IND 077219

WRITTEN REQUEST – AMENDMENT 1

Advanced Accelerator Applications
Attention: Christopher Jordan
Americas Head, Regulatory Affairs
57 East Willow Street
Millburn, NJ 07041

Dear Mr. Jordan:

Please refer to your correspondence dated December 22, 2020, requesting changes to FDA's October 26, 2020 Written Request for pediatric studies for lutathera.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on October 26, 2020, remain the same.

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 October 26, 2020, as amended by this letter must be submitted to the Agency on or before October 25, 2023, 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.

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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Kwadwo Korsah, Regulatory Project Manager, at 301-796-6630.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended (Clean and track changes)

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

IND 077219

WRITTEN REQUEST-AMENDMENT: 1

BACKGROUND:
Lutathera is a radiolabeled somatostatin analog that has high affinity for somatostatin subtype 2 receptor (SSTR2). The drug substance Lu 177 Lutathera® (Lutetium Lu 177 dotatate) is approved in the United States since January 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP- NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

GEP-NETs constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system and usually have high levels of SSTR2 expression. The main risks arising from treatment with Lutathera are radiation toxicities affecting either kidney function or bone marrow. The risk of renal toxicity is minimized through co-infusion of an amino acid solution during administration of Lutathera, which reduces the radiation dose to the kidneys by approximately 45%. Hematological toxicities are adequately managed via dose modifications recommended in the product label.

GEP-NETs are very rare in the pediatric population, with an incidence rate per 100,000 of 0.27 for adolescents aged 12–<18 years and 0.03 in children aged <12 years. GEP- NETs in children <12 years of age are nearly all represented by appendiceal NETs diagnosed at Stage 1 which rarely present with metastasis, can be removed surgically, and are not in scope of Lutathera or any other systemic treatment. GEP-NETs diagnosed in adolescents 12-<18 years of age range from Stage I to Stage IV, include metastatic disease, and are in scope for Lutathera treatment. There are currently no approved therapies for GEP-NETs in adolescents. The requested study will provide evidence for the safe and effective use of Lutathera in adolescent GEP-NETs

Reference ID: 4713583

patients, a patient population with high unmet need. Given the markedly diminished incidence in younger children, pediatric assessment of Lutathera will focus on the adolescent population. Accordingly, pediatric population from 0 to <12 years old will not be included in the investigation of Lutathera.

Pheochromocytomas and paragangliomas (PPGLs) are also rare neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla or sympathetic/parasympathetic ganglia. The pathophysiology of these diseases is not substantially different in adolescents compared to adult patients. The incidence of PPGL in the entire pediatric population is extremely low with only single cases recorded in SEER registry in 2019, corresponding to the rate lower than 0.03 per 100,000 population. Increased SSTR expression in PPGL, particularly that of SSTR2, has been demonstrated by uptake on somatostatin receptor scintigraphy, thus providing the rationale for the investigation of the potential use of Lutathera in these indications. Published literature (Satapathy 2019) and data from the Erasmus Medical Center study that supported the original NDA submission for Lutathera included a limited number of adult patients with PPGL treated with the approved dose and regimen of Lutathera suggesting that Lutathera may have activity for treatment of PPGL. The requested study will also explore the safety, dosimetry and efficacy of Lutathera in adolescent patients with PPGL.

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.

To obtain needed pediatric information on Lutathera, 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 nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

  Study 1: Study CAAA601A32201 (NETTER-P): a multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive GEP-NETs (Cohort 1, to support extrapolation from the adult indication) and PPGLs (Cohort 2, as an exploratory cohort to evaluate safety, dosimetry and efficacy).

