DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 22006
NDA 20427

Lundbeck Inc.
Attention: Mahlaqa Patel
Director, Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Patel:

Reference is made to your October 30, 2009 Proposed Pediatric Study Request for Sabril (vigabatrin) tablets and Sabril (vigabatrin) oral solution.

BACKGROUND:

The studies requested: (1) investigate the potential use of vigabatrin in the adjunctive treatment of pediatric patients age 10 years and above with refractory complex partial seizures, and (2) address post-approval issues in the use of vigabatrin as monotherapy for infantile spasms (IS).

To obtain needed pediatric information on vigabatrin, 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.

Background for Complex Partial Seizures:

Although several antiepileptic drugs have been approved for treatment of complex partial seizures in children, these seizures are often resistant to available drugs with up to 30% of pediatric patients not achieving acceptable seizure control. Vigabatrin has proved useful in controlling such seizures in treatment-resistant adults. One salient safety concern, loss of vision from vigabatrin-induced retinal damage, has resulted in the restriction of this drug's use to patients who have failed to achieve control with several alternative antiepileptic treatments; this has resulted in a REMS whose elements require patient and physician education and careful visual monitoring.

Vigabatrin may be a potentially useful drug in controlling seizures in pediatric patients. However, the extent of its usefulness and its safety profile are unknown. Approval for use in the pediatric population with refractory complex partial seizures will require studies of both vigabatrin's efficacy and its associated adverse effects, particularly decreased visual function, in the developing brain.

Efficacy in pediatric patients age 10 years and above with refractory complex partial seizures cannot be extrapolated and will be determined by the studies outlined in this Written Request.

Background for Infantile Spasms:

Vigabatrin is approved as monotherapy for IS in patients, ages 1 month -2 years. Several post-approval issues will be addressed for the IS population by the nonclinical and clinical studies outlined in this Written Request. Additional nonclinical studies are required to better understand the potential for developmental neurotoxicity in pediatric patients treated with vigabatrin. The pharmacokinetics of vigabatrin in very young infants age 1-5 months are not sufficiently defined and require further study. The optimal duration of treatment necessary to produce a sustained response to vigabatrin, defined as the cessation of spasms and hypsarrhythmia that persists after drug discontinuation, is not known and will be explored in a clinical study. The potential of cumulative toxicity of vigabatrin to vision and the difficulty in monitoring such changes makes it important to limit drug exposure.

NONCLINICAL STUDIES:

1. The neurotoxicity of vigabatrin in young animals needs to be further characterized. In addition to an increased sensitivity to the neurotoxic effects of vigabatrin seen in adults, the juvenile rat exhibits a different pattern of pathology. The brain lesions seen in the juvenile rat appear primarily in the neuropil (gray matter regions composed primarily of axons and dendrites), whereas in the adult rat the lesions appear primarily in white matter areas. In neither of the studies conducted in the juvenile rat (#OV-1007 or #OVNC-9004) were neuropathological examinations conducted at sufficiently early time points or conducted using appropriate histological techniques to definitively rule out the possibility of neuronal degeneration.

   In order to resolve this issue, a neurotoxicity study in the juvenile rat must be conducted and must use methodologies sufficient to more fully characterize the potentially unique neurotoxic effects of vigabatrin.

2. A juvenile animal toxicity study of vigabatrin in a non-rodent species must be performed in order to more fully understand the relevance to humans of the neurotoxicity findings observed in the juvenile rat. In this study, the age of the animals and the duration of dosing must be appropriate to the intended use in the pediatric population. Parameters to be assessed must include the standard toxicity parameters, as well as neurological examinations, bone densitometry, and an expanded neurohistopathologic evaluation.

The protocols for the above two nonclinical studies must be submitted to the Agency for review and approval before the studies are initiated.

CLINICAL STUDIES:

Indication: Intractable Complex Partial Seizures

Type of Study:

Study 1: Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study
Study 2: Long-Term Open Label Safety Study

Study Design:

Study 1: A multi-center, randomized, placebo-controlled, double-blind, parallel-arm design study evaluating the safety and efficacy of two fixed doses of vigabatrin as adjunctive therapy for a period of 18 weeks in pediatric patients age 10 to 16 years old with refractory complex partial seizures. There must be adequate stopping rules based upon visual deficits identified through monitoring.

