NDA 205422

WRITTEN REQUEST – AMENDMENT 2

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:[1]

Please refer to your correspondence dated March 22, 2019, amended April 26, 2019, and June 21, 2019, requesting changes to FDA's April 19, 2018 Written Request for pediatric studies for REXULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on April 19, 2018, and as amended on November 1, 2018, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

These studies investigate the potential use of brexpiprazole in the treatment of pediatric patients aged 5-17 with schizophrenia~~, acute manic or mixed episodes associated with bipolar I disorder,~~ and irritability associated with autism spectrum disorders (ASD). Because efficacy was not demonstrated in two multicenter, randomized, placebo-controlled efficacy and safety trials of brexpiprazole for the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, it will not be studied for this indication in the pediatric population.

~~Bipolar I Disorder~~
~~According to the DSM 5, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years, including neonates is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the 10 to 17 year old population is thought to be relatively common and phenomenologically similar~~

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

~~to bipolar disorder seen in adults. Thus, the study of bipolar disorder in 10 to 17 year olds should be feasible and should yield useful information.~~

~~We believe that a sufficiently strong case has been made for continuity between adult and pediatric bipolar disorder to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in pediatric bipolar disorder. In addition, a pediatric bipolar program would need to include pharmacokinetic information and safety information in pediatric patients in the 10-17 age range with bipolar disorder.~~

- *Clinical studies:*

Study 1: A safety, tolerability, and PK study in pediatric patients 6 to 12 years of age

Study 2: An adequate and well-controlled pediatric efficacy and safety study in patients 13 to 17 years of age with schizophrenia

~~*Study 3: An adequate and well-controlled pediatric efficacy and safety study in patients 10 to 17 years of age with acute manic or mixed episodes associated with bipolar I disorder*~~

Study ~~4~~ 3: First ~~A~~adequate and well-controlled pediatric efficacy and safety study in patients 5 to 17 years of age with irritability associated with ASD

Study 4: Second adequate and well-controlled pediatric efficacy and safety study in patients 5 to 17 years of age with irritability associated with ASD

- ☐ If Study 3 is positive for the primary efficacy endpoint, Study 4 will be initiated. If Study 3 is unsuccessful, this written request should be amended to remove Study 4.

Study 5: Pediatric long-term safety study in patients with schizophrenia~~, bipolar I disorder,~~ and irritability associated with ASD

- ☐ The pharmacokinetic study in pediatric patients 6 to 12 years old must be completed before the efficacy trials to inform dosing. Results of the study must be reported to the Agency prior to the initiation of clinical studies 3, 4, and 5. Justification for the selected study dose(s) in 5-year old patients with Autism Spectrum Disorder must be provided before initiation of the first efficacy trial in that age group.

- *Objective of each study:*

Study 1: To evaluate the safety, tolerability, and pharmacokinetics of ~~a multiple doses of~~ brexpiprazole and its major metabolite in pediatric patients ~~5~~ 6 to 12 years of age.

Study 2: To evaluate the efficacy, safety, and tolerability of brexpiprazole in pediatric patients 13 to 17 years of age with schizophrenia.

~~*Study 3: To evaluate the efficacy, safety, and tolerability of brexpiprazole in pediatric patients 10 to 17 years of age with acute manic or mixed episodes associated with bipolar I disorder.*~~

Study 3 and 4: To evaluate the efficacy and safety of brexpiprazole in the treatment of irritability associated with autism spectrum disorder in pediatric patients 5 to 17 years of age.

Study 5: To evaluate the long-term safety of brexpiprazole in pediatric patients with schizophrenia~~, bipolar I disorder,~~ or ASD.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:

  Study 1: Patients 6 to 12 years of age with ~~bipolar I disorder or~~ ASD

  Study 2: Patients 13 to 17 years of age with schizophrenia

  ~~*Study 3:* Patients 10 to 17 years of age with bipolar I disorder~~

  Study 3 and 4: Patients 5 to 17 years of age with ASD

  Study 5: Patients 13 to 17 years of age with schizophrenia~~, patients 10 to 17 years of age with bipolar I disorder,~~ or patients 5 to 17 years of age with ASD

  - *Number of patients to be studied:*

  Study 1
  - A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major metabolite(s) in the relevant age group must be studied.
  - The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
  - The study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for the parent and major (active) metabolite(s) in the entire age range, or utilize a method justified by the Sponsor and agreed upon with the Agency.

- Patients who complete Study 1 must then be enrolled in any of the other studies described in this Written Request in order to offer them the prospect of a direct benefit.

