CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208700Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

FROM: Steven Lemery, M.D., M.H.S.
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Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Addendum to Review, NDA 208700

Applicant: Advanced Accelerator Applications

On January 18, 2018, FDA and AAA held a telephone conference to discuss the appropriate administration recommendations for Lutathera. The primary concerns regarding the method of administration of Lutathera would be to administering health care staff as long as the intravenous line is intact and the instructions regarding "do not administer as a bolus" are followed [the risk of bolus administration may also be most pertinent to health care staff administering Lutathera due to manipulations that would be required to prepare the bolus]. (b) (4)

The FDA review team suggested to AAA during the review of the NDA that the product should be diluted and then hung. After further consideration, based on the applicant's justification, this procedure (to dilute), would increase the risk of radiation exposure to staff. The proposed procedure without dilution leaves the Lutathera vial in the lead container or behind appropriate shielding during the entirety of the infusion. Conversely, shielding a 500 mL bag may be a challenge to health care providers. Furthermore, AAA stated that they have no studies supporting the proposed dilution and that manipulation risks sterility failure.

AAA also stated that they have experience administering Lutathera safely during the NETTER-1 trial in more than 35 centers in the US and the EU. Lutathera has been administered to over 1,000 patients in the clinical development program and Lutathera stated during the call that they have not reported serious adverse events related to the procedure during the development program.

A review of the ADAE dataset for NETTER-1 was conducted to assess potential adverse events related to the procedure (e.g., in the SOCs General Disorders and Administration Site Conditions and Injury, Poisoning and Procedural Complications). There was one instance of extravasation

reported (verbatim term of right arm IV infiltration); however, the event was Grade 1 in severity and the patient recovered (infiltration can occur, however, irrespective of method for infusion). Other reports of injection site reaction or pain were included in the dataset; however, these occurred across both arms and the majority appeared related to IM injections of long-acting octreotide (which were administered in both arms). Grade 3 or greater events appeared unrelated to the infusion of Lutathera (e.g., pneumothorax during pacemaker insertion, SMV stent device occlusion, and G-tube malfunction). Review of SAEs from the Erasmus study did not appear to show any serious adverse events related to the administration of Lutathera (this reviewer acknowledges; however, that medication errors could have occurred without a report in the adverse event datasets if the patient was not affected).

Prior to the call, an internal meeting was held (see t-con memo) with review staff from DMEPA, ONDQA, DOP2, and DMIP. DMIP (with prior consultation with their radiopharmacist) agreed that the proposed procedure would be a safer procedure compared with the suggested method for dilution (and that the product should remain in the vial prior to administration). Although the administration procedure is unique, radiopharmaceuticals have a limited distribution and are only administered by physicians/centers that have met the requirements for an NRC license. Furthermore, there are a limited number of radiopharmaceuticals approved for the treatment of cancer. These products have different radioisotopes and different administration/storage considerations. DMIP stated that it is common for drug companies to submit brochures to the radiopharmacist (i.e., outside of the label). AAA has developed educational pieces intended to assist staff in the safe administration of the product. As stated above, these educational pieces will primarily be directed at the safety of the health care provider (and that these health care providers are limited to specially trained staff qualified in the safe handling and administration of radiopharmaceutical products).

During the call, DOP2 and DMEPA agreed that Section 2.5 of product labeling should be revised to provide more specific (and clear) instructions regarding the administration procedure. Educational pieces could then be drafted that are consistent with final agreed upon labeling.

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/s/

STEVEN J LEMERY
01/25/2018

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application/New Molecular Entity
Application Number(s)	208700
Priority or Standard	Priority review
Submit Date(s)	July 24, 2017 (resubmission)
Received Date(s)	July 26, 2017
PDUFA Goal Date	January 26, 2018
Division/Office	Division of Oncology Products 2/OHOP
Review Completion Date	
Established Name	Lutetium Lu 177 Dotatate
(Proposed) Trade Name	LUTATHERA
Pharmacologic Class	Radiolabeled somatostatin analog
Code name	None
Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Formulation(s)	Intravenous
Dosing Regimen	7.4 GBq every 8 weeks for four doses
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AESI	adverse events of special interest
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GBq	gigabecquerels
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mCi	milliCuries
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NET	neuroendocrine tumor
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PNET	pancreatic neuroendocrine tumors
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SWOG	South West Oncology Group
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

On March 31, 2016, Advanced Accelerator Applications, S.A. (AAA) submitted a New Drug Application (NDA) under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lutathera (lutetium Lu 177 dotatate) solution for intravenous use, a new molecular entity and radiolabeled somatostatin analogue (SSA) contained in a 30 mL single-use glass vial. A complete response (CR) letter was issued to AAA on December 19, 2016, listing deficiencies with the data submitted to support the application, and deficiencies in manufacturing sites identified during inspection. The current Type 2 NDA re-submission was received on July 26, 2017. The re-submission reasonably responds to all issues indicated in the CR letter, and correction of all inspection findings have been made with no recommendation for re-inspection deemed necessary. The drug formulation has a concentration of 370 MBq/mL, and is intended to be administered at a cumulative dose of 29.6 GBq divided into four separate administrations (b) (4) eight (b) (4) weeks apart. The proposed indication is treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendations for approval of Lutathera for the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults under 21 CFR 314 Subpart D are based on the results of two clinical trials. The trial providing primary support was an international, open-label trial of 229 patients in which statistically significant, robust, and clinically meaningful improvements in progression-free survival (PFS) were demonstrated for patients with histologically confirmed, advanced/inoperable or metastatic, somatostatin receptor (SSTR) positive midgut GEP-NETs that had progressed while on octreotide LAR who were treated with Lutathera. Support for the indication for the treatment of patients with GEP-NETs other than those arising in the midgut comes from a subset analysis of 360 patients in an investigator sponsored, open-label, single-arm, single-institution study of 1214 patients with SSTR positive neuroendocrine (NEC) tumors for whom improvement in overall response rates and response durations were both clinically meaningful and consistent with those for midgut NETs. In addition, the biology of this disease and the mechanism of action for Lutathera provide increased confidence that the benefits in PFS, overall response rate (ORR), and duration of response (DoR) observed in the clinical trials are accurate. This population of patients represents an unmet medical need, as available treatment options offer few true benefits. Lutathera has demonstrated consistent, statistically significant, and clinically meaningful improvements in PFS, ORRs, and DoRs for patients with GEP-NETs, and has met its burden of proof for demonstrating both safety and effectiveness under the prevailing statutory and regulatory standards.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The effectiveness of lutetium Lu 177 dotatate for adult patients with GEP-NETs is supported by data from two international, open-label trials demonstrating consistent, statistically significant, and clinically meaningful improvements in progression free survival and overall response rates for patients with GEP-NETs who were treated with lutetium Lu 177 dotatate. Health related Quality of Life (QoL) was assessed using the EOTC QLQ-30 and QLQ G.I.NET21 questionnaires in the NETTER-1 trial submitted in support of the application. The data were incomplete and flawed, preventing any inferences being drawn from the analyses of these data; therefore, the data were not considered in decision making during review of the application.

NETTER-1 enrolled 229 patients with histologically confirmed, advanced/inoperable or metastatic, SSTR positive midgut carcinoid tumors that had progressed while on octreotide LAR. Patients in NETTER-1 were randomized to lutetium Lu 177 dotatate (n=116) or octreotide LAR (113). Patients received either lutetium Lu 177 dotatate (7.4 GBq [200 mCi] every 8 weeks for up to 4 administrations; maximum cumulative dose of 29.6 GBq) with octreotide LAR (30 mg by intramuscular injection every 4 weeks) or octreotide LAR monotherapy (60 mg by intramuscular injection every 4 weeks). Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months). The primary endpoint was PFS based on an independent review assessment (IRC); and the trial was designed with 90% power at a 2-sided alpha level of 5%. ORR and overall survival (OS) were major secondary endpoint measurements that were tested in hierarchical order to adjust for multiplicity.

The statistical reviewer identified several flaws inherent in the NETTER-1 trial design. The trial used coin toss randomization for the first 28 patients and permuted block randomization for the remainder; the applicant's PFS and OS derivation used an imputed date, which does not provide a reliable estimate; there was an asymmetric delay in the first dose in the lutetium Lu 177 dotatate arm resulting in asymmetric time to tumor assessment from randomization; and the statistical analysis plan PFS analysis was intended to be performed when 74 PFS evaluable events were observed, with the same efficacy cut-off date, the application resubmission contained 91 PFS events, and FDA's analysis was based on 105 PFS events.

A statistically significant and clinically meaningful treatment effect on PFS was observed for patients treated with lutetium Lu 177 dotatate

compared to those treated with octreotide LAR. The estimated median PFS was not reached for patients in the lutetium Lu 177 dotatate arm compared to 8.5 months (95% CI: 5.8, 9.1) in the octreotide LAR arm; the un-stratified HR was 0.21 (95% CI: 0.13, 0.32); p-value <0.0001. Patients who received lutetium Lu 177 dotatate exhibited a statistically significant improvement in ORR as assessed by IRC compared to those treated with octreotide LAR. The ORR was 12.9% (95% CI: 7%, 19%) and 3.5% (95% CI: 0.1%, 7%) for lutetium Lu 177 dotatate and octreotide LAR, respectively, and the Fisher's exact test p-value is 0.0148. The estimated median OS for an updated analysis requested by FDA was not reached in the lutetium Lu 177 dotatate arm and 27.4 months (95% CI: 22.2, not evaluable) in the octreotide LAR arm, with a stratified HR of 0.52 (95% CI: 0.32, 0.84), and p-value of 0.0068.

The PFS analysis results for NETTER-1 with a HR=0.21 (95% CI: 0.13, 0.32); p-value <0.0001, together with the ORR of 12.9 in the lutetium Lu 177 dotatate arm and 3.5% in the octreotide arm, and a Fisher's exact p-value of 0.0068 represent statistically significant improvements for patients treated with lutetium Lu 177 dotatate and are consistent with the protocol pre-specified criteria. Regardless of the limitations in the study design described above and the data collection issues with the original application, the PFS result is both statistically significant and clinically meaningful for patients with this disease. This was confirmed by sensitivity analyses demonstrating an HR range from 0.15-0.46, which is supportive of the findings from this trial.

Additional support for the indicated population for Lutathera are based on the effects observed on ORR and DoR for patients with NETs other than those arising in the midgut. The ERASMUS Medical Center trial (ERASMUS) was an investigator-sponsored, open-label, single-arm, single-institution, expanded access study of 1214 patients with SSTR positive neuroendocrine (NEC) tumors conducted in The Netherlands from January 2000 through December 2012. Sixty-seven percent of enrolled patients were from the Netherlands, and the remaining 33% were referred from outside of the Netherlands. The study population was heterogeneous with respect to primary tumor site. Most patients had GEP-NETs of the foregut, midgut, hindgut, digestive tract, bronchus, and pancreatic neuroendocrine tumors (pNET). Other NETs were also included in the trial, specifically medullary thyroid cancer, pheochromocytoma, paraganglioma, neuroblastoma, and Merkel cell carcinoma. Non-NET SSRT positive tumors melanoma, non-differentiated thyroid cancers, non-small cell lung cancer, breast cancer, lymphoma, and malignant meningioma were also treated. In ERASMUS, lutetium Lu 177 dotatate 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. There was no pre-specified statistical analysis plan. The major efficacy outcome was investigator-assessed ORR. The response assessment criteria changed during the trial, with patients treated later being evaluated by RECIST, which is accepted for regulatory purposes.

To assess the impact of differences in response assessments in the trial, a sensitivity analysis was performed stratifying by date which correlates to responses assessed by investigators using SWOG criteria and converted algorithmically to RECIST criteria (patients before March 15, 2007) and responses assessed by investigators using RECIST (patients on or after 3/15/2007). Of 1214 patients enrolled in the trial, 360

(30%) had GEP-NETs and were included in the subset analysis. The mean age was 61 years, 52% were male, 61% had a baseline Karnofsky performance status of ≥ 90, 61% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. More than 90% of these patients received a concomitant somatostatin analogue.

The analysis of the two populations of patients demonstrated consistently higher estimates of ORR in the population assessed using SWOG criteria and converted to RECIST algorithmically. Limiting the analysis to patients evaluated on or after March 15, 2007, provided a more conservative estimate of benefit in this trial. There were 58 responders in the subgroup (CR: 3; PR: 55). The estimated response rate was 16% (95%CI: 12%, 20%). The median duration of response was 35 months (range: 0, 70+ months; 95% CI: 17.0, 38.0 months). Although from a subset of patients treated, these data provide statistically conservative estimates that were verifiable and are clinically meaningful for patients with GEP-NET. The results provide additional support for the indicated population that are consistent with the observed benefit in other populations of patients with the disease (i.e., in NETTER-1), the biology of the disease itself, the mechanism of action of lutetium Lu 177 dotatate, and the limited treatment options available for these patients.

