NDA 207318 (IND 068384)
NDA 210793 (IND 157863)

WRITTEN REQUEST – AMENDMENT #2

Acadia Pharmaceuticals Inc.
Attention: Heather Bradley, MPH
Vice President, Regulatory Affairs
12830 El Camino Real
Suite 400
San Diego, CA 92130

Dear Heather Bradley:

Please refer to your correspondence dated January 14, 2025, requesting changes to FDA's December 13, 2018, Written Request for pediatric studies for Nuplazid (pimavanserin).

We have reviewed your proposed changes and are amending the Written Request as follows:

> Given the negative results of Study 1, the exploratory proof-of-concept study for irritability associated with autism spectrum disorder (ASD), we have removed the requirement for two pediatric efficacy and safety studies in patients with irritability associated with ASD (previously Study 2 and Study 3).

All other terms stated in our Written Request issued on December 13, 2018, and as amended on September 1, 2021, remain the same. Refer to the attached document which shows the changes from the previous Written Request.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 13, 2018, as amended by this letter and by previous amendment dated September 1, 2021, must be submitted to the Agency on or before June 30, 2026, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact LCDR Jasmeet Kalsi, Regulatory Project Manager, at Jasmeet.Kalsi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Complete Copy of the Written Request as Amended, with Changes Marked
- Complete Copy of Written Request as Amended

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

NDA 207318
NDA 210793

WRITTEN REQUEST

Acadia Pharmaceuticals Inc.
Heather Bradley, MPH
Vice President, Regulatory Affairs
12830 El Camino Real, Suite 400
San Diego, CA 92130

Dear Ms. Bradley:

Reference is made to your August 20, 2018, Proposed Pediatric Study Request for pimavanserin.

BACKGROUND:

These studies investigate the potential use of pimavanserin for the treatment of pediatric patients aged 5 to 17 with irritability associated with autism spectrum disorders. Previous investigations of pimavanserin as adjunctive treatment of schizophrenia and major depressive disorder did not achieve statistical significance on the primary efficacy endpoints. Therefore, pediatric studies evaluating the effect of pimavanserin in schizophrenia and in bipolar I disorder have been removed from the Written Request. You are also investigating pimavanserin in adults for the treatment of negative symptoms of schizophrenia and dementia related psychosis (DRP). We do not require pediatric studies of the treatment of negative symptoms of schizophrenia or DRP because studies would be impossible or highly impracticable.

Autism Spectrum Disorder
Autism Spectrum Disorder (ASD) is a neuro-developmental disorder characterized by impairments in social interactions, communication, and restricted interests and stereotyped behaviors. In 2014, the CDC estimated that an average of 1 in 59 children in the United States has an ASD. The risk is 3 to 4 times higher in males than females. ASD is characterized by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities. These symptoms are present from early childhood, often recognized in children age 2 years or younger.

There are currently no medications specifically approved in the United States for the treatment of the core features of ASD. Risperidone and aripiprazole are indicated for the treatment of irritability associated with autistic disorder in patients 5 to 17 years of age (6 to 17 years for aripiprazole, 5 to 16 years for risperidone); this includes

symptoms of aggression towards others, deliberate self injuriousness, temper tantrums, and quickly changing moods. It is likely that other antipsychotics, including pimavanserin, will be used off-label for the treatment of irritability in children and adolescents with ASD. Therefore, it is important to evaluate the efficacy and safety of other atypical antipsychotics, including pimavanserin, in this patient population. This Written Request has been amended to remove two adequate and well-controlled pediatric efficacy and safety studies in patients with irritability associated with ASD because the results of a proof-of-concept, dose-ranging study of the efficacy, safety, and pharmacokinetics of pimavanserin in pediatric patients 5 to 17 years of age with irritability associated with ASD were negative. A pediatric long-term safety study is still required as the study has been conducted and may yield safety information.

