IND 65229
NDA 22128
NDA 208984

WRITTEN REQUEST – AMENDMENT 3

ViiV Healthcare Company
Attention: Mark Pace
Project Manager, Global Regulatory Affairs, GlaxoSmithKline
5 Moore Drive,
PO Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Pace:[1]

Please refer to your correspondence dated June 7, 2019, requesting changes to FDA's November 28, 2006 Written Request for pediatric studies for maraviroc.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 28, 2006, and as amended on December 21, 2010 and October 16, 2015, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

These studies investigate the potential use of maraviroc in the treatment of HIV-1 infection in pediatric patients and/or prophylaxis of HIV-1 infection in exposed neonates.

Background:

Maraviroc is an antiretroviral (ARV) drug product belonging to the therapeutic class CCR5 co-receptor antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5 present on the cell membrane, thereby preventing the interaction between HIV-1 glycoprotein gp120 and CCR5, a necessary step for CCR5-tropic HIV to enter cells.

The course of HIV infection and disease in pediatric patients is sufficiently similar to HIV infection and disease in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. As maraviroc is an antiretroviral drug, pediatric patients with HIV infection are expected to respond similarly to adults treated with maraviroc if they achieve similar drug exposures.

[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.

Maraviroc is not currently recommended by the U.S. DHHS HIV treatment guidelines for the treatment of HIV-1 infected pediatric patients. This, together with the availability of more effective ARVs and the need for testing patients to establish CCR5 tropism prior to initiation of maraviroc, makes trials for the treatment of HIV-1 infection in pediatric patients infeasible or highly impractical, particularly for children less than 2 years of age. However, below 2 years of age maraviroc may have a role in the interruption of mother-to-child transmission of HIV. Currently, there are limited therapeutic options for the management of newborns with perinatal HIV exposure. Due to its unique mechanism of action (i.e., maraviroc blocks HIV entry into cells), maraviroc may provide a potential therapeutic benefit. Therefore, collecting pharmacokinetic and short-term safety data in the HIV-exposed neonatal population (from birth to ≤ 6 weeks of age) could potentially provide substantial public health benefit.

Because of these reasons, the Agency is amending the Pediatric Written Request to modify the requirements for the treatment of HIV-1 infection in children 1 month of age to adolescents and HIV-exposed neonates, as currently written. The amended Pediatric Written Request will ask for pharmacokinetic and safety data in HIV-exposed pediatric patients from birth to ≤ 6 weeks of age (to prevent the mother-to-child transmission of HIV), and in pediatric patients ≥ 2 years of age to adolescence (for HIV treatment).

In addition, recent preliminary evidence suggests that very early initiation of intensive treatment of HIV in neonates may lead to HIV remission. Initiation of empiric HIV therapy can be viewed as an example of early intensive ARV treatment. Once initiated, therapy is continued well beyond the neonatal or infancy period. The mechanistic characteristics of maraviroc, in combination with the unique immune system of newborns, suggest of the possibility that maraviroc, in combination with other ARVs may be a good candidate for initiation of early intensive treatment in HIV infected neonates. However, unlike assessing the pharmacokinetics and safety of maraviroc in exposed neonates and young infants, conducting a clinical trial in HIV-infected pediatric patients > 6 weeks to 2 years of age is infeasible or highly impractical.

The Agency and the Sponsor have thus agreed to use modeling and simulation to determine dosing recommendation for the age group between 6 weeks and 2 years of age. The use of modeling and simulation will be based on pharmacokinetic data obtained from HIV-infected pediatric patients ≥ 2 years of age and HIV-exposed neonates and young infants from birth to ≤ 6 weeks of age. The Agency must agree to the adequacy of the proposed modeling and simulation.

To obtain needed pediatric information on maraviroc (GSK382178; UK-427,857), 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), that you submit information from the following studies:

Indications to be studied:

Treatment of HIV infection in pediatric patients and/or prophylaxis of HIV infection in exposed neonates.