The safety profile for lutetium Lu 177 dotatate in patients with GEP-NETS is characterized by exposure data from approximately 922 patients who received at least one dose of the drug and were treated in the two trials submitted to support safety: NETTER-1, and ERASMUS. The FDA safety review focused primarily on the patients treated in NETTER-1, with some additional analyses involving the Dutch patients from the ERASMUS trial, because data collection and follow-up data for these patients in the ERASMUS study appeared to be more complete.

Drug exposure in NETTER-1 was a total of ≥ 600 mCi of lutetium Lu 177 dotatate in 79.3% of patients treated, and 26% of patients received cumulative doses of ≥ 800 mCi. Seventy-six percent of patients received all four planned doses. Dose reductions were reported for 6% of patients and 13% of patients discontinued the drug. The median duration of follow-up for the lutetium Lu 177 dotatate and octreotide LAR arms was 24 and 20 months, respectively. The most common adverse reactions observed in patients treated with lutetium Lu 177 dotatate were nausea (65%), vomiting (53%), fatigue (38%), diarrhea (26%), abdominal pain (26%), and decreased appetite (21%). The most common Grade 3 and 4 adverse reactions with lutetium Lu 177 dotatate were lymphopenia (44%), increased GGT (20%) vomiting (7%), nausea and elevated AST (5% each), increased ALT, hyperglycemia, and hypokalemia (4% each).

Safety data from the ERASMUS trial included 811 patients; 65% received a total cumulative dose of ≥ 800 mCi, and 81% received a cumulative dose ≥ 600 mCi of lutetium Lu 177 dotatate. With a median follow-up time of more than 4 years, the most serious chronic toxicities reported were myelodysplastic syndrome (2%), renal failure (2%), cardiac failure (2%), acute leukemia (1%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

The benefit-risk assessment for lutetium Lu 177 dotatate weighs in favor of benefit for adult patients with SSTR positive GEP-NETs including foregut, midgut, and hindgut. There is an unmet medical need for these patients with inadequate treatment options with limited benefit. In addition to treatment of the tumor, patients with this disease can benefit from a prolonged progression-free interval and durable responses by a reduction in the often-debilitating symptoms associated with these tumors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neuroendocrine tumors (NETs) are a heterogenous group of tumors sharing a common origin, neuroendocrine cells of the embryological gut. • NETs are rare epithelial malignancies that are clinically diverse, and include both functional and non-functional tumors; they originate most commonly from the gastrointestinal tract and pancreas (gastroenteropancreatic neuroendocrine tumors [GEP-NETs]). • GEP-NETs are grouped by location and by whether the tumor is functional, i.e., whether they secrete peptide hormones that result in clinical symptoms. • Treatment of functional GEP-NETs requires management of clinical symptoms in addition to anti-cancer therapy.	Patients with inoperable, progressive, SSTR positive midgut carcinoid tumors represent a group of patients with an unmet medical need. These patients would not only benefit from alternative therapies to treat their tumors, but also the efforts to control the multiple hormone-related co-morbid conditions associated with these tumor types is lacking.
Current Treatment Options	• Systemic therapy options for well-differentiated, metastatic GEP-NETs include SSAs (e.g., octreotide, lanreotide), targeted therapies and chemotherapy. • SSAs are primarily used to manage the hormonal symptoms related to NETs; anti-proliferative activity has also been demonstrated by prolonged PFS in patients with NETs treated with octreotide and lanreotide. • Chemotherapeutic agents are streptozocin in combination with 5-fluorouracil or doxorubicin. Temozolomide, capecitabine, and oxaliplatin alone or in combination therapy have also demonstrated	A statistically significant and robust increase in PFS observed in the NETTER-1 trial represents a clinically meaningful advance for a tumor subpopulation with an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	anti-tumor activity. • Sunitinib is approved in the U.S. for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNETs) in patients with unresectable locally advanced or metastatic disease. Everolimus is approved in the U.S. for the treatment of progressive pNETs and progressive, well-differentiated, non-functional NETs of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic. • Peptide receptor radioligand therapy (PRRT) is a targeted approach using radiolabeled SSAs in patients with tumors that are determined to be SSTR-positive. The most commonly used radionuclides include yttrium-90 (90Y) and lutetium-177 (177Lu).	
Benefit	• NETTER-1 was a randomized (1:1), open-label, multi-national, and parallel-group trial comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate plus best supportive care to treatment with high dose octreotide LAR in patients with inoperable, SSTR positive, histologically proven, midgut carcinoid tumors, who exhibited progressive disease while on octreotide LAR. • The trial met its primary objective demonstrating an improvement in independent review committee-confirmed PFS compared to the control arm based on a total of 105 PFS events in the intent-to-treat (ITT) population. The un-stratified log-rank test p value was < 0.0001. Median PFS was not reached (95% CI: 18.4, NE) for the experimental arm and was 8.5 months (95% CI: 6.0, 9.1) for the control arm. The corresponding Cox un-stratified hazard ratio (HR) was 0.21 (95% CI: 0.13, 0.32) in the experimental arm compared to the control arm. The estimated HRs for the sensitivity analyses performed by FDA using different censoring methods ranged from 0.18 to 0.46.	A statistically significant, robust, and clinically meaningful increase in PFS observed in the NETTER-1 trial represents clinical benefit for this population of patients. Data from the ERASMUS trial provide relevant estimates of ORR and DoR that are clinically meaningful for patients and provide additional support for the indication. The biology of the disease, and the mechanism of action of lutetium Lu 177 dotatate provide further confidence that the estimates of the benefits observed in both clinical trials are accurate and clinically meaningful to patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• NETTER-1 also demonstrated ORRs of 12.9% (95% CI: 6.8%, 19.0%) and 4% (95% CI: 0.1%, 6.9%) in the experimental arm and control arm, respectively. The Fisher exact test p value was 0.0148. DoR was not reached for the Lutathera arm and was 1.9 (95% CI: 1.9, NE) for the octreotide arm. • The experimental arm for the NETTER-1 trial did not demonstrate a statistically significant improvement in OS compared with the control arm based on an immature analysis of 71 OS events from the ITT population as required by FDA. The pre-planned applicant's analysis of OS based on 46 deaths was also not statistically significant. The un-stratified log-rank test P value of 0.0094 was greater than the pre-planned two-sided significance level of 0.00008 at the applicant's OS interim analysis. Median OS was not reached for both arms. The corresponding un-stratified HR was 0.46 (95% CI: 0.25, 0.83) in the experimental arm compared to the control arm for the applicant's pre-planned analysis and 0.54 (95% CI: 0.33, 0.86) in the updated analysis. • In ERASMUS, lutetium Lu 177 dotatate 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses concurrently with the recommended amino acid solution. There was no pre-specified statistical analysis plan. The major efficacy outcome was investigator-assessed ORR. Of the 1214 patients enrolled, 360 (30%) had gastroentero-pancreatic neuroendocrine tumors (GEP-NETs) and were included in the subset analysis. The mean age was 61 years, 52% were male, 61% had a baseline Karnofsky performance status of ≥ 90, 61% had progressed within 12 months of treatment, and 15% had received prior chemotherapy. More than ninety percent (>90%) of these patients received a concomitant somatostatin analogue. There were 58 responders in this subgroup (CR: 3; PR: 55). The estimated response rate was 16% (95%CI: 12%, 20%). The median duration of response was 35 months (range: 0, 70+ months; 95% CI: 17.0, 38.0 months). Although from a subset of patients treated, these data provide statistically conservative	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	estimates that were verifiable and are clinically meaningful for patients with GEP-NET. Although from a subset of patients treated in this expanded access trial, these data provide statistically relevant estimates that are clinically meaningful for patients and provide additional support for the indication, especially when one considers the biology of the disease, the mechanism of action of lutetium Lu 177 dotatate, and the limited treatment options available for these patients.	
Risk and Risk Management	• The most significant risks arising from treatment with Lutathera are radiation toxicities affecting either bone marrow or kidney function. Kidney function risks are reduced by the use of an amino acid solution co-infusion during administration of 177Lu-DOTA0-Tyr3-Octreotate, which decreases radiation doses to the kidney by approximately 45%. Bone marrow toxicity occurs both acutely and chronically. The most frequent AEs with 177Lu-DOTA0-Tyr3-Octreotate were nausea (59%), and vomiting (47%), the majority related to the co-infusion of the commercial amino acids solution used for kidney protection. Other adverse events in the 177Lu-DOTA0-Tyr3-Octreotate arm included fatigue, diarrhea and abdominal pain; the large majority (≥97%) were grade 1 or 2 in severity. Among patients who received octreotide LAR, the most common AEs were gastrointestinal disorders and fatigue. Grade 3/4 AEs occurred at a similar frequency between the two arms; however, grade 3 and 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2% and 9% of patients in 177Lu-DOTA0-Tyr3-Octreotate arm versus none in controls. • 177Lu-DOTA0-Tyr3-Octreotate is intended to be administered by physicians who have expertise in the administration of radiolabeled drugs and in concert with physicians having expertise in radio-	In addition to labeling, two postmarketing requirements (PMR) under section 505(o) will be included with the approval to follow late toxicities from the drug, specifically renal toxicity, and the development of myelodysplastic syndrome and acute leukemia. Refer to section 13 of this review for the specifics of each PMR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	imaging. • Because of the mechanism of clearance for this drug, there is radioactivity retention in the kidneys. Concomitant administration of amino acids reduces renal uptake of radioactivity (by about half) without altering tumor uptake. Amino acids co-infusion is mandatory during treatment. Before each administration and during the treatment biological tests are required to re-assess the kidney and bone marrow function. • To avoid treatment-related nausea and vomiting, an intravenous bolus of an antiemetic drug is recommended 30 minutes before the start of the treatment. • It could be necessary to suspend treatment, adapt the dose after the first administration or even definitively discontinue the treatment. The criteria for these scenarios will be described in product labeling. • Patients with certain risk factors could be prone to develop adverse events, and in certain instances, e.g., previous external beam radiotherapy involving more than 25% of the bone marrow, treatment is not recommended. The criteria for these scenarios will be described in product labeling.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:					Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as				[e.g., Section 6.1 Study endpoints]
			x	Patient reported outcome (PRO) Health related Quality of Life (QoL), EOTC QLQ-30, and QLQ G.I.NET21 questionnaires		19.5.2
			□	Observer reported outcome (ObsRO)		
			□	Clinician reported outcome (ClinRO)		
			□	Performance outcome (PerfO)		
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)				
	□	Patient-focused drug development or other stakeholder meeting summary reports				[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data				
	□	Natural history studies				
	□	Patient preference studies (e.g., submitted studies or scientific publications)				
	□	Other: (Please specify)				
□	Patient experience data that was not submitted in the application, but was considered in this review.					

X _____

Suzanne G. Demko
Cross-Disciplinary Team Leader

2. Therapeutic Context

Analysis of Condition

(This section is reproduced from the original NDA review as written by Dr. Joohee Sul and is included here for continuity.)

Neuroendocrine tumors (NETs) are a relatively rare, clinically diverse group of epithelial malignancies that originate most commonly from the gastrointestinal tract and pancreas (gastroenteropancreatic neuroendocrine tumors [GEP-NETs]). In the U.S., an analysis of the Surveillance, Epidemiology, and End Results (SEER) data indicates a rise in the age-adjusted incidence of NETs from 1.9 to 5.25 cases per 100,000 people between 1973 and 2004.[1] These tumors can arise in the setting of inherited genetic syndromes such as multiple endocrine neoplasia (MEN) 1 and 2; however, most occur sporadically and are generally classified by site of origin, stage, ability to cause clinical symptoms and tumor differentiation.

These tumors are principally divided into those that are well-differentiated and poorly-differentiated, with the distinction made based on the degree of cell differentiation, tumor architecture, and tumor grade. The World Health Organization (WHO) classifies GEP-NETs into low-grade (G1), intermediate grade (G2), and high grade (G3) categories, based upon mitotic count, assessment for necrosis, and proliferative index or Ki-67.[2] The European Neuroendocrine Tumour Society (ENETS) stratifies tumors by grade and stage,[3,4] and both organizations combine grading with staging using the tumor-node-metastasis (TNM) system. GEP-NETs are also described by the tissue of origin with tumors of the lung, thymus, stomach, duodenum, and pancreas considered foregut tumors; tumors of the ileum, cecum and proximal colon are midgut tumors; and tumors of the distal colon and rectum are hindgut tumors.

GEP-NETs may be further characterized as functional or non-functional, depending on whether they secrete peptide hormones that result in clinical symptoms. Functional GEP-NETs are generally well-differentiated, and these tumors are codified to reflect the hypersecreted hormone (e.g. insulinoma, gastrinoma). The most commonly produced hormone is serotonin, which results in “carcinoid syndrome” that is characterized by flushing and diarrhea. The clinical symptoms associated with functional tumors frequently lead to their diagnosis at an earlier stage compared with non-functional tumors that often present with symptoms related to mass effect or metastatic disease. The majority of well-differentiated GEP-NETs express somatostatin receptors (SSTRs) and can be imaged using a radiolabeled form of the somatostatin analog octreotide (e.g. 111-In pentetreotide). Treatment of functional GEP-NETs requires management of clinical symptoms in addition to anti-cancer therapy.

