SMQ for QT prolongation were reported in two (2.6%) subjects who received placebo (syncope, and atrioventricular block first degree and sinus arrhythmia), one (1.3%) subject who received pimavanserin low dose (sinus tachycardia), and three (3.7%) subjects who received pimavanserin high dose (sinus tachycardia and two tachycardia). One (1.3%) subject who received placebo reported syncope AE that was within SMQ of Torsade de Pointes-QT prolongation.

In Study 70, as described by the Applicant, small mean changes in heart rate, PR interval, RR interval, and QRS duration from OL Baseline to each visit were recorded. No subjects had a postbaseline maximum QTcF >450 ms or change to postbaseline maximum QTcF >60 ms. Two subjects (1.0%) had a postbaseline change between 31 to 60 ms. AEs of cardiac disorders were reported in four (1.9%) subjects: three (1.4%) subjects reported atrioventricular block first degree, while atrioventricular block second degree, sinus arrhythmia, and tachycardia were reported in one (0.5%) subject each. All cardiac AEs were nonserious, mild, recovered, and all considered not related, except for one event of worsening tachycardia that was considered related to the study drug.

Study 69 and OLE Study 70 ECG results do not suggest a new or worsened safety signal. Pimavanserin labeling includes a Warning and Precaution for QT prolongation and the drug is known to prolong the interval, so it is not unexpected that more subjects on pimavanserin than placebo had a maximum postbaseline change in QTcF between 11 to 30 ms in Study 69. Importantly, no subjects had a postbaseline maximum QTcF >450 ms (or maximum change >60 ms; in fact, none >30 ms).

Immunogenicity

In Study 69, a higher percentage of subjects on pimavanserin overall (3.8%) versus placebo (0.0%) reported AEs of rash (grouped terms). (One subject on placebo reported an AE of hypersensitivity). In Study 70, one subject reported two AEs of drug hypersensitivity. The pimavanserin label currently includes postmarketing reports of adverse reactions of rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea). Therefore, these results do not suggest a new or worsened safety signal.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant assessed potential antipsychotic-class-related risks and other relevant risks. A review of the Applicant's SMQs and AEs related to such risks as hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, weight gain, and somnolence, demonstrated low overall reports of related AEs (if any), which were either balanced between treatment groups (with some more frequent on placebo), and/or lacked a dose-response in Study 69. See previous sections for discussions of related clinical laboratory assessments, vital signs, and ECGs.

Extrapyramidal Symptoms

The Applicant assessed EPS with the ESRS-A. In Study 69, all groups had baseline low total scores and demonstrated minimal changes from baseline (with pimavanserin high dose demonstrating the largest reduction). AEs using the SMQ for EPS were tremor and torticollis (one (1.3%) each) in subjects who received placebo, muscle spasms and tic (one (1.3%) each) in subjects who received pimavanserin low dose, and psychomotor hyperactivity (two (2.5%)), extrapyramidal disorder (one (1.2%)), and restlessness (one (1.2%)) in subjects who received pimavanserin high dose. The event of extrapyramidal disorder was assessed as mild and related, and the subject recovered spontaneously. The dose of study medication was not changed.

Suicidal Ideation and Behavior

The Applicant assessed SI/B with the C-SSRS. In Study 69, the frequency of postbaseline SI/B was low and balanced between treatment groups; for suicidal ideation (placebo two subjects (2.6%) versus pimavanserin overall two subjects (1.3%), and for self-injurious behavior without suicidal intent (placebo six subjects (7.7%) versus pimavanserin overall eight subjects (5.2%)). No suicidal behavior was reported. One event in one (1.3%) subject with suicidal ideation and three events in three (3.8%) subjects with intentional self-injury were considered AEs, all in subjects on placebo. Using an SMQ analysis, only one subject on placebo reported depressed mood.

In Study 70, overall, six (2.9%) subjects reported postbaseline suicidal ideation and 10 (4.8%) reported self-injurious behavior without suicidal intent on the C-SSRS; none of them were considered AEs. No subjects reported suicidal behavior.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant did not conduct safety analyses by demographic subgroups and the study was not powered for subgroup analyses allowing meaningful interpretation.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new human carcinogenicity or tumor development studies were submitted with this supplement.