Studies 2, 3, and 4

- Each trial must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo. For the purpose of satisfying the Written Request, the treatment effect might, for example, be defined as a 5-unit difference between drug and placebo in change from baseline on the Positive and Negative Syndrome Scale total score for the schizophrenia study~~, and a 4.5 unit difference in change from baseline to endpoint on the Young Mania Rating Scale for the bipolar I disorder study~~. The irritability subscale of the Aberrant Behavior Checklist (ABC) would be acceptable as the primary efficacy measure for the required study for irritability associated with autism. If you choose to use change from baseline in the irritability subscale of the ABC as the primary endpoint, the study must be powered to show a 6-unit difference between drug and placebo. 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 5

- This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or 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 combined total of at least 100 patients from the schizophrenia safety study~~, bipolar disorder safety study,~~ and ASD safety study together, diagnosed with ~~any~~ <u>either</u> of these ~~three~~ conditions and exposed to drug for at least 6 months, is the minimum requirement for long-term safety.

- *Study endpoints:*

  ☐ *Pharmacokinetic Endpoints:*
  The Sponsor must measure and collect data to develop adequate estimates of the pharmacokinetic profile, including important pharmacokinetic parameters for the parent compound and major (active) metabolite(s), i.e., AUC, half-life, Cmax, Tmax, and apparent oral clearance (this parameter for parent only). These estimates of pharmacokinetic parameters must be obtained using sufficient sampling.

  ☐ *Efficacy Endpoints:*

A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia (for Study 2)~~, bipolar disorder (for Study 3),~~ or irritability associated with ASD (for Study 3 and 4) in the target population must be used. The choice of the primary assessment instrument and the primary outcome will need to be justified and approved by the Agency. Specifically, if you choose scales and outcomes used in adult trials, you will need to justify that these measures are appropriate for use in the pediatric population. 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.

☐ The following adverse events must be actively monitored:

- 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 for products developed in the Division of Psychiatry Products, 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.

A Data Monitoring Committee (DMC) must be included for Studies 2, 3, and 4.

- *Statistical information, including power of study(ies) and statistical assessments:*

To ensure that studies 2, 3, and 4 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 Division for comment. You must obtain agreement on the final protocol and statistical analysis plan prior to initiation of the studies.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before ~~June 30, 2023~~December 31, 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.

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 April 19, 2018, as amended by this letter and by previous amendment dated November 1, 2018, must be submitted to the Agency on or before December 31, 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) 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, 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.[2]

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 CAPT Kofi Ansah, PharmD, Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation 1
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Complete Copy of Written Request as Amended

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205422

WRITTEN REQUEST

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:

Reference is made to your December 18, 2017 Proposed Pediatric Study Request for REXULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

BACKGROUND:

These studies investigate the potential use of brexpiprazole in the treatment of pediatric patients aged 5-17 with schizophrenia and irritability associated with autism spectrum disorders (ASD). Because efficacy was not demonstrated in two multicenter, randomized, placebo-controlled efficacy and safety trials of brexpiprazole for the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults, it will not be studied for this indication in the pediatric population.

Schizophrenia

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM-5, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is uncommon (AACAP Practice Parameters, 2001).

Given that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of treatment within this pediatric population, ages 12 and under. However, the very low incidence of schizophrenia diagnosed prior to the age 13, including neonates, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time.

Under current regulations [21 CFR 201.57(c)(9)(iv)], a new claim in an adolescent population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that schizophrenia was essentially the same disease in adults and adolescent patients. A claim might be based on a single study in adolescent patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the guidance document entitled "Guidance for Industry-Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." This approach also requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in adolescent and adult populations to make data from the adult efficacy studies pertinent to adolescent patients. We believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit an adolescent claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, an adolescent schizophrenia program would need to include pharmacokinetic information and safety information in adolescents (13 to 17 years-old) with schizophrenia.

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 68 children in the United States has an ASD. The risk is three to four 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.

There are currently no medications approved in the US 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 brexpiprazole, will be used off-label for the treatment of irritability in children and adolescents with autistic disorder. Therefore, it is important to evaluate the efficacy and safety of other atypical antipsychotics, including brexpiprazole, in this patient population, age 5 to 17 years.

Neonates

Psychiatric disorders and developmental disorders not associated with obvious congential abnormality cannot be diagnosed in neonates. Neonates will be excluded from studies in this Written Request.

The Agency acknowledges that a full study report for a multiple dose safety, tolerability, and pharmacokinetics (PK) study in pediatric patients (age 13 to 17 years) with a primary diagnosis of schizophrenia or bipolar disorder was submitted to IND101871 on August 1, 2017 (SN0527). Therefore, the requirement for the PK study in pediatric patients 13 to 17 years of age will not be discussed in this Written Request document.

To obtain needed pediatric information on brexpiprazole, 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(ies)*:

Based on review of the nonclinical toxicology data that have already been submitted, no additional animal studies are required at this time to support the clinical studies described in this Written Request. We acknowledge that in addition to standard nonclinical toxicology studies, you submitted results from a study assessing general toxicity, neurobehavioral development, and reproductive development in juvenile rats administered brexpiprazole orally from postnatal day (PND) 21 for eight weeks (PND 77). You also submitted results of a study in which juvenile dogs were treated orally with brexpiprazole for 26 weeks starting on PND 56 to 67 that assessed general toxicity and electrocardiography endpoints. We consider these studies adequate to support the use of brexpiprazole in pediatric patients 5 years of age and older.