The natural history of GEP-NET varies considerably and appears to be affected by the primary site of disease, degree of differentiation, expression of SSTRs, and presence of metastases at

diagnosis. Tumors of the gastrointestinal tract and pancreas have similar histologic appearances, but pancreatic NETs (pNETs) tend to have a more aggressive course, albeit with higher responses to systemic therapy. The approach to initial treatment of GEP-NET consists of wide surgical resection for limited or locally advanced disease, if feasible, and treatment of hormone-related symptoms. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option, while somatostatin analogs (SSAs) such as octreotide are used for patients with hormone-related symptoms. Although SSAs were primarily used to manage the hormonal symptoms related to NETs, in vitro studies demonstrated the potential for SSAs to exert anti-proliferative activity and clinical studies have demonstrated prolonged PFS in patients with NETs treated with octreotide and lanreotide.

The prognosis for patients with metastatic well-differentiated GEP-NETs is highly variable. Based on retrospective analyses of large databases, the median OS for patients with metastatic pancreatic NETs has been reported to range from 2-5.8 years[1,5] while the median OS for small bowel NET has been reported as 7.9 years.[6]

2.2 Analysis of Current Treatment Options

(This section is reproduced from the original review as written by Dr. Joohee Sul and is included here for continuity.)

Systemic therapy options for well-differentiated, metastatic GEP-NETs include SSAs (e.g., octreotide, lanreotide), targeted therapies, and chemotherapy.

Somatostatin analogs (SSAs):
Although SSAs are primarily used to manage the hormonal symptoms related to NETs, in vitro studies demonstrated the potential for SSAs to exert anti-proliferative activity and clinical studies have demonstrated prolonged PFS in patients with NETs treated with octreotide and lanreotide. SSAs exert their effects through binding to SSTRs and the presence of these receptors, determined using radionuclide scintigraphy, is generally predictive of response to these agents. Octreotide may be administered as a short acting formulation or as a longer active depot formulation. Octreotide is approved for the symptomatic treatment of patients with GEP-NETs. Lanreotide is another long-acting depot formulation that is approved in the U.S. for the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic GEP-NETs, to improve progression-free survival.

Chemotherapy:
Traditional chemotherapeutic agents include streptozocin in combination with 5-fluorouracil or doxorubicin. Temozolomide, capecitabine, and oxaliplatin alone or in combination therapy have also demonstrated anti-tumor activity. Streptozocin is approved in the U.S. for the treatment of metastatic pancreatic islet cell cancer, and has been the backbone of combination treatment regimens with 5-fluorouracil and doxorubicin; however, toxicity related to renal dysfunction has limited its use.

Targeted therapy:

Sunitinib is approved in the U.S. for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNETs) in patients with unresectable locally advanced or metastatic disease. Everolimus is approved in the U.S. for the treatment of progressive pNET and progressive, well-differentiated, *non-functional* NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic.

Sorafenib and pazopanib are tyrosine kinase inhibitors (b) (4)

Peptide Receptor Radioligand Therapy

Peptide receptor radioligand therapy (PRRT) is a targeted approach using radiolabeled SSAs in patients with tumors that are determined to be SSTR-positive. The most commonly used radionuclides include yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu). Toxicities associated with PRRT include renal dysfunction, pancytopenia, and myelodysplastic syndrome.

Table 1: Summary of FDA Approved Treatments for GEP-NETS

Product Name	Relevant Indication	Efficacy Information
Streptozocin (Zanosar)	Metastatic pancreatic islet cell cancer	Streptozocin + doxorubicin resulted in RR 69%, Median OS 2.2 years Used alone or with other antineoplastic agents
Octreotide acetate (Sandostatin)	Symptomatic treatment of metastatic carcinoid tumors	Similar control of symptoms and reduction of urinary 5-HIAA levels among 67 patients treated with Sandostatin LAR and 26 patients with Sandostatin injection.
Everolimus (Afinitor)	Progressive pNET and well-differentiated, non-functional NET of GI or lung origin that is unresectable, locally advanced or metastatic.	Results of a randomized, double-blind trial demonstrating a statistically significant improvement in PFS [median 11.0 vs 4.6 months, HR 0.35 (95% CI: 0.27, 0.45); p 0.001].
Sunitinib (Sutent)	Unresectable or metastatic, well differentiated pNETS with disease progression	Results of a randomized, double-blind, placebo-controlled study demonstrating a statistically significant improvement in PFS [median 10.2 vs 5.4 months, HR 0.43 (95% CI: 0.27, 0.67); p 0.001]
Lanreotide acetate (Somatuline Depot)	Metastatic, well differentiated, non-functional GEP-NETs	Results of a randomized, double-blind, placebo-controlled study demonstrating a statistically significant improvement in PFS (median >22.1 vs 16.6 months, HR 0.47 [95% CI: 0.30, 0.73] p 0.001)

RR: response rate, OS: overall survival, pNET: pancreatic neuroendocrine tumor, HR: hazard ratio, CI: confidence interval

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a New Molecular Entity (NME) and is not a marketed drug in the U.S.

3.2 Summary of Presubmission/Submission Regulatory Activity

The regulatory history as provided by Dr. Joohee Sul in the review of the original submission is reproduced here for continuity and updated to reflect events occurring on and after December 19, 2016.

- June 14, 2007: A pre-IND meeting was held with BioSynthema Inc. and FDA under IND 77219, to discuss the development program for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for patients with somatostatin receptor positive NETs.

- January 2009: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was designated as an orphan drug for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

- March 8, 2011: A pre-IND parallel scientific advice meeting was held with FDA and EMA to discuss the acceptability of a proposed trial comparing the ORR observed in patients with inoperable midgut carcinoid tumors who experienced progressive disease while being treated with octreotide LAR randomized to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with those randomized to Sandostatin LAR Depot. FDA stated that while the subpopulation of midgut carcinoid tumors was an acceptable population for study, given the biological and clinical heterogeneity of GEP-NETs, it would be unlikely that an indication for the treatment of (b) (4) somatostatin receptor positive GEP-NETs would be granted based upon data derived from the proposed trial.

- April 23, 2012: The IND-enabling study (NETTER-1) was submitted to IND 77219.

- September 3, 2014: FDA acknowledged change in the sponsorship of IND 77219 from Biosynthema to AAA.

- October 22, 2014: AAA informed FDA of the DSMB recommendation to stop enrolment and cross over all patients to the Lutathera arm due to observed PFS benefit. AAA followed FDA and EMA advice to continue the trial per protocol.

- April 2015: Fast Track Designation was granted for the investigation of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the treatment of patients with inoperable, progressive, well-

differentiated, octreoscan positive, carcinoid tumors of the mid-gut.

- August 27, 2015: AAA provided the top-line results of the PFS analysis from NETTER-1, which demonstrated an improvement in PFS; median PFS was 8.4 months in the control (Sandostatin LAR Depot 60 mg) arm and had not been reached in the ^{177}Lu-DOTA^{0}-. Tyr^{3}-Octreotate arm (HR 0.21 [95% CI 0.13, 0.34] p<0.001). The following key issues were discussed at this meeting:

    - A potential broader indication for patients with GEP-NET would require demonstration of a clinically meaningful anti-tumor effect (i.e. ORR by RECIST) as determined by independent review that is of sufficient magnitude and duration to be likely to predict clinical benefit and demonstrate an advance over available therapy in an adequate number of patients with progressive and inoperable bronchial NET or pancreatic NET treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at the dose and schedule employed in the NETTER-1 study, in one or more adequate and well-controlled trials.
    - The adequacy of the data from the EMC study to support the broader indication cannot be determined until the data is reviewed at the time of the NDA submission.
    - Possible approaches to developing an expanded access program were discussed.

- November 24, 2015: A pre-NDA meeting was scheduled. The pre-meeting package did not include completed analysis of safety data from NETTER-1; therefore, it was determined that there was insufficient information to reach agreement on the contents of an NDA under the PDUFA V program. The following key issues were discussed at the meeting:

    - FDA reiterated that a potential indication for patients with GEP-NET will require demonstration of a clinically meaningful anti-tumor effect as described above.
    - FDA requested additional information on the results of the EMC trial.
    - FDA did not object to AAA's proposal to open an expanded access trial at NETTER-1 study sites and to allow patients in the NETTER-1 study who progress during treatment with Sandostatin LAR 60 mg to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
    - FDA discouraged AAA from submitting the interim analysis of OS as the final analysis in the NDA and encouraged AAA to conduct additional analyses at later time points when a greater number of events have occurred. FDA emphasized that for the OS results to be included in the label, an effect on OS must meet the criteria for substantial evidence of efficacy.

- March 14, 2016: A pre-NDA meeting was held with FDA to discuss the submission of the NDA. The following key issues were addressed:

    - FDA reiterated ongoing concerns regarding the utility of the data presented from

the EMC and reiterated that a potential indication for patients with GEP-NET would require demonstration of a clinically meaningful ORR and DOR by RECIST as determined in one or more trials that are well designed, well executed and internally consistent.
  - Additional advice was provided concerning the content of the clinical pharmacology data
  - Additional advice was provided concerning the formatting of datasets.

- April 28, 2016: The NDA rolling submission was completed.

- A complete review of the data submitted in this NDA was found to be materially incomplete, inaccurate, untraceable, and inconsistent. As a result, it was not possible to confirm the effectiveness or safety of Lutathera for the proposed indication and a complete response letter (CR) was issued to the applicant on December 19, 2016.

- February 10, 2017: A type A teleconference was held with FDA to discuss the specific items presented in the CR letter, to detail the planned response, provide an overview of the response timing, and discuss the Expanded Access Program.

- July 26, 2017: The NDA was re-submitted.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Please see the original review for details.

The Division of Oncology Products 2 (DOP2) consulted the OSI to perform an audit of four clinical sites in the US for the NETTER-1 trial:

SITE	Principle Investigator
US08	Dr. Matthew Kulke
US12	Dr. James C. Yao
US13	Dr. Jonathan R. Strosberg
US14	Dr. Andrew E. Hendifar

In addition, two Contract Research Organizations (CROs) were selected for audit:

- (b) (4): responsible for national and international clinical project management, data management, medical review, medical coding, statistical analysis, and report writing, under the direction of AAA
- (b) (4): independent Imaging Reading Center (IRC)

The assessment of OSI was that the data used in the CSR from Study AAA-III-01 in support of NDA 208700 accurately reflects the clinical database at the data cutoff date (July 24, 2015). No additional audit was deemed necessary for the resubmission.

4.2 Product Quality

Please see FDA CMC review.

4.3 Clinical Microbiology

Please see FDA product quality microbiology review.

4.4 Devices and Companion Diagnostic Issues

There is no device or companion diagnostic test for review in support of this NDA.

5. Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radiolabeled somatostatin analog intended for use in the treatment of patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors. Limited nonclinical studies were conducted with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Instead, many nonclinical studies were conducted using ^{175}Lu-DOTA^{0}-TYR^{3}-Octreotate. As the only difference between the ^{177}Lu and ^{175}Lu is the radiolabel, the use of the cold construct is applicable for evaluating the non-radioactivity-mediated toxicity of the intended clinical product. In addition, the applicant submitted pharmacology studies using ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to help support the activity of the drug in the intended patient population.

Somatostatin receptor 2 (SSTR2) is commonly over-expressed in neuroendocrine tumors. In vitro binding data showed that DOTA^{0}-Tyr^{3}-Octreotate has high affinity for somatostatin receptor 2 (SSTR2) compared to somatostatin receptors 1, 3, 4, and 5, blocking binding of somatostatin to SSTR2 with an IC_{50} of 0.98 nM. The applicant also demonstrated cellular internalization of the construct following binding using an SSTR2-expressing pancreatic tumor cell line. In a series of in vivo studies examining the anti-tumor activity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in pancreatic tumor implanted male Lewis rats, the applicant demonstrated that repeated treatment with the construct resulted in SSTR2-dependent tumor regression at radioactive doses ≥ 2.5 mCi (approximately 92 MBq), but that long-term survival of effectively treated animals was impacted by renal damage characterized by increased creatinine and urinary protein levels as well as histopathological lesions. Administration of lysine along with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate offered a limited degree of kidney protection in these studies. Longer dosing intervals also resulted in an improvement in renal damage scores.

Safety pharmacology and toxicology studies submitted to support the safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were reviewed in depth by Dr. Ronald Honchel under NDA 208547. In vivo animal studies demonstrated high uptake of the radiolabeled peptide in the pancreas (high SSTR2 expressing organ). This finding correlated with observations of pancreatic acinar apoptosis at doses ≥ 5 mg/kg of ^{175}Lu-DOTA^{0}-TYR3-Octreoate in repeat dose toxicology studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥ 500 mg/kg. There were no other significant test-article related findings in the general toxicology studies of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate given by intravenous injection in either species. High levels of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were also present in both the bone and kidney. Distribution to the kidney, the main excretory organ for the peptide, was consistent with findings of long term renal damage in tumor implantation experiments. Renal damage is a common acute and long-term toxicity associated with administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate clinically as well. Hematological toxicity is also a major clinical toxicity.

