DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203441

WRITTEN REQUEST

NPS Pharmaceuticals, Inc.
Attention: Diane C. Fiorenza, BS, RAC
Sr. Director, Regulatory Affairs Product
550 Hills Drive, 3rd Floor
Bedminster, NJ 07921

Dear Ms. Fiorenza:

Reference is made to your May 31, 2013, Proposed Pediatric Study Request for Gattex (teduglutide [rDNA origin]).

BACKGROUND:

Gattex® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. The Written Request will include two clinical studies to investigate the potential use of teduglutide in the treatment of pediatric patients with SBS at least 1 year of age.

Short Bowel Syndrome (SBS) has an incidence of 3-24.5 per 100,000 births per year.[1, 2] In children, the most common causes of SBS include necrotizing enterocolitis, complicated meconium ileus, abdominal wall defects, intestinal atresia or volvulus. Trauma and Crohn's disease are also contributing causes of SBS in older children. Causes of SBS in adults are generally similar to those of older children; other causes in adults include malignancy and complications from radiation therapy. The greatest morbidity in children with SBS is parenteral nutrition-associated liver disease (PNALD), which is associated with significantly lower survival than children on parenteral nutrition (PN) without cholestatic liver disease. In addition, longer duration on PN is associated with more severe liver disease, more frequent catheter-related infections, and a higher likelihood of intestinal transplantation.[3] Currently, there are no approved pharmaceutical therapies to treat pediatric patients with SBS who are dependent on parenteral support.

[1] DeLegge M, Alsolaiman MM, Barbour E, Bassas S, Siddiqi MF, Moore NM. Short bowel syndrome: parenteral nutrition versus intestinal transplantation. Where are we today? *Dig Dis Sci* 2007; 52:876-92.
[2] Wales PW, de Silva N, Kim J, Lecce L, To T, Moore A. Neonatal short bowel syndrome: population based estimates of incidence and mortality rates. *J Pediatr Surg* 2004; 39(5):690-5.
[3] Squires et al. for the Pediatric Intestinal Failure Consortium. Natural History of Pediatric Intestinal Failure: Initial Report from the Pediatric Intestinal Failure Consortium. *J. Pediatr* 2012; 161:723-8.

Studies in infants under 3 months of age with SBS, including neonates, are not required as part of this Written Request because Gattex is intended to treat a pediatric patient population who is unable to decrease parenteral support for at least 3 months despite standard of care therapy.

Disease progression and response to intervention are sufficiently similar in adult and pediatric patients with SBS to support extrapolation of efficacy from adults to pediatric SBS patients. However, there are inadequate data to support a similar exposure-response relationship between the two patient populations to support full extrapolation. Therefore, partial extrapolation of efficacy can be based on an adequate dose-ranging study in children to select the dose that achieves the target pharmacodynamic effect.[4,5] The pharmacokinetic modeling must be conducted using all available adult and pediatric data to determine appropriate dose(s) for the pediatric patient population.

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

- *Nonclinical study(ies)*:

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

- *Clinical studies:*

  Study 1: A 12-week, multicenter, open-label, dose-finding, parallel group study evaluating pharmacokinetics, pharmacodynamics and safety of at least 3 doses of teduglutide in teduglutide-naïve pediatric patients less than 17 years of age with SBS who have not been able to decrease PN requirement for at least 3 months before study enrollment.

  Study 2: A 24-week, multicenter, randomized, double-blind, parallel group study evaluating pharmacodynamics and safety of at least 2 doses of teduglutide, compared to standard-of-care, in teduglutide-naïve pediatric patients less than 17 years of age with SBS who have not been able to decrease PN requirement for at least 3 months before study enrollment.

  Patients enrolled in Studies 1 and 2 will continue to be followed in a long-term extension safety study or registry that captures known and/or unexpected adverse reactions and evaluates for the persistence of efficacy for at least one year. This extension study would not need to be completed to fulfill the Written Request, but the study would need to be initiated and an interim clinical study report with datasets containing at least 6 months of evaluable safety data must be submitted to fulfill the Written Request.