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

- HIV-infected pediatric patients from ~~1 month~~ 2 years of age to adolescence, and
- HIV-exposed neonates (born to HIV-infected mothers) from birth to ≤ 6 weeks of age.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including but not limited to:

1. Hepatotoxicity
2. Infection
3. Malignancy
4. Tropism switching

Safety of maraviroc must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. ~~A~~ Safety data from a minimum of 100 patients ~~with at least 24 weeks safety data~~ is required. Safety data must be collected for a minimum of 24 weeks in HIV infected pediatric patients and 16 weeks for HIV-exposed neonates (on or off treatment, as appropriate). The shorter duration for collection of safety data in HIV-exposed neonates (16 weeks) is acceptable because maraviroc exposure for prevention of vertical transmission of HIV will be short-term, i.e. for 6 weeks total duration.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose

pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Birth to ≤ ~~<~~ 6 weeks: 8
~~6 weeks to < 6 months: 6~~
~~6 months to < 2 years: 6~~
2 years to < 6 years: 12
6 years to < 12 years: 8
12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients must be approximately evenly distributed across the age range studied.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of ~~24~~16 weeks after start of therapy. In addition, please also submit plans for long-term safety monitoring in ~~HIV-exposed neonates and~~ HIV-infected pediatric patients who have received maraviroc.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts in treatment of HIV-infected pediatric patients.

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 November 28, 2006, as amended by this letter and by previous amendments dated December 21, 2010, and October 16, 2015, must be submitted to the Agency on or before January 15, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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

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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- 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.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that maraviroc 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).

- 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 your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be 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 these requirements and the submission of this information can be found on the Clinical Trials website.[3]

If you have any questions, call Saebyeol Jang, Regulatory Project Manager at (240) 402-9953 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

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

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AMENDED WRITTEN REQUEST #3

ViiV Healthcare Company
Attention: Mark Pace
Project Manager, Global Regulatory Affairs, GlaxoSmithKline
5 Moore Drive,
PO Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Pace:[4]

These studies investigate the potential use of maraviroc in the treatment of HIV-1 infection in pediatric patients and/or prophylaxis of HIV-1 infection in exposed neonates.

Background:

Maraviroc is an antiretroviral (ARV) drug product belonging to the therapeutic class CCR5 co-receptor antagonists. Maraviroc selectively binds to the human chemokine receptor CCR5 present on the cell membrane, thereby preventing the interaction between HIV-1 glycoprotein gp120 and CCR5, a necessary step for CCR5-tropic HIV to enter cells.

The course of HIV infection and disease in pediatric patients is sufficiently similar to HIV infection and disease in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. As maraviroc is an antiretroviral drug, pediatric patients with HIV infection are expected to respond similarly to adults treated with maraviroc if they achieve similar drug exposures.

Maraviroc is not currently recommended by the U.S. DHHS HIV treatment guidelines for the treatment of HIV-1 infected pediatric patients. This, together with the availability of more effective ARVs and the need for testing patients to establish CCR5 tropism prior to initiation of maraviroc, makes trials for the treatment of HIV-1 infection in pediatric patients infeasible or highly impractical, particularly for children less than 2 years of age. However, below 2 years of age maraviroc may have a role in the interruption of mother-to-child transmission of HIV. Currently, there are limited therapeutic options for the management of newborns with perinatal HIV

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exposure. Due to its unique mechanism of action (i.e., maraviroc blocks HIV entry into cells), maraviroc may provide a potential therapeutic benefit. Therefore, collecting pharmacokinetic and short-term safety data in the HIV-exposed neonatal population (from birth to ≤ 6 weeks of age) could potentially provide substantial public health benefit.

Because of these reasons, the Agency is amending the Pediatric Written Request to modify the requirements for the treatment of HIV-1 infection in children 1 month of age to adolescents and HIV-exposed neonates, as currently written. The amended Pediatric Written Request will ask for pharmacokinetic and safety data in HIV-exposed pediatric patients from birth to ≤ 6 weeks of age (to prevent the mother-to-child transmission of HIV), and in pediatric patients ≥ 2 years of age to adolescence (for HIV treatment).