In rats, intravenous administration of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate at doses ≥ 1250 µg/kg had no effects on neurobehavioral endpoints (motor activity, behavior, co-ordination, somatic sensory/motor reflex responses and autonomic responses such as piloerection, pupil size, lachrymation, and salivation), or effects on overt cardiovascular and gastrointestinal function or body temperature in rats. Further support for the cardiovascular safety of the cold compound included its lack of effect on ECG parameters in the repeat dose toxicology study in dogs at single doses up to 3.2 mg/kg and an IC_{50} of > 100 µM in the in vitro hERG assay, though mild dose-independent effects (≤ 22% increases) on systolic, diastolic, and mean arterial blood pressure with concomitant decreases in heart rate did occur at doses as low as 40 µg/kg. At the highest dose of 20 mg/kg, ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate acted as a respiratory stimulant (increased respiratory rate, peak inspiratory and peak expiratory flows, inspiration and expiration times and minute volume). The no-observed-effect level (NOEL) of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate on respiratory parameters in conscious rats was 1250 µg/kg, when administered by the intravenous route.

The assessment of the potential for ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate to inhibit or induce human CYP450 enzymes showed that the compound does not act as an inhibitor or an inducer of the tested enzymes in the concentration range tested. ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not show any potential for P-gp specific interaction, either as a substrate or as an inhibitor. In general toxicology studies, the exposure to the test items increased in a dose-proportional manner without any accumulation in terms of exposure and peak concentration.

The applicant did not conduct carcinogenicity studies and these studies are not required to support the marketing application for a drug intended to treat advanced cancer. The cold product, ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate, was non-mutagenic in the Ames bacterial mutagenicity assay and negative in mouse lymphoma cells in vitro. As ^{177}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive product, it is considered genotoxic. Consistent with the ICH S9 Guidance, because ^{177}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate is a genotoxic drug, no reproductive toxicology studies were conducted or required to support the registration of the drug. The risk of radiopharmaceuticals to a developing fetus is well-established in the scientific literature. The nonclinical team recommends a warning for the potential for embryo-fetal toxicity.

5.2 Referenced NDAs, BLAs, DMFs

NDA 208547 for ^{68}Gallium-DOTA^{0}-Tyr^{3}-Octreotate

5.3 Pharmacology

Primary pharmacology

To support the receptor binding specificity of DOTA-Tyr^{3}- Octreotate, the applicant referenced Reubi et al., (Eur J Nucl Med 2000, 27:273-282). Membrane sections from CHO-K1 cells engineered to stably express somatostatin receptors (SSTRs) 1 or 5 and CCL39 cells engineered

to express SSTRs 2, 3, or 4 were mounted on slides. Affinity profiles for various somatostatin analogs were determined based on displacement of radiolabeled somatostatin 28. The DOTA-Tyr^3-Octreotate-based products bound to SSTR2 with high affinity and showed far more limited affinity for SSTR4 and SSTR5. There was no binding to SSTRs 1 or 3.

Table 2: IC_{50s} (nM) For Displacement of Somatostatin

Peptide	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
SS-28	8.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3
DOTA-Tyr^3-Octreotate	>10000	1.5±0.4	>10000	453±176	547±160
Y-DOTA-Tyr^3-Octreotate	>10000	1.6±0.4	>10000	523±239	187±50

Adapted from Reubi et al., 2000

The applicant determined the IC_{50} for competitive binding of for several somatostatin analogs for somatostatin receptors (unspecified) using cell membranes from CA20948 pancreatic tumor cells (Study #20000801). The DOTA-TYR^3-Octreotate construct inhibited binding to the cell membranes at IC_{50}s below those determined for some other somatostatin analogs, including the approved somatostatin OctreoScan product.

Table 3: Binding Activity of Somatostatin Analog Constructs

Compound	MP #	IC50 (nM)	SE
TYR^3-octreotide	2249	0.48	0.03
OctreoScan (DPTA-octreotide)	1661	2.50	0.15
CMDTPA-TYR^3-octreotate	2148	2.16	0.21
DOTA-TYR^3-octreatate	2325	0.98	0.03

The applicant investigated the internalization of labelled-DOTA^0-Tyr^3-Octreotate using somatostatin receptor (SST2R) expressing rat pancreatic acinar tumor cells (AR42J) (Study 20000420). Cells were maintained in F-12K medium and incubated at 37°C in triplicate with approximately 0.5 nM (0.1 to 0.25 µCi) of radiolabeled peptide for 4 hours, after which cellular uptake was terminated by removing medium from the cells and washing wells with 2 ml of PBS. The combined wash and media was counted to determine free activity at 4 hours. Fresh media was added to the cells and incubation was continued. At 16 hours, the wash cycle was repeated and the remaining cells were transferred into PBS for determination of retained activity. Free and internalized radioactivity levels were determined using a Packard Cobra Gamma counter (Picker International, USA). Pancreatic acinar tumor cells showed similar uptake for both compounds.

Table 4: Summary of Internalization and Retention of Radiolabeled Compounds in AR42J Cells

Compound	Total CPM added to well	% Internalized at 4 hours	% of Activity in cells at 16 hours	% of 4 hours Activity Retained at 16 Hours	Recovery (%)
^{111}Ln-DTPA-Tyr3-Octreotate	316837	27.7	21.1	71.3	102
^{177}Lu-DOTA-Tyr^{3}-Octreotate	19939	30.7	27.2	77.9	104

Internalized activity = total counts in well at t_0 minus counts in wash 1 plus counts in incubation media; %Activity in cells at 16 h = total count in cells at 16 h divided by total counts in well at 16h.

To study the biodistribution and activity of ^{177}Lu-DOTA-Y^{3}-Octreotate, the applicant treated CA20948 pancreatic tumor implanted Lewis rats with the compound (Study 2000701). Rats received single or multiple doses of ^{177}Lu-DOTA-Y^{3}-Octreotate administered at 30 day intervals by intravenous injection. In addition to tumors, organs with the highest exposure to ^{177}Lu-DOTA-Y^{3}-Octreotate included the pancreas, kidneys, and bone.

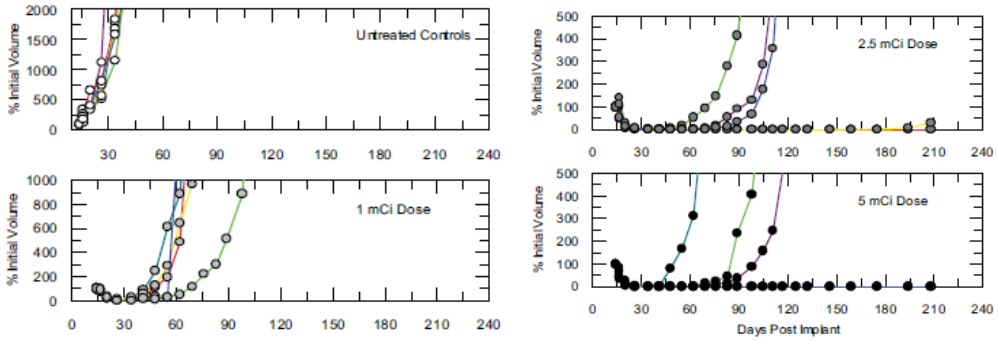
Table 5: Biodistribution of [177Lu]-DOTA-Y3-Octreotate in CA20948 Tumor Bearing Lewis Rats

	Time Post Injection (*hours*)					
Tissue Sample	***1***	***4***	***12***	***24***	***48***	***72***
Blood	0.777 ± 0.039	0.059 ± 0.001	0.030 ± 0.004	0.020 ± 0.004	0.012 ± 0.000	0.012 ± 0.000
Liver	0.500 ± 0.021	0.358 ± 0.015	0.348 ± 0.008	0.335 ± 0.008	0.304 ± 0.010	0.343 ± 0.024
Kidneys	2.606 ± 0.018	2.706 ± 0.077	3.609 ± 0.099	2.778 ± 0.123	2.672 ± 0.139	2.564 ± 0.088
Skeletal Muscle	1.651 ± 0.190	0.394 ± 0.077	0.311 ± 0.001	0.258 ± 0.037	0.218 ± 0.006	0.219 ± 0.005
Spleen	0.025 ± 0.002	0.016 ± 0.001	0.017 ± 0.002	0.017 ± 0.001	0.015 ± 0.001	0.015 ± 0.001
Heart	0.035 ± 0.001	0.011 ± 0.001	0.005 ± 0.000	0.005 ± 0.000	0.004 ± 0.000	0.004 ± 0.001
Pancreas	6.415 ± 0.403	7.964 ± 0.272	2.454 ± 0.144	2.666 ± 0.140	2.126 ± 0.123	2.207 ± 0.171
Stomach & Contents	2.573 ± 0.031	2.268 ± 0.117	3.432 ± 0.287	0.851 ± 0.237	0.922 ± 0.005	0.871 ± 0.030
Bone	6.547 ± 0.199	5.352 ± 0.099	4.417 ± 0.125	4.163 ± 0.194	3.510 ± 0.273	3.468 ± 0.260
Adrenals	0.623 ± 0.049	0.580 ± 0.010	0.457 ± 0.030	0.411 ± 0.013	0.330 ± 0.019	0.277 ± 0.012
Thyroid	0.007 ± 0.002	0.005 ± 0.000	0.004 ± 0.000	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.001
Tumor	11.883 ± 0.944	11.213 ± 1.645	13.776 ± 0.720	8.373 ± 1.137	7.740 ± 0.993	5.847 ± 1.250
Total Urine				66.608 ± 0.445	66.608 ± 0.445	70.167 ± 1.384
Total Feces				6.225 ± 0.758	10.189 ± 0.143	12.156 ± 0.731
Total Excreted				72.833 ± 1.007	76.797 ± 0.433	82.323 ± 1.544
Total Recovered				92.713 ± 0.606	94.653 ± 0.930	98.153 ± 0.671

(Applicant Table reproduced from Study Number 20000701)

Following a single dose of ^{177}Lu-DOTA-Y^{3}-Octreotate, there was a dose dependent decrease in tumor volume in CA20948 tumor bearing rats. At the high dose of 5 mCi (185 MBq), some animals remained tumor free 8 months after treatment (Figure 1).

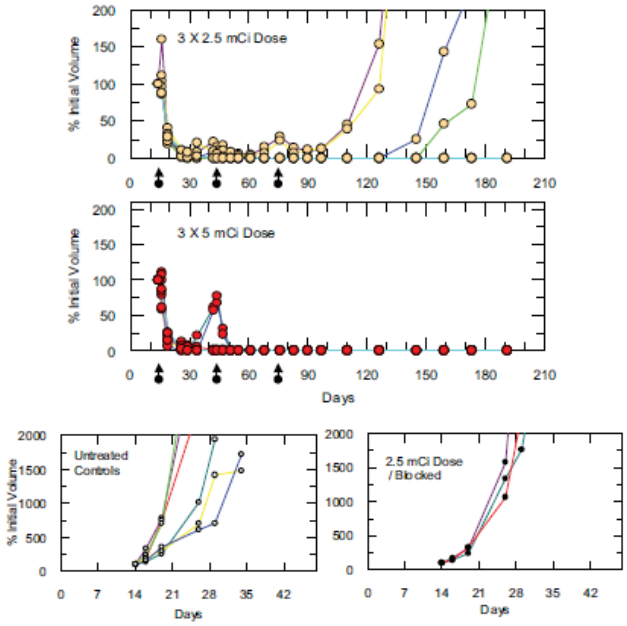
Figure 1: Radiotherapeutic Effect of a Single Dose Administration of [177Lu]-DOTA-Y3-Octreotate to CA20948 Tumor Bearing Lewis Rats (established tumors)



Tumor volumes at 24 hours post injection of radiolabeled material (1, 2.5 and 5 mCi per animal, n = 6 per group)
(Applicant Figure reproduced from Study Number 20000701)

Compared to single dose administration at the same dose level, an increased number of animals receiving 3 doses of ^{177}Lu-DOTA-Y^{3}-Octreotate had sustained tumor regression. Tumor growth in rats that received a 1 mg/kg blocking dose of cold peptide in addition to a single 2.5 mCi dose was, however, identical to the growth observed in untreated animals, showing that the radiotherapeutic effect was receptor mediated (Figure 2). Despite increases in tumor-free survival compared to that seen at lower doses, treatment of animals with multiple doses of ^{177}Lu-DOTA-Y^{3}-Octreotate at the high dose of 5 mCi did result in long term toxicity, with most animals in this group developing renal disease and dying beginning 9 months post-treatment. Renal lesions (nodules and large neoplasms) were the only observed neoplasms (macroscopic inspection) in these animals, indicating that the kidney is the critical organ for toxicity. No attempt was made to reduce kidney uptake using protecting agents (free amino acids) in this study (Figure 3).