Study 2: A multi-center open label long-term study of at least one year duration to monitor the safety of vigabatrin in pediatric patients age 10 to 16 years old with refractory complex partial seizures. There must be adequate stopping rules based upon visual deficits identified through monitoring.

Objectives/Rationale:

Study 1:

Primary objective:

To examine efficacy of two dosages of adjunctive vigabatrin treatment over a period of 18 weeks in pediatric patients 10-16 years of age with refractory complex partial seizures.

Secondary objectives:

To determine the general safety profile of vigabatrin when administered for up to 18 weeks and to specifically monitor for decreased visual function and other central nervous system effects which must include specific neurobehavioral and neurocognitive measures.

To characterize the population pharmacokinetics and PK/PD of vigabatrin in pediatric patients, 10-16 years of age, with refractory complex partial seizures.

Study 2:
To study long-term safety (up to one year) of vigabatrin in pediatric patients ages 10 years and above. The long-term safety data must come from this open-label study. This open-label study

may consist of an open-label extension from the controlled efficacy trial and/or a separate longer-term open safety study. The long-term safety data must be at or above the dose or doses identified as effective in the adequately designed trial, as described above. These data must include at least 50 patients, in the above noted age range, with exposures of at least 6 months and at least 20 patients with exposures of at least 1 year. Important elements of safety monitoring must include visual function testing as well as neurodevelopmental, neurobehavioral, and neurocognitive measures.

Indication to be studied:

Studies 1 and 2: The use of vigabatrin for the adjunctive treatment of refractory complex partial seizures in pediatric patients age 10 years and above who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. Vigabatrin is not indicated as a first line agent for complex partial seizures.

Patients to be studied:

- Age group in which studies will be performed:
  - Studies 1 and 2: Pediatric patients age 10 to 16 years of age inclusive.
- Number of patients to be studied (for both studies at least 35% of patients should be included in each of the two age groups of 10 to <13 years of age and 13 to 16 years of age):
  - Study 1: Sample size must be based upon results from studies of vigabatrin previously performed in pediatric patients with partial complex seizures and pivotal studies in adult patients with partial complex seizures, the latter of which was used for drug approval. The targeted power must be 90%. You must provide detailed justifications for parameter estimates used in sample size calculation in the protocol and the statistical analysis plan, and these must be found acceptable by Agency review.

    For the assessment of pharmacokinetics, the study must have 80% power to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution of vigabatrin.

  - Study 2: at least 50 patients exposed to drug for a period of at least 6 months and at least 20 patients exposed to drug for a period of at least one year.

Study endpoints:

Study 1:

- Pharmacokinetic Endpoints: Pharmacokinetic parameters such as area under the curve, maximum concentration, average concentration, clearance, volume of distribution, half-life and absorption rate must be reported. Relationship between PK parameters (such as clearance and volume of distribution) and covariates including drug-drug interactions and demographic variables must be evaluated.

- Pharmacokinetic/Pharmacodynamic Endpoints: PK/PD analysis for the primary efficacy endpoint and safety must be conducted.

- Efficacy Endpoints: The primary efficacy endpoint will be the change from Baseline in mean monthly (28 days) seizure frequency of both complex partial seizures (CPS) and partial seizures secondarily generalized. This must be assessed by comparing the Baseline Phase to the combined Titration and Maintenance Phases and be based on seizure diaries maintained by the patient or caregiver.

- Important secondary endpoints may include:

    - The change from Baseline in mean monthly (28 days) frequency of CPS plus partial seizures secondarily generalized comparing the Baseline Phase to the Maintenance Phase.
    - The number of therapeutic successes as defined by a decrease of 50% or more in the mean monthly frequency of CPS plus partial seizures secondarily generalized, comparing the Baseline Phase to the Maintenance Phase.
    - Global evaluation of efficacy, an evaluation performed by the investigator at the end of the Maintenance Phase.

- Compliance must be measured.

Studies 1 and 2:

- Safety Endpoints*:* Data must be collected in Studies 1 and 2. Safety assessments must be collected at baseline and at appropriate follow-up intervals. Safety will be monitored and evaluated by descriptive statistics.