To obtain needed pediatric information on pimavanserin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

***Nonclinical study*:**

Based on review of the available nonclinical toxicology data, the following study must be conducted prior to the start of dosing the corresponding age cohorts in the clinical studies described in this written request:

A repeat-dose toxicity study in the juvenile rat starting at the appropriate age that corresponds to children age 5 years, and to include appropriate developmental and neurobehavioral study endpoints. This study must be completed prior to initiation of pediatric clinical studies in children < 13 years of age. You must submit a protocol for review prior to initiation of the study.

Clinical Studies:

Study 1: A proof-of-concept (POC), dose-ranging study of the efficacy, safety, and pharmacokinetics (PK) of pimavanserin in pediatric patients 5 to 17 years of age with irritability associated with ASD. You must reach agreement with the Agency on the design of Study 1 prior to initiation. ~~If the results of Study 1 suggest benefit in the treatment of irritability associated with ASD, then Studies 2, 3, and 4 will be required. The need for Studies 2, 3, and 4 will be determined upon Agency review of the Study 1 results.~~

~~Studies 2 and 3: Two adequate and well controlled pediatric efficacy and safety studies in patients with irritability associated with ASD.~~

Study 42: Pediatric long-term safety study.

- The nonclinical study in support of dosing patients ages 5-12 years must be completed and draft results reported to the Agency prior to the initiation of clinical efficacy studies in those patients. The final report will be submitted to the Agency once available.

- Given that PK data in adults and adolescents are available for this drug, you may submit data from population PK modeling using data from adults and adolescents to justify the dose selection in adolescents and children with irritability associated with ASD in Study 1. The selected doses must be agreed upon by the Agency prior to the initiation of Study 1. In addition, sparse PK samples must be collected from Study 1 to further characterize the PK of pimavanserin in children and adolescents.

- For each study, you must submit a protocol for review and approval by the Agency prior to the initiation of the study.

Objective of each study:

Study 1: To evaluate the efficacy, safety, and PK of pimavanserin in a POC, dose-ranging study in pediatric patients 5-17 years of age with irritability associated with ASD.

~~*Studies 2 and 3: To evaluate the efficacy and safety of pimavanserin in the treatment of irritability associated with ASD in pediatric patients ages 5 to 17 years.*~~

Study 42: To evaluate the long-term safety of pimavanserin in pediatric patients with ASD.

Patients to be Studied:

- *Age group in which studies will be performed*:

  Study 1: Patients with ASD, ages 5 to 17 years

  ~~*Studies 2 and 3: Patients with ASD, ages 5 to 17 years*~~

  Study 42: Patients with ASD, ages 5 through 17 years.

- *Number of patients to be studied:*

  Study 1

  - A sufficient number of patients to adequately characterize the appropriate dose range, efficacy, tolerability, and PK of the study drug and its major active metabolite(s) in the relevant age group must be studied.

- The gender distribution of participants in this study should reflect the distribution of those affected with this condition.

- The key PK parameters could be estimated using traditional pharmacokinetic methods or population pharmacokinetic approaches. Sufficient blood samples should be collected to enable evaluation of the shape of plasma concentration time profiles of pimavanserin and each active metabolite measured in the relevant age range. ~~The PK data obtained from Study 1 would be used to inform dose selection for the Studies 2 and 3.~~

- Patients who complete Study 1 should then be enrolled into the long-term safety study.

~~*Studies 2 and 3*~~

- ~~The efficacy, safety, and tolerability studies must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo based on the results of Study 1. You must conduct an interim analysis to estimate variance late in the trial and increase the sample size if necessary to ensure that the trial has adequate power (see Statistical Information).~~

Study 2~~4~~

- This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at doses identified as effective in an adequately designed trial or, if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A total of at least 100 patients with ASD exposed to drug for at least 6 months is the minimum requirement for long-term safety.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study endpoints:

- *Pharmacokinetic Endpoints:* You must measure and collect data to develop adequate estimates of the PK profile in Study 1, including important PK parameters for the parent compound and major active metabolites, i.e., AUC, half-life, Cmax, Tmax, and apparent oral clearance (this parameter for parent only), apparent

volume of distribution at steady state (this parameter for parent only). These estimates of PK parameters must be obtained using sufficient sampling.