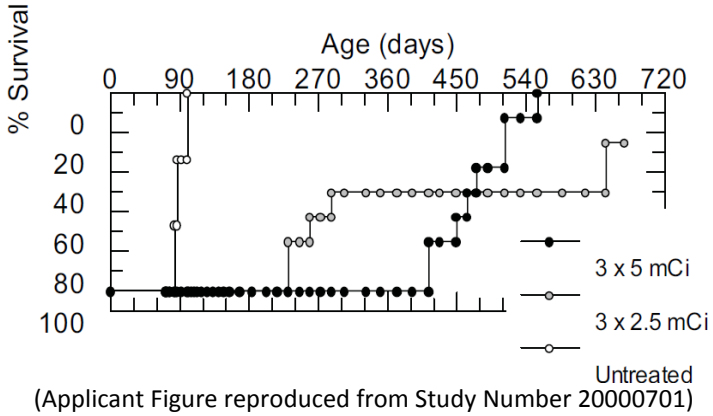
Figure 2: Effects of Multiple Dose Administration on Tumor Volume



(Applicant Figure reproduced from Study Number 20000701)

Radiotherapeutic effect of multiple dose administrations of [^{177}Lu]-DOTA-Y3-Octreotate to CA20948 tumor-bearing Lewis rats. At 14 days post tumor implant, rats were injected with 2.5 or 5 mCi of radiolabeled peptide (n=8 per group) or received no treatment (controls, n=6). Additional doses were administered at 30 day intervals (3 doses total) to the 2.5 and 5 mCi treatment groups.

Figure 3: Survival of Rats Treated with [^{177}Lu]-DOTA-Y3-Octreotate (3 doses at 30-day interval)

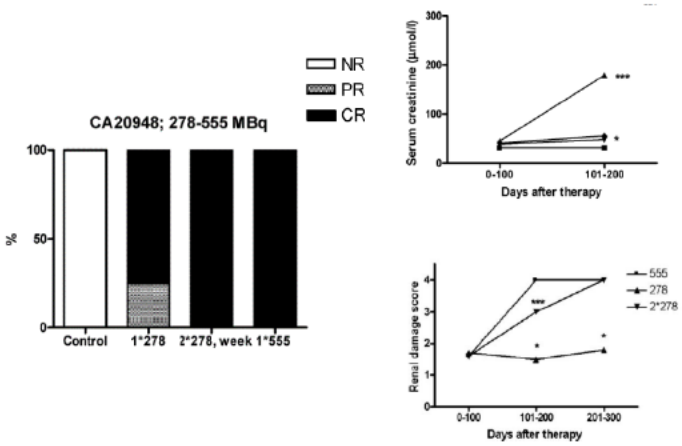


(Applicant Figure reproduced from Study Number 20000701)

Rollerman et al. (Eur J Nucl Med Mol Imaging 2007, 34:219-227) explored the effects of dose level, dose fractionation, and administration of the amino acid lysine on anti-tumor effects as well as the long-term renal and bone marrow effects of administration of ^{177}Lu-DOTA-Tyr^3 Octreotate in rats. Male Lewis rats were implanted with CA20948 or AR42J pancreatic tumor cell lines. Octreotate treatment of CA20948-implanted animals with a single dose of 555 MBq

or with 1 or 2 once weekly doses of 278 MBq each resulted in prolonged anti-tumor activity. Twice weekly administration of 278 MBq resulted in a higher response rate than a single dose at this dose level. Renal damage was clear at the 555 MBq dose level based on increased creatinine levels compared to single or 2 weekly doses at 278 MBq as well as a renal damage score based on histopathological assessment of kidney tissue. Administration of 2 weekly doses of 278 MBq ^{177}Lu-DOTA-Tyr^3 Octreotate did, however, result in histopathological findings of renal damage similar to those seen in animals treated with 555 MBq. This damage progressed more slowly at the 278 MBq dose compared to the 555 MBq dose without the same degree of rise in serum creatinine (Figure 4).

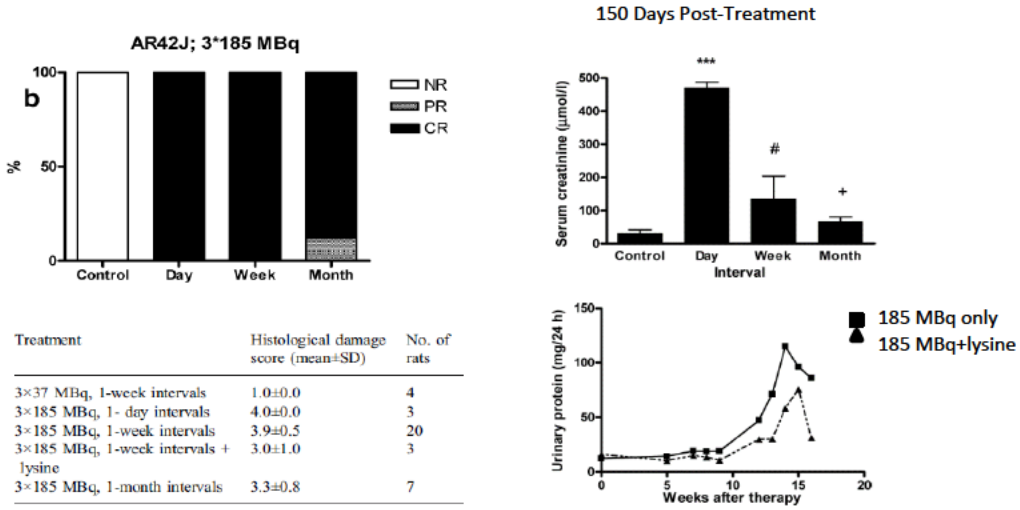
Figure 4: Anti-Tumor Activity and Renal Injury in CA20948-Implanted Rats



(Figure adapted from Rollerman et. al.)

To further investigate the effects of fractionation on long-term renal damage mediated by octreotate, the authors treated AR42J-implanted rats at an ^{177}Lu-DOTA-Tyr^3 Octreotate dose level of 185 MBq given for a total of 3 doses on a daily, weekly, or monthly schedule. On the weekly schedule, the authors also examined the effects of amino acid administration on renal protection. Treatment on any of the three schedules resulted in similar anti-tumor activity, but increasing the dosing interval from daily to weekly or monthly resulted in decreases in serum creatinine levels and urinary protein levels. The addition of amino acid treatment also decreased the levels of urinary protein and serum creatinine compared to radiation alone. Histopathologically, amino acid pretreatment effects were unclear.

Figure 5: Fractionation and Amino Acid Effects on Renal Damage



Treatment	Histological damage score (mean±SD)	No. of rats
3×37 MBq, 1-week intervals	1.0±0.0	4
3×185 MBq, 1- day intervals	4.0±0.0	3
3×185 MBq, 1-week intervals	3.9±0.5	20
3×185 MBq, 1-week intervals + lysine	3.0±1.0	3
3×185 MBq, 1-month intervals	3.3±0.8	7

(Figure adapted from Rollerman et. al.)

Safety Pharmacology

All safety pharmacology studies submitted were previously reviewed by Dr. Ronald Honchel under NDA 208547 for the use of ^{68}Ga-DOTATATE as a radioactive diagnostic agent for the management of gastroenteropancreatic neuroendocrine tumors (NETs).

5.4 ADME/PK

Type of Study	Major Findings
Absorption	
Biodistribution of [Lu-177]-MP (DTPA-Tyr^3-Octreotate) in CA20948 tumor bearing Lewis rats. Study Report-19980721	^{177}Lu-DOTA-Tyr^3-Octreotate when injected intravenously to rats was mostly absorbed in the pancreas, which is known to have high levels of somatostatin sub-type 2 receptors.
Distribution	
Effect of Blocking Dose on Biodistribution of [Lu-177]-MP2325 (DOTA-Tyr^3-Octreotate) in AR42J tumor bearing Lewis rats. Study Report 20000906	Uptake of Lu-177-MP2325 decreased in target tissues (tumor, pancreas, bone, stomach, small intestine, and adrenals) and increased in non-target tissues (kidneys) in the presence of blocking dose of Tyr^3-Octreotate.
Metabolism	
Comparative *in vitro* metabolism studies of ^{175}Lu-DOTA^0- Tyr^3-	^{175}Lu-DOTA^0-Tyr^3-Octreotate was metabolized by the Sprague-Dawley rat, Beagle dog and male human kidney homogenate but not metabolized by the rat, dog or human hepatocytes.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Octreotate with rat, dog and human kidney homogenate.
Study Report aaa05.

Assessment of the potential for ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate to inhibit human CYP450 enzymes in vitro (AAA/02)</td><td>Analysis of the 10 µM incubation samples detected the presence of five rat, eight dog, and seven human metabolites. No human specific metabolites were observed

^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate in pooled human liver microsomes can act as a mild direct inhibitor of CYP2C9 (32.9% at 10 µM). All IC_{50} values were greater than 10 µM.
^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not inhibit CYP1A2, 2B6, 2C8, 2C19, 2D6, 2E1 or 3A4 enzymes up to a concentration of at least 10 µM.</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Biodistribution of [Lu-177]-MP2325 (DOTA-Y3-Octreotate) in CA20948 tumor bearing Lewis rats.
Study Report 19990111</td><td>The urinary excretion was 65.0% at 24 hours. Fecal excretion was 8% at 24 hours (overall excretion rate of (Lu-177)-MP2138 was 73% at 24 hours). Overall recovery of the injected dose was 94% at 24 hours.</td></tr>
<tr><td>DDI</td><td></td></tr>
<tr><td>^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate: Assessment of the potential for P-gp mediated interactions using the Caco-2 cell line. (AAA/4)</td><td>^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate showed low to moderate passive permeability with no significant P gp involvement.
P-gp-mediated digoxin transport was only slightly reduced in the presence of ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not show any P-gp specific interaction as a substrate or inhibitor.</td></tr>
<tr><td>TK data from general toxicology studies
42-day intravenous toxicity study in the rat including recovery period and toxicokinetics.
Study Number 20100180TRP.</td><td><u>Rat</u>
T1/2: Approximately 22 to 24 minutes
Accumulation: No accumulation in terms of exposure and peak concentration
Dose proportionality: Increased in a dose proportional manner.
Toxicokinetic parameters Day 1 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>1250</td><td>5000</td><td>20000</td><td>1250</td><td>5000</td><td>20000</td></tr>
<tr><td>Cmax (ng/mL)</td><td>1581</td><td>7029</td><td>27238</td><td>1359</td><td>6931</td><td>28435</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>21.5</td><td>25.5</td><td>19.5</td><td>21.6</td><td>24.4</td><td>20.4</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>45110</td><td>175137</td><td>588732</td><td>40170</td><td>189919</td><td>670289</td></tr>
<tr><td>Cmax/Dose</td><td>1.26</td><td>1.41</td><td>1.36</td><td>1.09</td><td>1.39</td><td>1.42</td></tr>
<tr><td>AUC all/Dose</td><td>36.1</td><td>35.0</td><td>29.4</td><td>32.1</td><td>38.0</td><td>33.5</td></tr>
</table>
Toxicokinetic parameters Day 42 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>1250</td><td>5000</td><td>20000</td><td>1250</td><td>5000</td><td>20000</td></tr>
<tr><td>Cmax (ng/mL)</td><td>2149.2</td><td>6975.0</td><td>26257.9</td><td>1863.6</td><td>6299.2</td><td>26631.7</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>21.2</td><td>20.1</td><td>28.4</td><td>21.0</td><td>21.5</td><td>33.0</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>59576</td><td>184101</td><td>687521</td><td>47260</td><td>164712</td><td>719279</td></tr>
<tr><td>Cmax/Dose</td><td>1.72</td><td>1.40</td><td>1.31</td><td>1.49</td><td>1.26</td><td>1.33</td></tr>
<tr><td>AUC all/Dose</td><td>47.7</td><td>36.8</td><td>34.4</td><td>37.8</td><td>32.9</td><td>36.0</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>43-day intravenous toxicity study in the dog including recovery and toxicokinetics.
Study Number 20100182TCP</td><td><u>Dog:</u>
T1/2: Approximately 60 minutes
Accumulation: No accumulation
Dose proportionality: Yes
Toxicokinetic parameters Day 1 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>80</td><td>500</td><td>3200</td><td>80</td><td>500</td><td>3200</td></tr>
<tr><td>Cmax (ng/mL)</td><td>109±6</td><td>590±77</td><td>4245±169</td><td>100±7</td><td>681±66</td><td>4340±417</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>72±11</td><td>69±5</td><td>73±4</td><td>57±3</td><td>65±3</td><td>62±2</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>8027±549</td><td>32129±2094</td><td>253960±19697</td><td>6347±270</td><td>40981±3066</td><td>240018±14656</td></tr>
<tr><td>Cmax/Dose</td><td>1.4±0.1</td><td>1.2±0.2</td><td>1.3±0.1</td><td>1.3±0.1</td><td>1.4±0.1</td><td>1.4±0.1</td></tr>
<tr><td>AUC all/Dose</td><td>100±7</td><td>64±4</td><td>79±6</td><td>79±4</td><td>82±6</td><td>75±5</td></tr>
</table>
Toxicokinetic parameters Day 43 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>80</td><td>500</td><td>3200</td><td>80</td><td>500</td><td>3200</td></tr>
<tr><td>Cmax (ng/mL)</td><td>154±11</td><td>799±106</td><td>4309±313</td><td>142±8</td><td>649±96</td><td>4643±397</td></tr>
<tr><td>Tmax (min)</td><td>5±0</td><td>9±4</td><td>5±0</td><td>5±0</td><td>5±0</td><td>5±0</td></tr>
<tr><td>T1/2 (min)</td><td>38±6</td><td>57±5</td><td>59±3</td><td>49±2</td><td>54±4</td><td>64±5</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>6428±647</td><td>41714±4043</td><td>234594±7282</td><td>7817±607</td><td>35324±4243</td><td>228921±10396</td></tr>
<tr><td>Cmax/Dose</td><td>1.9±0.1</td><td>1.6±0.2</td><td>1.4±0.1</td><td>1.8±0.1</td><td>1.3±0.2</td><td>1.5±0.1</td></tr>
<tr><td>AUC all/Dose</td><td>80±8</td><td>84±8</td><td>73±2</td><td>98±7</td><td>71±8</td><td>72±3</td></tr>
</table></td></tr>
<tr><td>TK data from reproductive toxicology studies</td><td>Neither submitted nor required due to radioactive drug acting on rapidly dividing cells.</td></tr>
<tr><td>TK data from Carcinogenicity studies</td><td>None submitted</td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

All general toxicology studies submitted were previously reviewed by Dr. Ronald Honchel under NDA 208547 for the use of ^{68}Ga-DOTATATE as a radioactive diagnostic agent for the management of gastroenteropancreatic neuroendocrine tumors (NETs).