- *Clinical studies:*

Study 1: A safety, tolerability, and PK study in pediatric patients 6 to 12 years of age

Study 2: An adequate and well-controlled pediatric efficacy and safety study in patients 13 to 17 years of age with schizophrenia

Study 3: First adequate and well-controlled pediatric efficacy and safety study in patients 5 to 17 years of age with irritability associated with ASD

Study 4: Second adequate and well-controlled pediatric efficacy and safety study in patients 5 to 17 years of age with irritability associated with ASD

- ☐ If Study 3 is positive for the primary efficacy endpoint, Study 4 will be initiated. If Study 3 is unsuccessful, this written request should be amended to remove Study 4.

Study 5: Pediatric long-term safety study in patients with schizophrenia and irritability associated with ASD

- ☐ The pharmacokinetic study in pediatric patients 6 to 12 years old must be completed before the efficacy trials to inform dosing. Results of the study must be reported to the Agency prior to the initiation of clinical studies 3, 4, and 5. Justification for the selected study dose(s) in 5-year old patients with Autism Spectrum Disorder must be provided before initiation of the first efficacy trial in that age group.

- *Objective of each study:*

Study 1: To evaluate the safety, tolerability, and pharmacokinetics of brexpiprazole and its major metabolite in pediatric patients 6 to 12 years of age.

Study 2: To evaluate the efficacy, safety, and tolerability of brexpiprazole in pediatric patients 13 to 17 years of age with schizophrenia.

Study 3 and 4: To evaluate the efficacy and safety of brexpiprazole in the treatment of irritability associated with autism spectrum disorder in pediatric patients 5 to 17 years of age.

Study 5: To evaluate the long-term safety of brexpiprazole in pediatric patients with schizophrenia or ASD.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:

  Study 1: Patients 6 to 12 years of age with ASD

  Study 2: Patients 13 to 17 years of age with schizophrenia

  Study 3 and 4: Patients 5 to 17 years of age with ASD

  Study 5: Patients 13 to 17 years of age with schizophrenia or patients 5 to 17 years of age with ASD

  - *Number of patients to be studied:*

  Study 1
  - A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major metabolite(s) in the relevant age group must be studied.
  - The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
  - The study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for the parent and major (active) metabolite(s) in the entire age range, or utilize a method justified by the Sponsor and agreed upon with the Agency.
  - Patients who complete Study 1 must then be enrolled in any of the other studies described in this Written Request in order to offer them the prospect of a direct benefit.

  Studies 2, 3, and 4

  - Each trial must have a sufficient number of patients to provide 85% statistical power to show a clinically meaningful difference between drug and placebo. For the purpose of

satisfying the Written Request, the treatment effect might, for example, be defined as a 5-unit difference between drug and placebo in change from baseline on the Positive and Negative Syndrome Scale total score for the schizophrenia study. The irritability subscale of the Aberrant Behavior Checklist (ABC) would be acceptable as the primary efficacy measure for the required study for irritability associated with autism. If you choose to use change from baseline in the irritability subscale of the ABC as the primary endpoint, the study must be powered to show a 6-unit difference between drug and placebo. 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 5

- This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or 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 combined total of at least 100 patients from the schizophrenia safety study and ASD safety study together, diagnosed with either of these conditions and 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:*
  The Sponsor must measure and collect data to develop adequate estimates of the pharmacokinetic profile, including important pharmacokinetic parameters for the parent compound and major (active) metabolite(s), i.e., AUC, half-life, Cmax, Tmax, and apparent oral clearance (this parameter for parent only). These estimates of pharmacokinetic parameters must be obtained using sufficient sampling.

  ☐ *Efficacy Endpoints:*
  A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia (for Study 2) or irritability associated with ASD (for Study 3 and 4) in the target population must be used. The choice of the primary assessment instrument and the primary outcome will need to be justified and approved by the Agency. Specifically, if you choose scales and outcomes used in adult trials, you will need to justify that these measures are appropriate for use in the pediatric population. 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 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:
    - 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 for products developed in the Division of Psychiatry Products, 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.

    A Data Monitoring Committee (DMC) must be included for Studies 2, 3, and 4.

- *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 or liquid*
  - *route of administration: oral*
  - *regimen: once daily*

  Use an age-appropriate formulation in the study(ies) 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; and
3) you have not marketed the formulation within one 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 study(ies) and statistical assessments:*

  To ensure that studies 2, 3, and 4 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 Division 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 study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that brexpiprazole 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 study(ies). 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 study(ies).

- *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 study(ies) 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 post-market 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/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 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 study(ies). 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 study(ies), 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 study(ies) 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 study(ies) 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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); or
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.

If you have any questions, contact CAPT Kofi Ansah, PharmD, Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

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/

ELLIS F UNGER
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