DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205831

WRITTEN REQUEST

Rhodes Pharmaceuticals L.P.
Attention: Todd M. Delehant, Ph.D.
Director Regulatory Affairs
498 Washington Street
Coventry, RI 02816

Dear Dr. Delehant:

Reference is made to your January 14, 2016, Proposed Pediatric Study Request for Aptensio XR® (methylphenidate hydrochloride extended-release) capsules.

These studies investigate the potential use of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 4 and 5 years of age.

The studies included in this PPSR investigate the potential use of Aptensio XR® (methylphenidate hydrochloride extended-release) capsules in preschool children (ages 4 and 5 years) for the treatment of Attention Deficit and Hyperactivity Disorder (ADHD). ADHD is not recognizable or diagnosed in neonates.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE PRESCHOOL POPULATION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents. It is characterized by a pattern of developmentally inappropriate and maladaptive inattentiveness, impulsivity, and hyperactivity resulting in clinically significant impairment in family, social, academic, and occupational functioning. ADHD symptoms often manifest several years prior to entry into elementary school. The estimated prevalence of ADHD in the preschool population (ages 3 to 5 years) is 3-5%, which is similar to the prevalence of ADHD throughout childhood and adolescence (3-5%). Preschool-age children with ADHD demonstrate significant impairments in family, social, and pre-academic function. They are often aggressive towards others and sustain injuries secondary to the disorder. Data suggest that only a small proportion of preschool-age children with ADHD respond adequately to behavioral therapy. The diagnosis of ADHD is likely to be stable and to lead to a wide range of long-term negative consequences.

It would be highly beneficial to obtain controlled data regarding pharmacotherapy for ADHD in the preschool population to guide treatment decisions. Reliable diagnostic tools and age-appropriate assessments of ADHD symptom severity are available for use in clinical trials. There are very few adequate and well-controlled studies of pharmacotherapy in preschool-age children with ADHD. Many of the studies lacked a control group or had inadequate sample sizes. However, there are

studies that demonstrate the efficacy of ADHD medication for preschool children. The efficacy of methylphenidate was demonstrated in 303 children 3 to 5.5 years of age with a diagnosis ADHD (who continued to meet specific ADHD severity criteria after 10 weeks of parent training). This was a 5-week, randomized, double-blind, placebo-controlled cross-over trial of four different methylphenidate doses compared with placebo treatment.[1]

Clinicians currently prescribe stimulants, such as methylphenidate, for the treatment of preschool-age children with ADHD. However, it is currently unclear whether one can extrapolate efficacy and safety findings from the school-age population (ages 6-17) to the preschool-age population. During the Pediatric Advisory Committee meeting (held on 11 September 2012), there was discussion regarding the use of stimulants (including methylphenidate) in preschool-age children. The committee expressed concern over a lack of data regarding the safe and effective use of methylphenidate in patients aged 0-5 years of age. In the United States in 2013, approximately 3.6% of the nearly 1.3 million methylphenidate IR prescriptions and approximately 2.6% of the nearly 2.4 million methylphenidate ER prescriptions written for children and adolescents (ages 0 to 17 years) were written for preschool-age children (0 to 5 years of age). The lack of controlled safety and efficacy data, combined with the substantial prevalence of off-label prescribing of stimulants such as methylphenidate to preschool-age children with ADHD suggests that controlled efficacy and safety studies of stimulants in this population would be of value to inform clinicians regarding the safety, efficacy, pharmacokinetics, and appropriate dose selection for stimulant treatment in the preschool-age population.

To obtain needed pediatric information on methylphenidate, 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.

GENERAL ADVICE FOR DEVELOPING A DRUG FOR ADHD IN THE PEDIATRIC POPULATION

A demonstration of the efficacy and safety of stimulants (e.g., methylphenidate or amphetamine products) for the treatment of ADHD in preschool-age children would require at least one adequate and well-controlled clinical trial in this population. The efficacy and safety study must be a randomized, double-blind and placebo-controlled trial. A placebo control is necessary for providing fully interpretable efficacy and safety results. There are no significant ethical concerns regarding pediatric patients treated with placebo in the ADHD clinical trials, because of the nature of this disorder. Moreover, there would be ethical concerns about conducting a pediatric study without a placebo control group, because such a study could not provide interpretable safety and efficacy data. Furthermore, subjects could be immediately discontinued from the studies and directed to standard treatments if they had an inadequate response.

An ADHD program in this pediatric population must include collection of adequate short-term and

[1] Greenhill L, Kollins S et al " Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD" *J.Am.Acad. Child Adolesc. Psychiatry,* 45:11, Nov 2006: pp 1285-1293.

longer-term safety data and pharmacokinetic data in the relevant age group (ages 4 and 5 years).