- *Study Objectives:*

Reference ID: 4737533

Co-primary objectives:

- Evaluate organ absorbed radiation doses from peptide receptor radionuclide therapy (PRRT) with Lutathera in adolescent patients with SSTR-positive GEP-NETs
- Evaluate safety and tolerability of Lutathera in adolescents with SSTR- positive GEP-NETs

Secondary objectives:

- Evaluate cumulative safety of Lutathera in adolescents with SSTR-positive GEP-NETs
- Evaluate long-term safety of Lutathera in adolescents with SSTR-positive GEP-NETs
- Perform comparative assessment of dosimetry and pharmacokinetics (PK) between adolescent patients with GEP-NETs and adult patients using the extrapolation model developed for the clinical study

Exploratory objectives:

- Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent patients with SSTR-positive PPGL
- Evaluate safety and tolerability (after 1st administration, cumulative and long-term) of Lutathera in adolescents with SSTR-positive PPGL
- Perform comparative assessment of dosimetry and pharmacokinetics (PK) between adolescent PPGL patients and adult patients using the extrapolation model developed for the clinical study
- Assess the Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) in adolescent patients with SSTR-positive GEP- NETs and PPGL after treatment with Lutathera

- *Patients to be Studied:*

  - *Age groups to be studied:* Patients $\geq$ 12 year of age and <18 years

  - *Number of patients to be studied:*
    - A minimum of 8 patients $\geq$ 12 years of age with GEP-NETs for primary analysis

    - There is no minimum of patients to be studied with PPGLs and endpoint analyses will be conducted only on data derived from adolescent patients with GEP-NETs.

Reference ID: 4713583

- *Study endpoints:*

  Primary endpoints:
  - Target organ (e.g. kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive GEP-NETs
  - Incidence of adverse events (AEs) and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive GEP-NETs

  Secondary endpoints:
  - Incidence of AEs and laboratory toxicities until 6 months after the last Lutathera dose (short-term follow-up) in adolescents with SSTR-positive GEP-NETs
  - Incidence of AEs and laboratory abnormalities during the long term follow-up of 5 years after the last Lutathera dose in adolescents with SSTR-positive GEP-NETs
  - Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent patients with SSTR-positive GEP-NETs compared to the predicted distribution / organ absorbed doses

  Exploratory endpoints:
  - Target organ (e.g. kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive PPGL
  - Incidence of adverse events (AEs) and laboratory toxicities after the1st Lutathera administration in adolescents with SSTR-positive PPGL
  - Incidence of AEs and laboratory toxicities until 6 months after the last Lutathera dose (short-term follow-up) in adolescents with SSTR-positive PPGL
  - Incidence of AEs and laboratory abnormalities during the long term follow-up of 5 years after the last Lutathera dose in adolescents with SSTR-positive PPGL
  - Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent patients with SSTR-positive PPGL compared to the predicted distribution / organ absorbed doses from the extrapolation model developed for the study
    - ORR (rate of complete and partial responses), PFS (time from enrollment to the disease progression or death), and OS (time from enrollment to the dayof death) in adolescent patients with SSTR-positive GEP-NETs and PPGL

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

The tolerability and safety of Lutathera is well established in adults. The most frequent AEs with Lutathera are nausea, vomiting, fatigue, abdominal pain, diarrhea, decreased appetite, thrombocytopenia, lymphopenia, and anemia. The most common Grade 3-4

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adverse reactions are lymphopenia, increased GGT, vomiting, nausea, increased AST, increased ALT, hyperglycemia, and hypokalemia.

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

  Study 1: All statistical analyses will be descriptive in nature and will include summaries and graphical presentations of data. No statistical hypothesis will be tested.

  The primary analysis will focus on the extrapolation of adult data to adolescents in the GEP-NETs population. It will be performed after the last GEP-NETs has completed the first cycle (to include all data collected before the second dose of Lutathera), at which time both dosimetry and safety assessments of the first cycle will be complete for the assessment of the primary objective. Should the dosimetry assessments be done at a later cycle instead of first cycle, the primary analysis will be done after the dosimetry assessments are performed. Exploratory analysis of PPGL cohort will be provided at the same time.

  No formal sample size or power calculations were made in the context of this safety study.

  Literature review:
  AAA will conduct a comprehensive search for and review of all available safety data for Lutathera in the pediatric population (published literature and case reports in the Lutathera safety database, irrespective of indications).