In addition, recent preliminary evidence suggests that very early initiation of intensive treatment of HIV in neonates may lead to HIV remission. Initiation of empiric HIV therapy can be viewed as an example of early intensive ARV treatment. Once initiated, therapy is continued well beyond the neonatal or infancy period. The mechanistic characteristics of maraviroc, in combination with the unique immune system of newborns, suggest of the possibility that maraviroc, in combination with other ARVs may be a good candidate for initiation of early intensive treatment in HIV infected neonates. However, unlike assessing the pharmacokinetics and safety of maraviroc in exposed neonates and young infants, conducting a clinical trial in HIV-infected pediatric patients > 6 weeks to 2 years of age is infeasible or highly impractical.

The Agency and the Sponsor have thus agreed to use modeling and simulation to determine dosing recommendation for the age group between 6 weeks and 2 years of age. The use of modeling and simulation will be based on pharmacokinetic data obtained from HIV-infected pediatric patients ≥ 2 years of age and HIV-exposed neonates and young infants from birth to ≤ 6 weeks of age. The Agency must agree to the adequacy of the proposed modeling and simulation.

To obtain needed pediatric information on maraviroc (GSK382178; UK-427,857), 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), that you submit information from the following studies:

Type of studies:

1. A multiple-dose pharmacokinetic, safety and activity study of maraviroc in combination with other antiretroviral agents in HIV-infected pediatric patients

2. A multiple-dose pharmacokinetic and safety study of maraviroc in HIV-exposed neonates (born to HIV-infected mothers)

The objective of these studies will be to determine the pharmacokinetic and safety profile of maraviroc across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients and exposed neonates, and evaluate the activity of this dose (or doses) in treatment and/or prophylaxis.

Indications to be studied:

Treatment of HIV infection in pediatric patients and/or prophylaxis of HIV infection in exposed neonates.

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

- HIV-infected pediatric patients from 2 years of age to adolescence, and
- HIV-exposed neonates (born to HIV-infected mothers) from birth to ≤ 6 weeks of age.

Drug Information

Dosage form: age appropriate-formulation

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age- appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially-marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, 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 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 label 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 should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including but not limited to:

1. Hepatotoxicity
2. Infection
3. Malignancy
4. Tropism switching

Safety of maraviroc must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. Safety data from a minimum of 100 patients is required. Safety data must be collected for a minimum of 24 weeks in HIV infected pediatric patients and 16 weeks for HIV-exposed neonates (on or off treatment, as appropriate). The shorter duration for collection of safety data in HIV-exposed neonates (16 weeks) is acceptable because maraviroc exposure for prevention of vertical transmission of HIV will be short-term, i.e. for 6 weeks total duration.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Birth to ≤ 6 weeks: 8
2 years to < 6 years: 12
6 years to < 12 years: 8
12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients must be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics
Parameters such as C_{max}, C_{min}, T_{max}, $t_{1/2}$, AUC and apparent oral clearance.

Safety and tolerability
HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of 16 weeks after start of therapy. In addition, please also submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received maraviroc.

Activity
Assessment of changes in plasma HIV RNA levels and in CD4 cell counts in treatment of HIV-infected pediatric patients.

Resistance
Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving maraviroc, particularly from those who experience loss of virologic response.

Labeling that may result from the study (ies):

Information regarding dosing, safety and activity in HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers)

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to 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 one of the following designations should be used:

Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study (ies):

Reports of the above studies must be submitted to the Agency on or before **January 15, 2021**. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to your approved NDA with the proposed labeling changes you believe would be 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, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

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

2. The status of the supplement (withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, “Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions,” is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- 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.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that maraviroc 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).

- 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, approvable, not approvable); or
  - the exclusivity determination (i.e., granted or denied).

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 may be 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 these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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/

JOHN J FARLEY
10/03/2019 01:38:25 PM