Non-clinical:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

SPECIFIC STUDY REQUIREMENTS FOR DEVELOPMENT PROGRAMS IN PEDIATRIC/ADOLESCENT ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Clinical studies include:

- Study 1: Pediatric Pharmacokinetic (PK) Study for patients age 4 to 5 years
- Study 2: Pediatric Efficacy and Safety Study for in patients age 4 to 5 years with ADHD
- Study 3: Pediatric Open-Label Safety Study for patients age 4 to 5 years (at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD

Overall Objectives/Rationale

The overall goals of the development program are to establish the safety and efficacy of monotherapy treatment with methylphenidate on the core symptoms of Attention Deficit/ Hyperactivity Disorder in 4 and 5 year-old preschool children.

Efficacy in patients age 4 to 5 years-old cannot be fully extrapolated and will be determined by the studies outlined in the WR.

The PK study (Study 1) must be completed before the efficacy trial (Study 2) to inform dosing. Results of the study must be reported to the Agency prior to the initiation of Study 2.

Pediatric 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 and will appear 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.

Study 1: Pharmacokinetic Study

- *Objective of each study:* The primary objective of Study 1 is to evaluate the pharmacokinetics, safety, and tolerability of methylphenidate hydrochloride.

- *Patients to be studied:*
  - *Age group in which studies will be performed*:
    - Pediatric patients 4 to 5 years old with ADHD

  - *Number of patients to be studied:*
    - A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics 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 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 parent and major (active) metabolites in the entire age range, or utilize a method justified by the sponsor and agreed upon with the Agency.
    - 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, i.e., AUC, half-life, Cmax, Tmax, and apparent oral clearance (this parameter for parent only) in 4 to 5 year-old pediatric patients with ADHD. These estimates of pharmacokinetic parameters must be obtained using sufficient sampling.

- *Statistical Information:*
  - A descriptive analysis of the safety data must be provided.

Study 2: Pediatric Efficacy and Safety Study for patients age 4 to 5 years with ADHD

- *Objective of each study:* The primary objective of Study 2 is to evaluate the efficacy and safety of methylphenidate in the treatment of ADHD.

- *Patients to be studied:*
  - *Age group in which studies* will be *performed*:
    - Pediatric patients 4 to 5 years old with ADHD.

  - *Inclusion* and *Exclusion Criteria*

- Screening procedures and inclusion and exclusion criteria must be agreed upon by the Agency in the protocol.
- Patients must have a DSM-5-defined diagnosis of ADHD using a clinically validated instrument for diagnosing psychiatric illnesses in preschool-aged children and confirmed with a clinical interview of patients and caregivers conducted by a clinician with appropriate clinical training and expertise in diagnosing psychiatric disorders in children.
- Study subjects must have:
  - Previously undergone an adequate course of non-pharmacological treatment or
  - Met *a priori*-specified ADHD severity criteria and, in the investigator's opinion, the child's condition was severe enough to warrant enrollment in this trial without having undergone non-pharmacological treatment.

- *Number of patients to be studied:*
  - Preschool-aged children (ages 4 and 5 years) to reflect the distribution of those affected with this condition.
  - 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.
  - The gender distribution of participants in this study must reflect the distribution of those affected with this condition.

- *Study Design:*
  - You must conduct a randomized, double-blind, placebo-controlled trial with a recommended duration of at least 6 weeks in preschool-aged children (ages 4 and 5 years). A flexible dose titration design may be used. This trial must provide the opportunity to detect a treatment effect of the drug in this population to inform labeling recommendations on dosing. For patients who discontinue study medication or discontinue from the trial, the reasons underlying such decisions must be collected and submitted (withdrawal of consent does not constitute an adequate explanation for such actions). The protocol must be submitted for comment prior to initiation of this study. You must obtain agreement on the final protocol prior to initiation of this study.

- *Study Endpoints:*
  - *Efficacy Endpoints*
    - Study 2 must use scales specific to ADHD that are sensitive to the effects of drug treatment in preschoolers with ADHD and have been validated for use within the preschool population and as agreed upon by the Agency in the protocol.

  - *Safety Endpoints*
    - Routine safety assessments must be collected at baseline and at appropriate time points during the study and at follow-up. These must include assessments and time points that are agreed upon by the Agency in the protocol.

- Safety endpoints must include vital signs (pulse rate and blood pressure), weight, height (using a stadiometer), ECG, clinical laboratory measures (creatinine, BUN, electrolytes), and adverse events.
- The study must include specific assessments of suicidal ideation and suicidal behavior.
- The study must include specific assessments of sleep, using a validated clinical rating scale, as agreed upon by the Agency in the protocol.