  Pharmacokinetics/Pharmacodynamics Assessment
  Dosimetry and PK endpoints (i.e., AUC, Cmax, clearance) must be adequately determined with samples obtained from all the adolescent patients who participate in the study. Combine data from all studies to conduct population PK analysis (i.e., assess the effect of body weight and age on the PK/dosimetry of lutetium Lu 177 dotatate) to support extrapolation of efficacy to adolescent patients (12 to <18 years) with somatostatin receptor- positive GEP NETs. Efficacy in adolescent patients (12 to <18 years) will be supported by extrapolation based on similar dosimetry in adolescent patients with somatostatin receptor- positive GEP NETs compared to those in adults. Additional support will also be provided by analysis of adult and pediatric systemic exposures.

The following information pertains to all clinical studies in the Written Request.

- *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

Reference ID: 4713583

discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - Dosage form: Lutathera is available as 370 MBq/mL (10 mCi/mL) insingle-dose vial for infusion.
  - Route of administration: Intravenous.
  - Regimen: 7.4 GBq (200 mCi) administered intravenously every 8 weeks for a total of 4 doses (recommended Lutathera cumulative dose of 29.6GBq).

- *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 FD&C Act, regardless of whether the study(ies) demonstrate that Lutathera Lu 177 dotatate 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 FD&C 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 FD&C 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 600.80 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.[1] 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

[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.

Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before October 25, 2023. Please keep in mind that pediatric exclusivity attaches only to existing exclusivity, 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.

In accordance with section 505A(k)(1) of the FD&C 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

[4] www.ClinicalTrials.gov

Reference ID: 4737533

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.[3]

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 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 on the Clinical Trials website.[4]

If you have any questions, call Kwadwo (Kwajo) Korsah, Regulatory Project Manager, at 301-796-6630.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

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

[4] www.ClinicalTrials.gov

IND 077219

WRITTEN REQUEST

Advanced Accelerator Applications
Attention: Christopher Jordan
Americas Head, Regulatory Affairs 57
East Willow St
Millburn, NJ 07041

Dear Mr. Jordan:

Reference is made to your June 29, 2020 Proposed Pediatric Study Request (PPSR) for Lu 177 Lutathera® (Lutetium Lu 177 dotatate). We also reference your updated PPSR submitted on September 15, 2020, the Written Request issued on October 26, 2020, and the rescinded Written request issued December 7, 2020.

These studies investigate the potential use of Lu 177 Lutathera® (Lutetium Lu 177 dotatate) in the treatment of pediatric patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and pheochromocytomas/paragangliomas.

BACKGROUND:
Lutathera is a radiolabeled somatostatin analog that has high affinity for somatostatin subtype 2 receptor (SSTR2). The drug substance Lu 177 Lutathera® (Lutetium Lu 177 dotatate) is approved in the United States since January 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP- NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

GEP-NETs constitute a heterogeneous group of neoplasms arising from the diffuse neuroendocrine system and usually have high levels of SSTR2 expression. The main risks arising from treatment with Lutathera are radiation toxicities affecting either kidney function or bone marrow. The risk of renal toxicity is minimized through co-infusion of an amino acid solution during administration of Lutathera, which reduces the radiation dose to the kidneys by approximately 45%. Hematological toxicities are adequately managed via dose modifications recommended in the product label.

GEP-NETs are very rare in the pediatric population, with an incidence rate per 100,000 of 0.27 for adolescents aged 12–<18 years and 0.03 in children aged <12 years. GEP- NETs in children <12 years of age are nearly all represented by appendiceal NETs diagnosed at Stage 1 which rarely present with metastasis, can be removed surgically, and are not in scope of Lutathera or any other systemic treatment. GEP-NETs diagnosed in adolescents 12-<18 years of age range from Stage I to Stage IV, include metastatic disease, and are in scope for Lutathera treatment. There are currently no approved therapies for GEP-NETs in adolescents. The requested study will provide evidence for the safe and effective use of Lutathera in adolescent GEP-NETs

patients, a patient population with high unmet need. Given the markedly diminished incidence in younger children, pediatric assessment of Lutathera will focus on the adolescent population. Accordingly, pediatric population from 0 to <12 years old will not be included in the investigation of Lutathera.