- *Efficacy Endpoints:* A scale specific to irritability associated with ASD in the target population must be used in Study 1. ~~The choice of the primary assessment instrument and the primary outcome will need to be justified and approved by the Agency. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. It is essential to identify a primary outcome for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.~~

- *Safety Endpoints:* Safety outcomes in all clinical protocols must include routine safety assessments collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; and urinalysis), ECG's, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e., worsening of psychosis, depressed mood, suicidal and homicidal ideation) as part of this written request.

The following adverse events must be actively monitored in all clinical protocols:

- You must adequately assess antipsychotic class safety concerns including hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, akathisia and other extrapyramidal symptoms, weight gain, and somnolence.

- All clinical protocols, whatever the indication, must include a prospective assessment for suicidal ideation and behavior. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development.

All adverse events must be monitored until symptom resolution or until the condition stabilizes in all clinical protocols.

A Data Monitoring Committee (DMC) must be included in all clinical protocols.

Extraordinary results:
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the

case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug information:

- *Dosage form: tablet and capsule*
- *Route of administration: oral*
- *Regimen: once daily*

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1. You develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval).

2. The Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act.

3. You have not marketed the formulation within 1 year after the Agency publishes such notice the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

~~***Statistical information, including power of studies and statistical assessments:***~~

~~The outcome of Study 1 will inform the sample size calculation and statistical assessments of Studies 2 and 3. To ensure that studies 2 and 3 are adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. The interim analysis must be performed when the study is close to completion (for example, at >75% of initially randomized patients who have completed/discontinued). You may estimate the variability based on a blinded and pooled analysis of all groups, in which case no alpha spending adjustment is required for the interim analysis. If, however, you want to perform an efficacy assessment at these or some other interim analyses, an appropriate alpha adjustment would be required.~~

~~With respect to the primary efficacy analysis, the protocol will need to describe the estimand of primary interest. Please refer to ICH E9 draft addendum for specific components of an estimand. You should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses.~~

~~The protocol and statistical analysis plan must be submitted to the Agency for comment. You must obtain agreement on the final protocol and statistical analysis plan prior to initiation of the studies.~~

Labeling that may result from the studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that pimavanserin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

***Format and types of reports to be submitted*:**

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native

Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 333969.pdf.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before Juaneuary 3029, 20269. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If

you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. The type of response to the Written Request (i.e. complete or partial response)

2. The status of the application (i.e. withdrawn after the supplement has been filed or pending)

3. The action taken (i.e. approval, complete response)

4. The exclusivity determination (i.e. granted or denied)

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in

large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an “applicable clinical trial” under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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WRITTEN REQUEST

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BACKGROUND:

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symptoms of aggression towards others, deliberate self injuriousness, temper tantrums, and quickly changing moods. It is likely that other antipsychotics, including pimavanserin, will be used off-label for the treatment of irritability in children and adolescents with ASD. Therefore, it is important to evaluate the efficacy and safety of other atypical antipsychotics, including pimavanserin, in this patient population. This Written Request has been amended to remove two adequate and well-controlled pediatric efficacy and safety studies in patients with irritability associated with ASD because the results of a proof-of-concept, dose-ranging study of the efficacy, safety, and pharmacokinetics of pimavanserin in pediatric patients 5 to 17 years of age with irritability associated with ASD were negative. A pediatric long-term safety study is still required as the study has been conducted and may yield safety information.

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Clinical Studies:

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Study 2: Pediatric long-term safety study.

- The nonclinical study in support of dosing patients ages 5-12 years must be completed and draft results reported to the Agency prior to the initiation of clinical efficacy studies in those patients. The final report will be submitted to the Agency once available.