- *Known Drug Safety concerns and monitoring:*
  - Suicidality Assessments in Clinical Studies

    The Division of Psychiatry Products (DPP) has developed a policy that all clinical protocols for products developed in DPP, whatever the indication, include a prospective assessment for suicidal ideation and behavior. These assessments would need to be age-appropriate and be included in every clinical protocol, at every planned visit, and in every phase of development.

    For additional information, please see our draft guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf

    There are two reasons for implementing this policy. One is to ensure that patients in clinical trials who are experiencing suicidal ideation or behavior are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidal ideation/behavior. A second reason is to ensure that we collect better data than we have up to now, so that in the future we will be able to conduct additional metaanalyses on this matter.

  - *Data Monitoring Committee*
    A Data Monitoring Committee (DMC) must be included, because these will be large, multicenter studies of relatively long duration.

    See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees,*
    http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Statistical Information*
  - Study 2 must have a detailed statistical plan. The preliminary statistical analysis plan must be submitted for review and comment prior to initiation of this study. You must obtain agreement on the final statistical analysis plan prior to initiation of this study.
  - The study must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect (probably based on typical effects in children and adolescents) at a Type I error rate of 5% (two-sided). You must obtain agreement with the Division on the estimated size of the treatment effect prior to initiating the study. With respect to the primary efficacy analysis, the protocol will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients

randomized regardless of adherence, 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. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, following the recommendation from the National Academy of Sciences report on missing data in clinical trials. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

- To ensure your study is 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. Please provide the postulated magnitude of treatment effect and its standard deviation in your sample size planning.

- *Extraordinary results:*
  - In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR. 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.

Study 3: Pediatric Open-Label Safety Study for patients age 4 to 5 years with ADHD

- *Objective of each study:* The primary objective of Study 3 is to evaluate the long-term safety of methylphenidate in the treatment of ADHD.

- *Patients to be studied:*
  - *Age group in which studies will be performed*:
    - Pediatric patients 4 to 5 years old with ADHD.
    - The age and diagnosis will be assessed at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3.

  - *Inclusion and Exclusion Criteria*
    - Screening procedures and inclusion and exclusion criteria must be agreed upon by the Agency in the protocol.
    - For patients directly enrolling into Study 3, patients must have a DSM-5-defined diagnosis of ADHD using a clinically-validated instrument for diagnosing psychiatric illnesses in preschool-aged children and confirmed with a clinical

interview of patients and caregivers conducted by a clinician with appropriate clinical training and expertise in diagnosing psychiatric disorders in children.
- Study subjects must have
  - Previously undergone an adequate course of non-pharmacological treatment or
  - Met *a priori*-specified ADHD severity criteria and, in the investigator's opinion, the child's condition was severe enough to warrant enrollment in this trial without having undergone non-pharmacological treatment.

- *Number of patients to be studied:*
  - At least 50 preschool-aged children (ages 4 and 5 years at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled in Study 3) exposed for a minimum of 12 months.
  - 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.
  - The sex distribution of participants in this study must reflect the distribution of those affected with this condition.

- *Study Endpoints:*
  - *Safety Endpoints*
    - The safety study must include the identical safety assessments required in the controlled study. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
    - You must collect adequate longer-term safety data, with minimum drug exposure of 12 months. The longer-term safety data could come from an open-label study, e.g., a longer-term open-label extension study from the controlled efficacy trials, or from a separate longer-term open safety study(ies).

- *Known Drug Safety concerns and monitoring:*
  - *Suicidality Assessments in Clinical Studies*

    The Division of Psychiatry Products (DPP) has developed a policy that all clinical protocols for products developed in DPP, whatever the indication, include a prospective assessment for suicidal ideation and behavior. These assessments would need to be age-appropriate and be included in every clinical protocol, at every planned visit, and in every phase of development. For additional information, please see our draft guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf.

    There are two reasons for implementing this policy. One is to ensure that patients in clinical trials who are experiencing suicidal ideation or behavior are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidal ideation/behavior. A second reason is to ensure that

we collect better data than we have up to now, so that in the future we will be able to conduct additional metaanalyses on this matter.

- *Data Monitoring Committee*

  A Data Monitoring Committee (DMC) must be included because these will be large, multicenter studies of relatively long duration.

  See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees,*
  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Statistical Information:*
  - A descriptive analysis of the safety data must be provided.

- *Extraordinary results:*
  - In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR. 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.

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 methylphenidate 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 postmarket 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 Specification* at http://www.fda.gov/Cder/guidance/7087rev.htm.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before 31 December 2019. 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 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, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971, or email shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
05/11/2016