5.5.2 Genetic Toxicology

Genetic toxicology studies for ^{175}Lutetium-DOTA ^{0}-Tyr^{3}-Octreotate were previously submitted and reviewed under NDA 208547 by Dr. Ronald Honchel. ^{175}Lutetium-DOTA ^{0}-Tyr^{3}-Octreotate was not mutagenic in these assays. As ^{177}Lu is a radioactive isotope, the intended clinical product is genotoxic.

5.5.3 Carcinogenicity

None submitted or required

5.5.4 Reproductive and Developmental Toxicology

None submitted or required as ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive product with an understood risk to development.

5.5.5 Other Toxicology Studies

None

M. Anwar Goheer, PhD	Whitney S. Helms, PhD
Primary Reviewer	Team Leader

6. Clinical Pharmacology

6.1 Executive Summary

The applicant seeks approval of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the treatment of patients with (b) (4) somatostatin receptor positive, neuroendocrine (b) (4) tumors of the midgut (b) (4) The proposed dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 7.4 gigabecquerels (GBq) as a 30-min intravenous (IV) infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid solution 30 minutes before and 3 (b) (4) hours after administration of each dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Patients will also receive 30 mg octreotide LAR as an intramuscular (IM) injection the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and then every 4 weeks (b) (4) The proposed dosing regimen is supported by the clinically significant improvement in progression-free survival (PFS) and an acceptable safety profile from the registration trial (NETTER-1 study).

The primary data to support the Clinical Pharmacology components of the NDA are from the pharmacokinetics (PK) and biodistribution studies and the NETTER-1 study conducted in patients with the proposed indication. The selection of the therapeutic dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was based on dosimetry data from a dose escalation study (Erasmus) which resulted in a cumulative radiation dose that remained near but below the defined radiation toxicity threshold to the kidney (23 Gy) and bone marrow (2 Gy). No exposure-response analysis for either efficacy or safety could be performed because PK samples were collected in only 8% (19/249) of patients in the NETTER-1 study. Based on the lack of relationship between creatinine clearance and hematological toxicities in the NETTER-1 study, no dose adjustment is recommended for patients with mild to moderate renal impairment. The use of lysine/arginine amino acid solution as a renal protectant is supported by the pharmacokinetics and biodistribution sub-study in the Erasmus study. Co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (range: 34%-59%) and increased the mean beta phase blood clearance of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate by 36% (CV: 21%).

6.2 Recommendations

The proposed dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment is acceptable, as it is supported by the clinically significant improvement in PFS for effectiveness and an acceptable safety profile. From a Clinical Pharmacology standpoint, the NDA is approvable, provided the applicant and the FDA reach agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from the NETTER-1 study. The proposed dosing regimen is supported by the clinically significant improvement in progression-free survival (PFS) and acceptable safety profile observed in this trial.
General dosing instructions	7.4 GBq as a 30-min IV infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with co-infusion of a commercially available amino acid solution 30 minutes before and 3 (b) (4) hours after administration of each dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Patients will also receive 30 mg octreotide LAR as an intramuscular (IM) injection the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and then every 4 weeks (b) (4).
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients with mild to moderate renal impairment. The safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.
Labeling	The review team provided extensive modifications to all sections of the proposed labeling as the content and format provided by the applicant were inconsistent with current labeling practices. Significant additions to the label by the FDA included radiation risk assessment and QT prolongation information.
Bridge between the to-be marketed and clinical trial formulations	The to-be-marketed formulation was administered in the NETTER-1 study that demonstrated effectiveness and safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the proposed indication.

6.3 Postmarketing Requirements and Commitments

There are no postmarketing requirements (PMR) or postmarketing commitment (PMC) studies requested by the Office of Clinical Pharmacology.

6.4 Summary of Clinical Pharmacology Assessment

The Clinical Pharmacology Section of the NDA includes single-dose pharmacokinetic (PK) studies and biodistribution studies of ^{177}Lu-DOTA^{0}-Tyr^{3}- Octreotate based on dosimetry scans from

multiple images of the whole body, kidney, heart, liver and bone marrow, QT/QTc prolongation study, and in vitro metabolism and protein binding studies.

6.5 Pharmacology and Clinical Pharmacokinetics

The PK parameters were generated by noncompartmental analyses with intensive PK sampling in the Netter-1 PK sub-study and measured by total radioactivity in blood assuming this only represents the parent compound. The mean blood exposure ($AUC_{0\text{-}inf}$) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36 %] with the mean maximum blood concentration (C_{max}) of 10 ng/mL (CV 50%), which generally occurred at the end of the infusion.

Distribution
The non-radioactive form (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) is 43% bound to human plasma proteins. The mean volume of distribution for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 460 L (CV 54%). Within 4 hours after administration, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid.

Five patients received a single dose of 1.85 GBq (50 mCi) ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate without the Lysine/Arginine containing amino acid solution, then they (N=4) received a second dose of 1.85 GBq (50 mCi) with the amino acid solution. The median gray dose to the kidneys was reduced by 47% (range: 34%-59%) by the co-administration of amino acids. Additionally, a 36% (21% CV) increase in the mean beta phase blood clearance of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was observed with the co-administration of amino acids.

Metabolism
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate does not undergo hepatic metabolism.

Elimination
The mean clearance (CL) is 4.5 L/h (CV 31%) for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The mean (standard deviation) effective blood elimination half-life is 3.5 (1.4) hours and the mean terminal blood half-life is 71 (28) hours. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration.

6.6 General Dosing and Therapeutic Individualization

6.6.1 General Dosing

The proposed dosing regimen of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 7.4 GBq as a 30-min IV infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid solution 30 minutes before and 3 (b) (4) hours after administration of each dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Patients will also receive 30 mg octreotide LAR as an

intramuscular (IM) injection the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and then every 4 weeks (b) (4).

The proposed dosing regimen is supported by the clinically significant improvement in PFS and the acceptable safety profile observed in the NETTER-1 study. PK samples were collected in only 8% (19/249) of patients in NETTER-1; therefore, no exposure-response analysis for either efficacy or safety could be performed.

6.6.2 Therapeutic Individualization

Patients with Renal Impairment: Based on the results from NETTER-1, no dose adjustment is recommended for patients with mild to moderate renal impairment. Although renal function is associated with ^{177}Lu-DOTA0-Tyr3-Octreotate exposure, no correlation ($R^2 < 0.001$) was observed in hematological toxicities (e.g. anemia, leukopenia, thrombocytopenia, and neutropenia) associated with radiation due to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy. The safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault) or end-stage renal disease has not been studied.

Patients with Hepatic Impairment: ^{177}Lu-DOTA0-Tyr3-Octreotate is mainly eliminated renally with little to no hepatic elimination. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy in patients with severe hepatic impairment (total bilirubin > 3 times upper limit of normal and any AST) has not been studied.

6.6.3 Outstanding Issues

No outstanding issues are identified from a Clinical Pharmacology perspective.

6.6.4 Summary of Labeling Recommendations

Prolonged elimination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in the urine is expected; however, based on the half-life of lutetium 177 and terminal half-life of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, greater than 99% of the radiation risk will be eliminated in 2 weeks after administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. After the 2-week period, the median radiation remaining in the patients' urine will be within an acceptable limit based on the U.S. Nuclear Regulatory Commission guidelines (8.39); any individual who has been administered radiopharmaceuticals or permanent implants containing radioactive material if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (0.5 rem). During this 2-week time period, every effort should be made to minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate consistent with institutional good radiation safety practices and patient management procedures.

The ability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to prolong the QTc interval at the therapeutic dose was assessed in an open label study in 20 patients with somatostatin receptor positive midgut

carcinoid tumors. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

6.7 Comprehensive Clinical Pharmacology Review

A Complete Response Letter (CRL) was issued on December 19, 2016, because the datasets provided in the NDA were inaccurate, incomplete, and inconsistent across databases. Thus, the FDA could not verify the information provided in the clinical study reports nor verify data proposed in the product labeling (see Clinical Pharmacology DARRTS date 11/21/2016).

In this resubmission, the applicant provided updated clinical study reports (CSR) and datasets for both the NETTER-1 and ERASMUS studies. The applicant has adequately addressed the deficiencies and provided justification for missing data identified by the FDA in the CRL. In addition, the applicant provided datasets that use Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards for tabulations data and the CDISC Analysis Data Model (ADaM) standard for analysis data.

6.7.1 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant SSRT2-positive tumors, the compound is internalized. The beta emission from Lu 177 induces cellular damage by formation of free radicals in SSRT2-positive cells and in neighboring cells.
Active Moieties	No metabolite was identified with clinically relevant contribution to efficacy and safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
QT Prolongation	A large change (i.e., >20 ms) in QTc interval was not detected in the NETTER-1 ECG sub-study (N=20) for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; however, mean changes above 10 ms were observed at 8 hours and 24 hours post-dosing. The largest mean change from baseline QTcF was 11.3 (5.7, 16.9) ms. The largest upper bound of the 2-sided 90% CI for the mean change from baseline in QTcF (ΔQTcF) was 16.9 ms at 24 hours post the end of infusion. Placebo and ECG positive controls were not included in the sub-study. Increased heart rate (HR) was observed. The mean change from baseline in HR (ΔHR) peaked at 8 hours post infusion with ΔHR value of 18.7 bpm (90% CI: 12.4 to 25.0 bpm).
General Information	
Bioanalysis	Plasma and urine concentrations for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were determined by total radioactivity using an auto-gamma counting detector (e.g. NaI spectrometer) in both the ERASMUS and NETTER-1 PK substudies. The detector was calibrated with a reference source of ^{177}Lu

	of known activity counted in the same geometry (e.g. 1 ml in a vial) and energy setting (energy windows at one or both gamma peaks of ^{177}Lu within 15%). The calibration factor was obtained as the ratio between the activity of the reference source (kBq) and the mean of the five count rate (cps or cpm) measurements. The total activity at each time was derived by multiplying the activity in each sample by the total blood volume as determined specifically for the patient based on sex, weight and height. Percent time-activity curve was derived by normalization to the injected activity.
Healthy vs. Patients	No healthy volunteer studies were conducted with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Multi-dose PK samples were not collected given that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was administered every 8 weeks. Based on single dose PK, the mean $AUC_{0\text{-}inf}$ of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at the recommended dose is 41 ng.h/mL (CV 36%) and the mean C_{max} is 10 ng/mL (CV 50%).
Range of Effective Dose or Exposure	Not available. A single dose level was evaluated in the NETTER-1 study in support of the application.
Maximally Tolerated Dose or Exposure	The recommended therapeutic dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was based on safety and dosimetry data from a dose escalation study (ERASMUS) which resulted in a cumulative radiation dose that remained near but below the defined radiation toxicity threshold to the kidney (23 Gy) and bone marrow (2 Gy). Single doses higher than 7.4 GBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate have not been assessed clinically.
Dose Proportionality	Over the studied doses of 1.85, 3.7 and 7.4 GBq, the dose normalized mean exposure ($AUC_{0\text{-}last}$) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was 32 (CV 23%), 35 (CV 57%) and 26 (CV 31%), respectively. The $AUC_{0\text{-}inf}$ for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was not calculated as the majority of patients in this study did not have at least 3 quantifiable concentration data in the terminal elimination phase.
Accumulation	Based on terminal half-life (71 hr) and once every 8 weeks dosing interval for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, little to no accumulation is expected to occur.
Absorption	
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was administered as a 30-min IV infusion. No studies were performed with other routes of administration.	
Distribution	
Volume of Distribution	After a single therapeutic dose, the mean volume of distribution for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 460 L (CV 54%).
Plasma Protein Binding	The non-radioactive form (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) is 43% bound to human plasma proteins.
As Substrate of	The non-radioactive form (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) is not a

Transporters	substrate for P-gp transporter based on results from a study with Caco-2 cell line.
Elimination	
Terminal Elimination Half-Life (SD)	The mean terminal blood half-life is 71 (28) hours.
Effective Elimination Half-Life (SD)	The mean effective blood elimination half-life is 3.5 (1.4) hours.
Metabolism	
Fraction Metabolized, %dose	Based on radiometric HPLC analysis, the majority of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was recovered intact in the urine (mean 99.8%, range 92.4 to 100%).
Primary Metabolic Pathway(s)	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was not metabolized by rat, dog or human hepatocytes (Study Report No. AAA-01). ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was catabolized by rat, dog and human kidney homogenate (Study Report No. AAA-05) consistent with the catabolic fate of other peptides.
Excretion	
Primary Excretion Pathways, % dose (SD)	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is primarily eliminated renally with cumulative excretion of 24% (15%) in 2.5 hours, 44% (19%) in 5 hours, 58% (24%) in 24 hours, and 65% (26%) in 48 hours following administration.
Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism	The non-radioactive form (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 in vitro.
Inhibition/Induction of Transporter Systems	The non-radioactive form (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 transporters in vitro.