- Safety outcomes must include: vital signs, weight, height (using a stadiometer), clinical laboratory measurements (including CBC, electrolytes, renal function, hepatic function, glucose, cholesterol, total protein, calcium, CPK), ECGs, and monitoring for adverse effects.
  The following adverse events must be actively monitored for in both studies: sedation, dizziness, ataxia, tremor, weight gain, peripheral edema, peripheral neuropathy, loss of visual function and neurocognitive adverse events. The following adverse events for study 2: neurodevelopmental adverse events, and effects on somatic growth and sexual development. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- All adverse events must be captured when spontaneously reported.
- A Data Monitoring Committee must be used.

Known Drug Safety concerns and monitoring:

- Visual Toxicity: To determine the effects of vigabatrin on retinal structure and function, the following must be monitored as appropriate for individual patients: spectral domain optical coherence tomography (SD-OCT), automated static perimetry (full field horizontal meridian test and 30-2 SITA Fast test), extended tangent screen visual field testing, visual acuity Early Treatment Diabetic Retinopathy Study (ETDRS), and color vision (Roth-28). Visual testing must include baseline testing and post drug evaluations at least every 3 months.
- Animal studies indicate significant neurodevelopmental effects. Somnolence and fatigue have been identified in adult studies. Because of these findings you must monitor neurobehavioral, neurocognitive, and neurodevelopmental endpoints.
- Suicidality: Suicidality has been identified as a significant class effect of antiepileptic drugs. Because of this, you must include frequent prospective assessment of suicidality. An acceptable instrument should map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument. You can obtain information about the C-SSRS from Dr. Kelly Posner at Columbia University. (posnerk@childpsych.columbia.edu).
- Anemia in adults and children: Anemia must be monitored for and appropriately evaluated including necessary studies to determine etiology.
- Symptoms of peripheral neuropathy: Symptoms of peripheral neuropathy have been observed in adults. These have not been corroborated with objective measures. Patients must be monitored for signs and symptoms of peripheral neuropathy, and any patient who develops a suspected neuropathy must be fully evaluated with appropriate clinical testing which must include EMG, nerve conduction studies and diagnostic testing to rule out alternative causes.
- Weight Change: Patients' weight must be monitored.
- Edema. Edema has been observed in adults, which has not proven to be related to cardiovascular, renal or hepatic dysfunction. This must be assessed clinically and when detected cardiac, renal and hepatic causality should be ruled out.

Drug information:

- dosage form: an age-appropriate formulation
- route of administration: oral
- *regimen (Study 1):*
  - There must be three arms:
    - Low dose using 20 mg/kg/day (maximum dose of 1 g/day in BID dosing
    - High dose using 60 mg/kg/day (maximum dose of 3 g/day in BID dosing
    - Matching placebo in BID dosing
- *regimen (Study 2):* Dosage at or above dosages shown to be effective in Study 1.

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

Primary efficacy analysis (Study 1): The primary efficacy analysis will be the analysis of covariance (ANCOVA) on the ranked mean change from Baseline compared to the combined Titration and Maintenance Phases in monthly (28 days) seizure rate. The ANCOVA will include treatment group as a fixed factor and ranked baseline seizure rate as a covariate. This analysis will be performed on the Full Analysis Set (FAS) defined by the modified intent to treat set, which consists of patients who have received drug and have at least one post-drug primary endpoint evaluation. Several sensible sensitivity analyses for the primary efficacy endpoint will be pre-specified.

*Safety Analysis***:**

All analyses of vision testing will be descriptive and no formal hypothesis testing will be performed. Vision related tests will be summarized on each eye. Other safety analyses will also use descriptive statistics.

Population Pharmacokinetics:

The nonlinear mixed-effects modeling should be used for the analysis. Descriptive statistics should be provided for all pharmacokinetic parameters. Inter- and intra-individual variability for all parameters should be estimated. The relationship between PK parameters (such as clearance and volume of distribution) and covariates including drug-drug interactions and demographic variables must be evaluated.