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[4] Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf)

[5] Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

Efficacy in SBS patients less than 17 years will be supported by partial extrapolation of efficacy from adequate and well-controlled studies in adults. Dose selection must be supported by the exposure-response (ER) relationship based on the pharmacodynamic measurement of decreased PN requirement in children. Additionally, adequate safety data will be collected for all doses that are identified and for all ages for which the drug will be labeled, including affected children up to and including 12 years and adolescents ages 13 to less than 17 years.

There must be multiple dose arms over an adequate dose range. The number of patients in each dose group and age group must be reviewed and agreed upon with the Agency.

Study 1 must be conducted prior to Study 2. In addition, population pharmacokinetic modeling must be performed using all available adult and pediatric data upon completion of Study 1.

- *Objective of each study:*

  Study 1: To assess the pharmacokinetics, pharmacodynamics and safety of a minimum of 3 doses of teduglutide

  Study 2: To assess the pharmacodynamics and safety of multiple doses of teduglutide (a minimum of 2 doses determined from Study 1, blinded to both investigators and patients), compared to a standard-of-care arm

- *Patients to be Studied:*

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

    Studies 1 and 2: less than 17 years old

  - *Number of patients to be studied:*

    Study 1: at least 24 patients (at least 8 per each of the three dose arms)

    Study 2: at least 28 patients (at least 10 per each of the two dose arms and 8 in the standard-of-care arm)

Diligent and reasonable efforts must be made to encourage enrollment across all age groups to provide adequate dosing information for labeling, and these efforts must be documented in the study report.

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

- *Study endpoints:*

  ☐ *Pharmacokinetic Endpoints:*
  The pharmacokinetic endpoints for Study 1should include AUC, Cmax, Tmax, $T_{1/2}$, CL/F, and Vd/F. The data collected must be able to identify doses to be used in study 2.

  ☐ *Efficacy/Pharmacodynamic Endpoints:*
  - ☐ The primary efficacy/pharmacodynamic endpoint is at least 20% reduction in parenteral nutrition (PN) volume at 12 weeks (Study 1) or 24 weeks (Study 2) or end of therapy if the participant comes entirely off of PN support before study completion, compared to baseline.

  - ☐ Important secondary endpoints for Study 1 and Study 2 should include:
    - 100% reduction in PN/IV volume support (i.e., able to completely wean off PN/IV support), compared to baseline, at study completion
    - Decrease in parenteral support (calories and volume)
    - Increase in enteral nutritional tolerance (calories and volume)
    - Change in weight, height/length, and head circumference (where appropriate)
    - Change in hours per day or days per week of PN/IV support
    - Ostomy output/stool balance testing

  ☐ *Safety Endpoints (Study 1 and Study 2):*
  - ☐ Safety outcomes must include reporting of adverse events, tolerability, vital signs (including blood pressure and heart rate), laboratory parameters (including electrolytes, glucose, liver enzymes, lipase, and amylase), growth parameters (including replicated weight, height/length, and head circumference), intake and output (both urinary and fecal), and antibodies to teduglutide.

  - ☐ A Data Safety Monitoring Board (DSMB) must be employed. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf.

- *Known Drug Safety concerns and monitoring:*
  The following known drug specific safety concerns will be actively monitored, assessed with the appropriate intervention when indicated (e.g., colonoscopy, imaging, etc.), and reported: neoplastic growth, intestinal obstruction, biliary and pancreatic disease, and fluid overload. If patients develop any of these adverse events, they must be monitored until symptom resolution or until the condition stabilizes.

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

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

- *Drug information:*

  - *dosage form*: single-dose vials containing the following amount of teduglutide as a lyophilized powder: 1.25mg/vial, 2.5mg/vial and 5mg/vial. The lyophilized powder will be reconstituted with 0.5mL of sterile water for injection, which will be provided in a prefilled syringe
  - *route of administration:* subcutaneous injection
  - *regimen:* once daily

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

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

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

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

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

- *Statistical information, including power of study(ies) and statistical assessments:* Efficacy will be based on partial extrapolation from adult efficacy data; therefore, Studies 1 and 2 are neither designed nor powered to demonstrate differences between treatment groups. Descriptive statistics will be performed to summarize the data. The number of patients in each dose group and age group must be reviewed and agreed upon with the Agency.

- *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 teduglutide 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 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 Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before June 21, 2018. 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 CDR Matthew Brancazio, Pharm.D., Regulatory Project Manager, at (301) 796-5343

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JULIE G BEITZ
06/12/2015