Human Reproduction and Pregnancy

No new information regarding human reproduction was submitted with this application. No pregnancies were reported in the studies.

Pediatrics and Assessment of Effects on Growth

See vital signs assessment above regarding weight analysis.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no AEs suggestive of overdose, abuse potential, withdrawal, or rebound safety signals reported in the clinical studies.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Currently labeled postmarketing adverse reactions include rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea), somnolence, falls, agitation, aggression, and fecal incontinence. A review of the Applicant's most recent NDA annual report and Periodic Adverse Drug Experience Report did not identify any new or worsened safety signals. The Applicant did not report any off-label pediatric use and a review of line listings for "off label" use or "unapproved" indications did not specify pediatric use cases.

Expectations on Safety in the Postmarket Setting

Information about efficacy and safety findings in the ASD clinical studies will be added to Section 8.4 based on the data submitted in this supplement (see Labeling Recommendations). The inclusion of these data will inform healthcare professionals that the efficacy and safety of pimavanserin for the treatment of irritability associated with ASD in pediatric patients ages 5 to 17 years have not been established.

8.2.9. Integrated Assessment of Safety

The Applicant submitted sufficient information to adequately assess safety in the pediatric irritability associated with ASD clinical trials population. As expected given the notable differences in populations (e.g., related to age, treatment indication, comorbidities,

concomitant medications) between the approved indication of adults with PDP and the pediatric population with irritability associated with ASD in the clinical trials, the reported AEs also included some differences. For this reason, Section 8.4 will report the most common AEs in Studies 69 and 70.

8.3. Statistical Issues

There are no statistical issues impacting the interpretation of the results.

8.4. Conclusions and Recommendations

This submission is intended to support an update to labeling Section 8.4 with clinical data (not to support a new indication). As per the WR, Study 69 was intended as a phase 2, POC, dose-finding study to investigate pimavanserin efficacy and safety in pediatric subjects with irritability associated with ASD. The negative results of Study 69 do not support a new indication for the treatment of irritability associated with ASD, and further phase 3 studies were removed from WR Amendment 2. The Pediatric Exclusivity Board has determined that the Applicant met the terms of the WR. Labeling Section 8.4 will be updated with safety and efficacy results of Study 69 and Study 70.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not required or convened for this submission.

10 Pediatrics

The completion of Study 69 and Study 70 with submission of the clinical study reports and datasets meets the terms of the amended pediatric WR (see Section 3.2), as adjudicated by the Pediatric Exclusivity Board.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant is not pursuing an expanded indication based on the negative results from Study 69. Section 8.4 of labeling will address the findings of the pediatric clinical studies, as discussed in consultation with the Division of Pediatric and Maternal Health.

The label will state that safety and effectiveness of NUPLAZID in pediatric patients have not been established, provide a brief description of the 6-week, double-blind, placebo-controlled, fixed-dose clinical study conducted in 237 pediatric subjects 5 to 17 years of age with irritability associated with autism spectrum disorder, list the most common adverse events (incidence ≥5%) reported among NUPLAZID-treated pediatric subjects, and note how many NUPLAZID-treated pediatric subjects discontinued due to adverse events.

The label will also provide a brief description of the open-label treatment study, again listing the most common adverse events and how many subjects discontinued due to adverse events.

A description of the juvenile animal study conducted to support pediatric trials will be included in Section 8.4 as well. This section will describe major findings, including a decrease in growth observed in males at ≥ 30 mg/kg/day and in females at all dose levels which reversed following dose cessation, a delay in sexual maturation in males at ≥ 30 mg/kg/day, no effect on fertility or reproductive performance for males or females, a slight decrease in the number of implantations and viable embryos in mated females at all dose levels, and no adverse effects on neurobehavioral development or learning and memory up to the highest dose tested.

12 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is not appropriate or indicated based upon the data from this submission.

13 Postmarketing Requirements and Commitment

No new postmarketing requirements or commitments will be issued.

14 Division Director Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

15 Appendices

15.1. Financial Disclosure

No investigators had disclosable financial interests for either Study 69 or 70.

Covered Clinical Studies (Name and/or Number): ACP-103-069, ACP-103-070

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 67, 52		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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