6.8 Clinical Pharmacology Questions

6.8.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of effectiveness was obtained from the NETTER-1 study. NETTER-1 was a randomized, open-label, parallel-group study of ^{177}Lu-DOTA0-Tyr3-Octreotate plus best

supportive care (30 mg octreotide LAR) compared to high dose (60 mg) octreotide LAR in patients with inoperable somatostatin receptor positive, neuroendocrine carcinoid tumors of the midgut that progressed after treatment with octreotide LAR. As shown in the clinical review, the hazard ratio was 0.21 (95% CI: 0.13, 0.32) with median PFS (95% CI) that was not reached for the ^{177}Lu-DOTA0-Tyr3-Octreotate arm and 8.5 months (5.8, 9.1) for high dose octreotide LAR arm per independent review committee assessment. PK samples were collected in only 8% (19/249) of patients in the NETTER-1 study; therefore, no exposure-response analysis for either efficacy or safety could be performed.

6.8.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 7.4 GBq as a 30-min IV infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid is appropriate for the general patient population for which the indication is being sought.

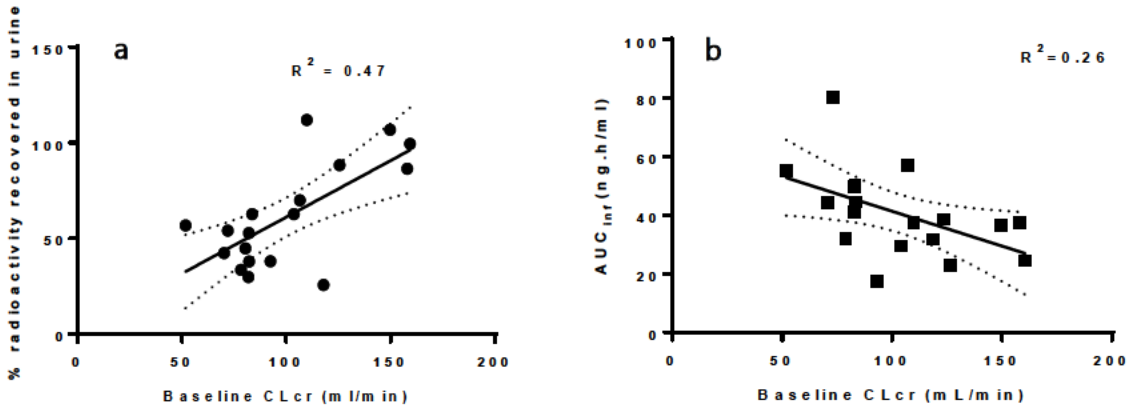
In the NETTER-1 study, 76% of patients received all four planned doses (29.6 GBq) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and 79% received a cumulative dose of greater than 22.2 GBq. Also, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was generally tolerable during the NETTER-1 study as only 6% of patients required a dose reduction and 13% of patients discontinued ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The most common (≥ 20%) adverse reactions observed in the NETTER-1 study in patients treated with^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were nausea (65%), vomiting (53%), fatigue (38%), diarrhea (26%), abdominal pain (26%), and decreased appetite (21%).

6.8.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen is recommended for subpopulations based on the intrinsic factors.

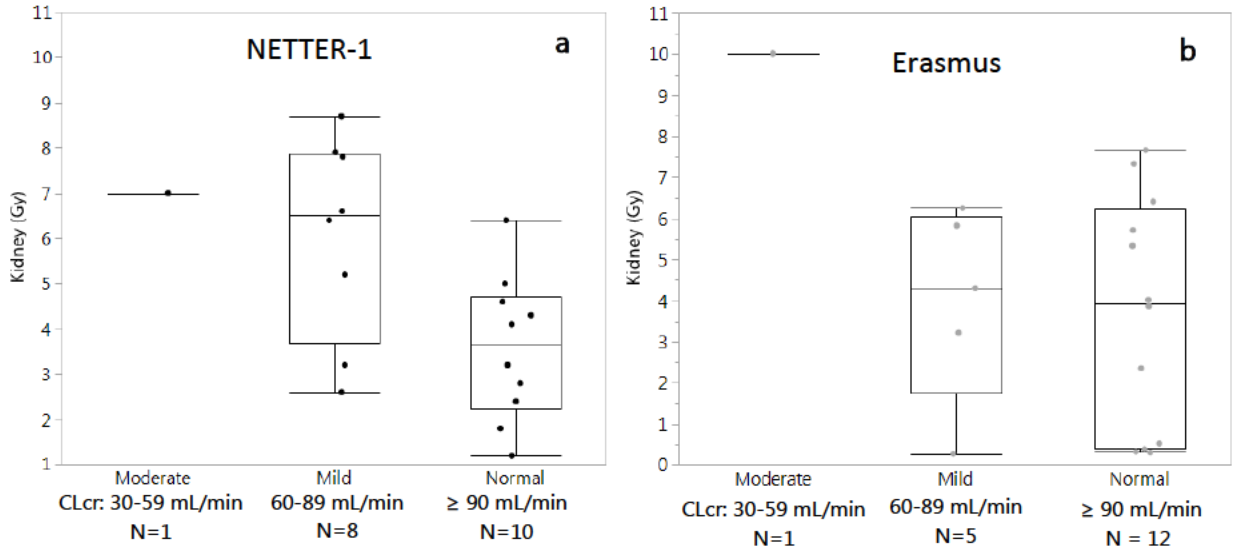
Renal impairment: No dedicated renal impairment studies were conducted during the development of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; however, 35 patients with moderate (CLcr 30-59 mL/min) and 75 patients (CLcr 60-89 mL/min) with mild renal impairment and 25 patients with normal renal function (CLcr ≥ 90 mL/min) were enrolled in the NETTER-1 study and received ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is predominately renally eliminated. Based on available data from the NETTER-1 PK substudy, the percent of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate recovered in the urine decreases with decreasing CLcr, Figure 6a. This finding is supported by the exposure ($AUC_{0\text{-}inf}$) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate that also increases with decreasing CLcr levels, Figure 6b. The trend of increasing radiation dose to the kidneys and decreasing CLcr (Figure 7a) was also observed in the NETTER-1 study; however, this trend was less obvious compared with the kidney dosimetry results from the ERASMUS study, Figure 7b.

Figure 6: Association of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Exposure and Baseline Creatinine Clearance



Source: FDA Analysis

Figure 7: Association of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate kidney exposure and renal function using Cockcroft-Gault equation

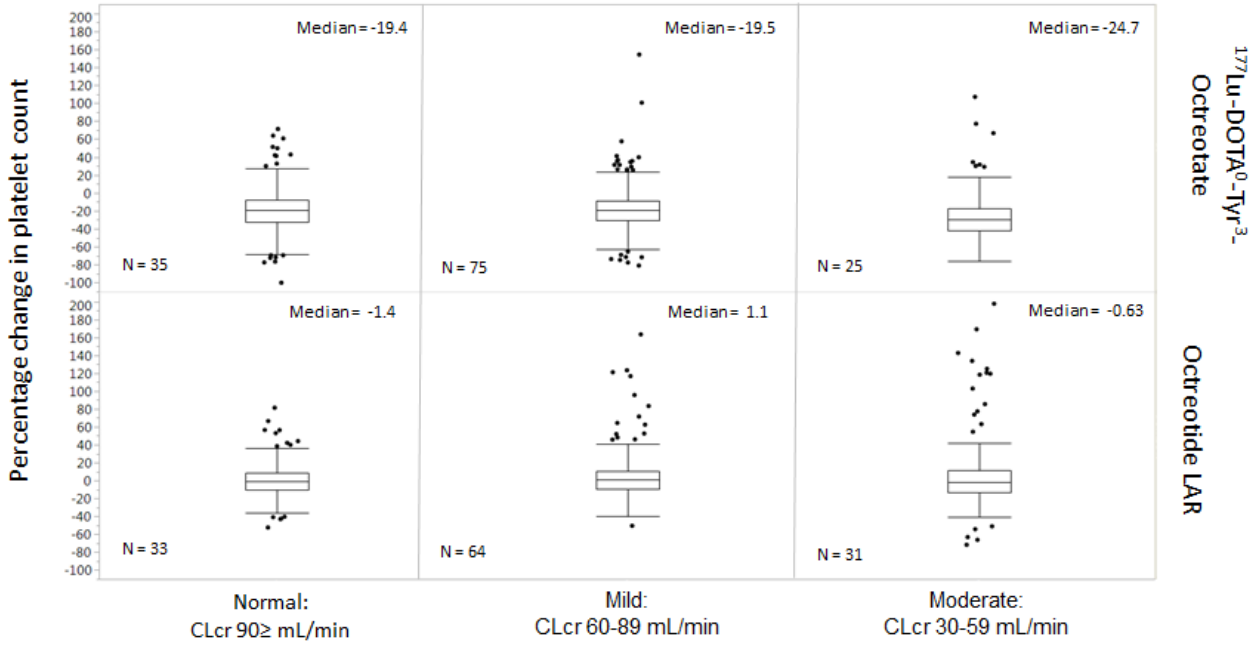


Source: FDA Analysis

Radiotherapies like ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are commonly associated with myelosuppression. The most common hematological toxicities were anemia (81%), leukopenia (55%), thrombocytopenia, (53%) and neutropenia (26%). Although renal impairment is associated with increased ^{177}Lu-DOTA0-Tyr3-Octreotate exposure, no correlations ($R < 0.001$) were found between hematological toxicities (e.g. leukocyte, neutrophils, basophils, eosinophils and monocytes) and renal impairment status. As depicted below, the percentage change in platelet count remained comparable regardless of a patient's renal impairment status after ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or octreotide LAR treatment, Figure 8 . Furthermore, the

majority of patients (> 80%) were renally impaired as defined by FDA criteria using the Cockcroft-Gault equation. Therefore, no dose adjustment is recommended for patients with mild to moderate renal impairment.

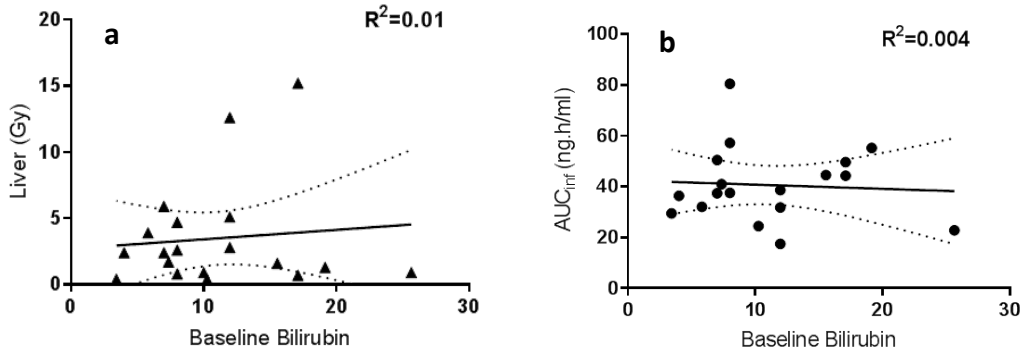
Figure 8: Effect of Renal Dysfunction on Platelet Levels per Treatment Group



Source: FDA Analysis

Hepatic impairment: No dedicated hepatic impairment studies were conducted during the development of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. No dose adjustment is recommended for patients with mild to moderate hepatic impairment as ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is predominately renally eliminated. Consistent with primary elimination pathway, no correlation was observed between radiation dose absorbed to the liver and baseline bilirubin (**Figure 9**a) and between the exposure ($AUC_{0\text{-}inf}$) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and baseline bilirubin, (**Figure 9**b).