Pheochromocytomas and paragangliomas (PPGLs) are also rare neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla or sympathetic/parasympathetic ganglia. The pathophysiology of these diseases is not substantially different in adolescents compared to adult patients. The incidence of PPGL in the entire pediatric population is extremely low with only single cases recorded in SEER registry in 2019, corresponding to the rate lower than 0.03 per 100,000 population. Increased SSTR expression in PPGL, particularly that of SSTR2, has been demonstrated by uptake on somatostatin receptor scintigraphy, thus providing the rationale for the investigation of the potential use of Lutathera in these indications. Published literature (Satapathy 2019) and data from the Erasmus Medical Center study that supported the original NDA submission for Lutathera included a limited number of adult patients with PPGL treated with the approved dose and regimen of Lutathera suggesting that Lutathera may have activity for treatment of PPGL. The requested study will also explore the safety, dosimetry and efficacy of Lutathera in adolescent patients with PPGL.

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.

To obtain needed pediatric information on Lutathera, 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 nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

  Study 1: Study CAAA601A32201 (NETTER-P): a multicenter open-label study to evaluate safety and dosimetry of Lutathera in adolescent patients with somatostatin receptor positive GEP-NETs (Cohort 1, to support extrapolation from the adult indication) and PPGLs (Cohort 2, as an exploratory cohort to evaluate safety, dosimetry and efficacy).

- *Study Objectives:*

Co-primary objectives:

- Evaluate organ absorbed radiation doses from peptide receptor radionuclide therapy (PRRT) with Lutathera in adolescent patientswith SSTR-positive GEP-NETs
- Evaluate safety and tolerability of Lutathera in adolescentswith SSTR- positive GEP-NETs

Secondary objectives:

- Evaluate cumulative safety of Lutathera in adolescents with SSTR-positive GEP-NETs
- Evaluate long-term safety of Lutathera in adolescents with SSTR-positive GEP-NETs
- Perform comparative assessment of dosimetry and pharmacokinetics (PK) between adolescent patients with GEP-NETs and adult patients using the extrapolation model developed for the clinical study

Exploratory objectives:

- Evaluate organ absorbed radiation doses from PRRT with Lutathera in adolescent patients with SSTR-positive PPGL
- Evaluate safety and tolerability (after 1st administration, cumulative and long-term) of Lutathera in adolescents with SSTR-positive PPGL
- Perform comparative assessment of dosimetry and pharmacokinetics (PK) between adolescent PPGL patients and adult patients using the extrapolation model developed for the clinical study
- Assess the Objective Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) in adolescent patients with SSTR-positive GEP- NETs and PPGL after treatment with Lutathera

- *Patients to be Studied:*

  - *Age groups to be studied:* Patients ≥ 12 year of age and <18 years

  - *Number of patients to be studied:*
    - A minimum of 8 patients ≥ 12 years of age with GEP-NETs for primary analysis

    - There is no minimum of patients to be studied with PPGLs and endpoint analyses will be conducted only on data derived from adolescent patients with GEP-NETs.

Commented [O1]: This title was accidently removed. Adding the title back in to be in line with the corresponding endpoints described later in the WR.

- *Study endpoints:*

  Primary endpoints:
  - Target organ (e.g. kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive GEP-NETs
  - Incidence of adverse events (AEs) and laboratory toxicities after the 1st Lutathera administration in adolescents with SSTR-positive GEP-NETs

  Secondary endpoints:
  - Incidence of AEs and laboratory toxicities until 6 months after the last Lutathera dose (short-term follow-up) in adolescents with SSTR-positive GEP-NETs
  - Incidence of AEs and laboratory abnormalities during the long term follow-up of 5 years after the last Lutathera dose in adolescents with SSTR-positive GEP-NETs
  - Calculated organ absorbed doses and PK parameters based on imaging/blood radioactivity concentration data from adolescent patients with SSTR-positive GEP-NETs compared to the predicted distribution / organ absorbed doses