Indication: Infantile Spasm (IS)

Type of Study:

Study 3*:* Pharmacokinetic Study in pediatric patients with IS 1-5 months of age

Study 4: Clinical Study in patients with IS to characterize the minimum duration of therapy required for sustained cessation of spasms

Study Design:

Study 3*:* Single or multiple dose pharmacokinetic study in pediatric patients with IS. The study may be a separate PK study or a PK substudy of an ongoing clinical study, such as Study 4.

Study 4: Randomized, multicenter superiority study comparing the results of 3 months duration of therapy to that of 6 months duration of therapy in patients with IS. The protocol for this study must be submitted to the Agency for review and approval before it is initiated.

Objectives/Rationale:

Study 3*:* To characterize the pharmacokinetics of vigabatrin in pediatric patients, 1-5 months of age, with infantile spasms.

Study 4: To compare spasm freedom during and following 3 months versus 6 months of treatment.

Indication to be studied:

Studies 3 and 4: Monotherapeutic treatment of IS

Patients to be studied:

Age Group:

Study 3: Patients 1-5 months of age inclusive with IS

Study 4: Patients 1 month to 2 years of age inclusive requiring vigabatrin as initial therapy for IS

Number of patients to be studied:

Study 3: For the assessment of pharmacokinetics, the study must have 80% power to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution of vigabatrin.

Study 4: Sample size for each arm should be based upon 80 % power to demonstrate superiority of one arm over the other. However, the sample size may be limited to lower numbers based upon feasibility of recruitment with proof of due diligence with regard to recruitment.

Study endpoints:

Study 3: Pharmacokinetic parameters such as area under the curve, maximum concentration, average concentration, clearance, volume of distribution, half-life and absorption rate must be reported.

Study 4: Comparison of the number of patients relapsing after 3 months of therapy compared to the number after 6 months of therapy

Known safety concerns and monitoring:

Safety Endpoints: Data must be collected in Studies 1 and 2. Safety assessments must be collected at baseline and at appropriate follow-up intervals. Safety will be monitored and evaluated by descriptive statistics.

- Visual Toxicity: Retinal toxicity with reduction in visual fields has been observed in adults and older children. Visual assessments testing to the extent possible for the infant population must include baseline testing and post drug evaluations at least every 3 months.
- Animal studies indicate significant neurodevelopmental effects. Somnolence and fatigue have been identified in adult studies. Because of these findings you must monitor neurobehavioral and neurocognitive, neurodevelopmental endpoints.
- Anemia in adults and children: Anemia must be monitored for and appropriately evaluated. This would include monitoring of routine lab work (i.e. CBC) and any other additional studies necessary to determine etiology.
- Weight Change: Patients weight must be monitored.
- Edema. Edema has been observed in adult, which has not proven to be related to cardiovascular, renal or hepatic dysfunction. This must be assessed clinically and when detected cardiac, renal and hepatic casualty should be ruled out.
- Other safety outcomes must include: vital signs, weight, length/height, clinical laboratory measurements (including CBC, electrolytes, renal function, hepatic function, glucose, cholesterol, total protein, calcium, CPK), ECGs, and monitoring for adverse effects.
- The following adverse events must be actively monitored: ataxia, tremor, sedation, loss of visual function. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- All adverse events must be captured when spontaneously reported.
- A Data Monitoring Committee must be used.

Drug information:

- *dosage* form: an age-appropriate formulation
- *route of administration: oral*
- *regimen (Study 3): approved doses in 1 to 5 months of age*
- *regimen (Study 3): approved doses in 1 month to 2 years of age*

Statistical Information:

Study 3: Statistical information must include descriptive statistics of vigabatrin pharmacokinetic parameters. These results must be compared to pharmacokinetic parameters obtained in infants (5 months -2 years) and children (4-14 years) in previous studies.

Study 4: Descriptive statistics must be used. Inferential statistics should be used depending on the adequacy of recruitment.

For Clinical Trials (Both Indications):

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- *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.

- 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.

- 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 compounded 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 compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded 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 compounding 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 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 vigabatrin 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 FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.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 http://wcms.fda.gov/InsideFDA/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/UCM027829?SSContributor=true.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before May 18, 2014. 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, 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 Stephanie N. Keefe-Parncutt, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Robert Temple, 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/

ROBERT TEMPLE
08/25/2011