- Given that PK data in adults and adolescents are available for this drug, you may submit data from population PK modeling using data from adults and adolescents to justify the dose selection in adolescents and children with irritability associated with ASD in Study 1. The selected doses must be agreed upon by the Agency prior to the initiation of Study 1. In addition, sparse PK samples must be collected from Study 1 to further characterize the PK of pimavanserin in children and adolescents.

- For each study, you must submit a protocol for review and approval by the Agency prior to the initiation of the study.

Objective of each study:

Study 1: To evaluate the efficacy, safety, and PK of pimavanserin in a POC, dose-ranging study in pediatric patients 5-17 years of age with irritability associated with ASD.

Study 2: To evaluate the long-term safety of pimavanserin in pediatric patients with ASD.

Patients to be Studied:

- *Age group in which studies will be performed*:

  Study 1: Patients with ASD, ages 5 to 17 years

  Study 2: Patients with ASD, ages 5 through 17 years.

- *Number of patients to be studied:*

  Study 1

  - A sufficient number of patients to adequately characterize the appropriate dose range, efficacy, tolerability, and PK of the study drug and its major active metabolite(s) in the relevant age group must be studied.

  - The gender distribution of participants in this study should reflect the distribution of those affected with this condition.

  - The key PK parameters could be estimated using traditional pharmacokinetic methods or population pharmacokinetic approaches. Sufficient blood samples should be collected to enable evaluation of the shape of plasma concentration time profiles of pimavanserin and each active metabolite measured in the relevant age range.

- Patients who complete Study 1 should then be enrolled into the long-term safety study.

Study 2

- This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at doses identified as effective in an adequately designed trial or, if this trial fails to detect a drug effect, at doses equivalent to the adult exposure of the drug. A total of at least 100 patients with ASD exposed to drug for at least 6 months is the minimum requirement for long-term safety.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study endpoints:

- *Pharmacokinetic Endpoints:* You must measure and collect data to develop adequate estimates of the PK profile in Study 1, including important PK parameters for the parent compound and major active metabolites, i.e., AUC, half-life, Cmax, Tmax, and apparent oral clearance (this parameter for parent only), apparent volume of distribution at steady state (this parameter for parent only). These estimates of PK parameters must be obtained using sufficient sampling.

- *Efficacy Endpoints:* A scale specific to irritability associated with ASD in the target population must be used in Study 1.

- *Safety Endpoints:* Safety outcomes in all clinical protocols must include routine safety assessments collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, as measured by stadiometer, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; serum lipids; and urinalysis), ECG's, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Given recent concerns regarding psychiatric adverse events with psychiatric medication use, particularly in children, you must provide an assessment of psychiatric adverse events (i.e., worsening of psychosis, depressed mood, suicidal and homicidal ideation) as part of this written request.

The following adverse events must be actively monitored in all clinical protocols:

- You must adequately assess antipsychotic class safety concerns including hyperglycemia, leucopenia/neutropenia/agranulocytosis, orthostatic hypotension/bradycardia/syncope, QTc prolongation, akathisia and other extrapyramidal symptoms, weight gain, and somnolence.

- All clinical protocols, whatever the indication, must include a prospective assessment for suicidal ideation and behavior. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development.

All adverse events must be monitored until symptom resolution or until the condition stabilizes in all clinical protocols.

A Data Monitoring Committee (DMC) must be included in all clinical protocols.

Extraordinary results:
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug information:

- *Dosage form: tablet and capsule*
- *Route of administration: oral*
- *Regimen: once daily*

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1. You develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval).

2. The Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act.

3. You have not marketed the formulation within 1 year after the Agency publishes such notice the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

Labeling that may result from the studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that pimavanserin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

***Format and types of reports to be submitted*:**

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm 333969.pdf.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before June 30, 2026. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. The type of response to the Written Request (i.e. complete or partial response)

2. The status of the application (i.e. withdrawn after the supplement has been filed or pending)

3. The action taken (i.e. approval, complete response)

4. The exclusivity determination (i.e. granted or denied)

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an “applicable clinical trial” under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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/

TIFFANY R FARCHIONE
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