  Exploratory endpoints:
  - Target organ (e.g. kidney and bone marrow) absorbed radiation doses in adolescents with SSTR-positive PPGL
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    - ORR (rate of complete and partial responses), PFS (time from enrollment to the disease progression or death), and OS (time from enrollment to the dayof death) in adolescent patients with SSTR-positive GEP-NETs and PPGL

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

The tolerability and safety of Lutathera is well established in adults. The most frequent AEs with Lutathera are nausea, vomiting, fatigue, abdominal pain, diarrhea, decreased appetite, thrombocytopenia, lymphopenia, and anemia. The most common Grade 3-4

adverse reactions are lymphopenia, increased GGT, vomiting, nausea, increased AST, increased ALT, hyperglycemia, and hypokalemia.

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

  Study 1: All statistical analyses will be descriptive in nature and will include summaries and graphical presentations of data. No statistical hypothesis will be tested.

  The primary analysis will focus on the extrapolation of adult data to adolescents in the GEP-NETs population. It will be performed after the last GEP-NETs has completed the first cycle (to include all data collected before the second dose of Lutathera), at which time both dosimetry and safety assessments of the first cycle will be complete for the assessment of the primary objective. Should the dosimetry assessments be done at a later cycle instead of first cycle, the primary analysis will be done after the dosimetry assessments are performed. Exploratory analysis of PPGL cohort will be provided at the same time.

  No formal sample size or power calculations were made in the context of this safety study.

  Literature review:
  AAA will conduct a comprehensive search for and review of all available safety data for Lutathera in the pediatric population (published literature and case reports in the Lutathera safety database, irrespective of indications).

  Pharmacokinetics/Pharmacodynamics Assessment
  Dosimetry and PK endpoints (i.e., AUC, Cmax, clearance) must be adequately determined with samples obtained from all the adolescent patients who participate in the study. Combine data from all studies to conduct population PK analysis (i.e., assess the effect of body weight and age on the PK/dosimetry of lutetium Lu 177 dotatate) to support extrapolation of efficacy to adolescent patients (12 to <18 years) with somatostatin receptor- positive GEP NETs. Efficacy in adolescent patients (12 to <18 years) will be supported by extrapolation based on similar dosimetry in adolescent patients with somatostatin receptor- positive GEP NETs compared to those in adults. Additional support will also be provided by analysis of adult and pediatric systemic exposures.

The following information pertains to all clinical studies in the Written Request.

- *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: Lutathera is available as 370 MBq/mL (10 mCi/mL) insingle-dose vial for infusion.
  - Route of administration: Intravenous.
  - Regimen: 7.4 GBq (200 mCi) administered intravenously every 8 weeks for a total of 4 doses (recommended Lutathera cumulative dose of 29.6GBq).

- *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 FD&C Act, regardless of whether the study(ies) demonstrate that Lutathera Lu 177 dotatate 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 FD&C 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 thestudy(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 FD&C 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 600.80 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.[1] 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

[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.

Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before October 25, 2023. Please keep in mind that pediatric exclusivity attaches only to existing exclusivity, 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.

~~If FDA has not determined whether Lutathera Lu 177 dotatate is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.~~

- *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 ~~biologics license~~new drug application (~~BLA~~NDA) or as a supplement to your approved ~~BLA~~ 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**

[4] www.ClinicalTrials.gov

Commented [O2]: The Agency added this paragraph which refers to the section 351(k)(7) of the PHS Act (Guidance for Industry - Reference Product Exclusivity for **Biological Products** Filed Under 351(a) of the PHS Act.)

As Lutathera is currently approved under a NDA, we believe that this section was inadvertently added.

Commented [O3]: As commented above, Lutathera is approved under NDA

EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C 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.[3]

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 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 on the Clinical Trials website.[4]

If you have any questions, call Kwadwo (Kwajo) Korsah, Regulatory Project Manager, at 301-796-6630.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

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

[4] www.ClinicalTrials.gov

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/s/

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GREGORY H REAMAN
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