Figure 9: Association of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Exposure and Baseline Bilirubin



Source: FDA Analysis

6.8.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is administered as a 30-minute intravenous infusion. No inhibitory or induction effects on human CYP450 enzymes and P-gp specific interactions were observed in the in vitro studies suggesting that there is little potential for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to mediate clinically relevant drug-drug interactions.

Somatostatin and its analogs competitively bind to somatostatin receptors and can interfere with the efficacy ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Long-acting somatostatin analogs should be avoided at least 6 weeks prior to the first dose, since these analogs have a prolonged elimination half-life. Short-acting somatostatin analogs can be used until 24 hours before the first ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dose.

X X

Brian D. Furmanski
Primary Reviewer

Hong Zhao
Team Leader

7. Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

The NDA submission contained a single randomized trial entitled *"A multicentre, stratified, open, randomized, comparator-controlled, parallel group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours"* also referred to as the NETTER-1 trial. The NETTER-1 trial was the primary source of data used to substantiate claims of safety and efficacy.

NETTER-1 included a non-randomized sub-study conducted in 20 patients who received ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at selected sites to evaluate dosimetry, PK, and 24-hour Holter cardiac monitoring. All patients included in the sub-study were treated as were other patients randomized to the NETTER-1 investigational treatment arm (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg octreotide LAR). Please see the clinical pharmacology review for additional details regarding the sub-study.

The NDA submission also included a single-center, investigator-sponsored study entitled *"Phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumors,"* referred to as the Erasmus Medical Center (EMC) trial. This trial was conducted in Rotterdam, the Netherlands, between January 2000 and March 2007. The study enrolled patients with various inoperable, SSTR positive tumors. The primary objective of the study was to assess the safety and activity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate given as 4 doses of 7.4 GBq at 6-13 week intervals. AAA performed a retrospective review of the data in 2012, and updated the analysis in 2015. Data from the EMC trial was submitted to provide supportive evidence of the safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, to confirm the efficacy findings of the NETTER-1 trial in the subset of patients with midgut neuroendocrine tumors, and to provide evidence to extend the proposed indication to include patients with [redacted](b) (4) pancreatic neuroendocrine tumors.

Table 6: Listing of Clinical Trials Relevant to this NDA

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Primary studies to support safety and efficacy						
NETTER-1 AAA-III-01 (Main Study)	International, open-label, randomized, stratified, phase III study	Investigational Arm: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 7.4 GBq every 8 weeks for four doses + Octreotide LAR 30 mg every 4 weeks Control Arm: Octreotide LAR 60 mg.	Primary: PFS Secondary: ORR per RECIST 1.1, OS, TTP, safety, HRQoL	N=229 Lutathera arm=116 Control arm=113	Patients with metastatic or locally advanced, midgut carcinoid tumors with centrally confirmed progressive disease by RECIST	41 active sites 27 in Europe 14 in US
Secondary studies						
NETTER-1 AAA-III-01 (Sub-Study)	Single-arm, non-randomized cohort from NETTER-1 Main Study to evaluate dosimetry	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 7.4 GBq every 8 weeks for four doses + Octreotide LAR 30 mg every 4 weeks	To evaluate whole body and organ radiation dosimetry	N=22	Same as NETTER-1 main study	7 sites 5 in Europe 2 in US
EMC Study	Investigator-sponsored, open-label, single-arm study	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 29.6 GBq cumulative dose	Primary: ORR (CR, PR, MR) per modified SWOG criteria Secondary: Safety based on SAEs	N=1214 Dutch patients=810 Dutch patients with GEP-NET=558	Patients with various SSTR positive NETs	Single-center: Erasmus Medical Center in Netherlands

GBq: gigabecquerel, PFS: progression free survival, ORR: objective response rate, CR: complete response, PR: partial response, MR: minor response, SAE: serious adverse event

7.2 Review Strategy

The FDA joint statistical and clinical review consisted of one primary statistical reviewer and one primary clinical reviewer for the safety and efficacy data.

The joint clinical and statistical review focused primarily on data from the NETTER-1 trial. Data from the EMC trial was reviewed to assess the degree to which this trial provided supportive data on safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and the anti-tumor effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with midgut carcinoid tumors. Data from the EMC trial was also reviewed to assess the basis for the applicant's request for an expanded indication to include patients with pancreatic neuroendocrine tumors.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on the epidemiology and treatment of GEP-NETs.
- Review of the current literature on the use of PPRTs.
- Review of the Common Technical Documents: Clinical Overview (Section 2.5), Summary of Clinical Efficacy (Section 2.7.3) and Summary of Clinical Safety (Section 2.7.4).
- Review of NETTER-1 trial, including the CSR, protocol V1.0 to V4.1, protocol amendment for US version 1.0, SAP V3 dated 03 April 2017.
- Review and assessment of the applicant's analyses of the safety and efficacy of Lutathera as presented in the NETTER-1 CSR.
- Review of EMC trial, including the CSR, protocol V2.0 dated 18 November 2008.
- Review and assessment of the applicant's analyses of the safety and efficacy of Lutathera as presented in the EMC CSR.
- Review of datasets submitted to the NDA from the NETTER-1 and EMC trials.
- Review of patient narratives of serious adverse events and deaths from the NETTER-1 and EMC trials.
- Review of minutes of key meetings conducted during the development history of Lutathera.
- Requests for additional information from AAA and review of applicant's responses.
- Review of consultation reports from OSI and the Division of Medical Imaging Products (DMIP).
- Review and evaluation of proposed labeling.

Data Sources

The electronic submission including the study Protocols, SAPs, CSRs, datasets in SDTM and ADAM format, and SAS codes for this NDA submission are at the following network paths:

- CSR V2, Protocol, SAP, SDTM and ADAM datasets: \\CDSESUB1\evsprod\NDA208700\036\

- Dataset and SAS programs for Efficacy and Safety: \\CDSESUB1\evsprod\NDA208700\039\, \\CDSESUB1\evsprod\NDA208700\045\, \\CDSESUB1\evsprod\NDA208700\048\, and \\CDSESUB1\evsprod\NDA208700\055\

Data and Analysis Quality

Upon further clarifications from the applicant per FDA's information requests (IRs) and mid-cycle communication, the statistical reviewer could:

- Reproduce the applicant's analysis dataset and analysis results from SDTM dataset
- Evaluate documentations of data quality control/assurance procedures
- Verify the randomized treatment assignments
- Conduct FDA analyses for PFS and OS

The overall assessment was that the data provided in the re-submission was adequate for review.

8. Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 NETTER-1 (AAA-III-01; NCT01578239) Trial Design

Title: *"A multicentre, stratified, open, randomized, comparator-controlled, parallel group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours"*

NETTER-1 is an international, open-label trial which randomized 229 patients with histologically confirmed, advanced/inoperable or metastatic, somatostatin receptor (SSTR) positive midgut carcinoid tumors that had progressed while on octreotide LAR. The study was conducted at 41 sites in 8 countries—27 sites in Europe and 14 sites in the U.S. The study was initiated with protocol version 1.0 dated November 14, 2011. The first patient was enrolled July 10, 2012, the first patient was randomized on September 6, 2012, the last patient was randomized on June 30, 2016, and the study completion date was September 14, 2015.

The original protocol randomized patients using a coin toss method. In July 2013, at FDA's advice and following randomization of the first 28 patients, the randomization method was changed to the permutated block method. According to the permuted block randomization scheme, patients were randomized and stratified by 1) somatostatin receptor scintigraphy tumor uptake score centrally assessed (Grade 2, 3 and 4, the highest score measured among all the target lesions will be used for stratification purpose); and 2) length of time that a patient has been on the most recent constant dose of octreotide prior to randomization (≤ 6 and > 6 months).

FDA's review of efficacy was limited to the primary measure PFS and key secondary measures: ORR, OS, and DoR for NETTER-1. The efficacy cut-off date was July 24, 2015. The OS updated analysis was conducted using a cut-off date of June 30, 2016, as agreed to by FDA.

Study Population:

Key eligibility criteria include:

- Presence of locally advanced/inoperable or metastatic, histologically proven, midgut carcinoid tumor with at least 1 measurable site of disease (centrally confirmed).
- Ki67 index ≤ 20% (centrally confirmed).
- Treated with octreotide LAR at a fixed dose of 20 or 30 mg at 3-4 week intervals for at least 12 weeks prior to randomization on the study.
- Progressive disease (centrally confirmed), assessed using RECIST Criteria (Version 1.1) while receiving an uninterrupted fixed dose of octreotide LAR (20-30 mg/at 3- week

intervals).

- Presence of somatostatin receptors based on positive OctreoScan imaging with tumor uptake observed in each target lesion ≥ normal liver uptake on planar imaging obtained within 24 weeks prior to randomization (centrally confirmed).
- Karnofsky Performance Score (KPS) ≥ 60.
- Laboratory Exclusions:
    - Serum Creatinine >150 µmol/L (>1.7 mg/dL) or creatinine clearance < 50 mL/min (Cockroft Gault).
    - Hb concentration < 5.0 mmol/L (<8.0 g/dL); WBC <2x10^9/L (2000/mm^3; platelet count <75 x10^9/L (75 x10^3/mm^3).
    - Total bilirubin >3xULN.
- Prior treatment with peptide receptor radionuclide therapy (PRRT).
- Prior external beam radiation therapy to more than 25% of the bone marrow.

Dosimetry, Pharmacokinetics, and ECG Sub-study:

Twenty-two patients were enrolled in the NETTER-01 trial but were not randomized. These patients participated in a sub-study to provide a more complete assessment of the safety of ^{177}Lu-DOTA^0-Tyr^3-Octreotate. These patients met all study eligibility criteria and were treated and assessed as were patients randomized to the Lu study arm. However, these patients were not included in the efficacy analysis. Please see the FDA Clinical Pharmacology Reviewer's review for details of the findings from this sub-study.

Study Treatment:

Patients were randomized to one of two treatment arms:

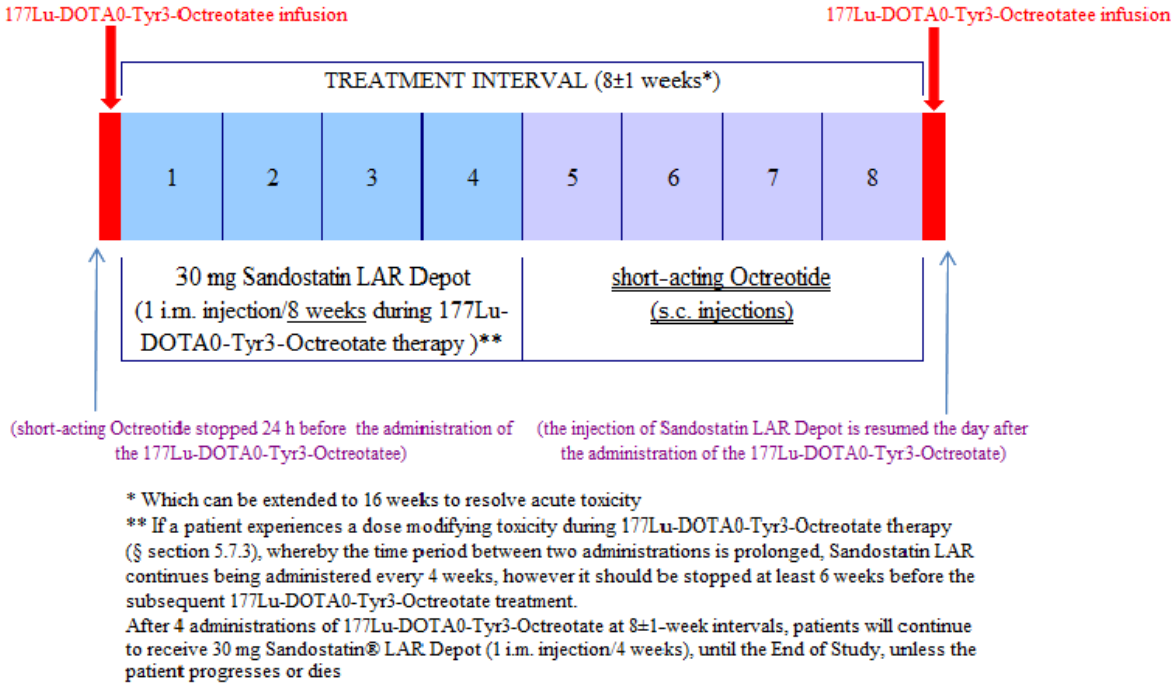
- Lutathera (LU)(N=112): ^{177}Lu-DOTA^0-Tyr^3-Octreotate (Lutathera®) plus best supportive care (30 mg octreotide LAR), or
- Octreotide (N=111): High dose (60 mg) octreotide LAR.

^{177}Lu-DOTA^0-Tyr^3-Octreotate (LU) Treatment Arm

Patients in the LU arm received a maximum of 4 doses of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, 7.4 GBq per dose at 8 week intervals (±1 week) for a maximum cumulative dose of 29.6 GBq (800 mCi). Treatment could be delayed for up to 16 weeks to allow for resolution of acute toxicities and the subsequent dose could be reduced for excessive toxicity or treatment delay. Concurrent with ^{177}Lu-DOTA0-Tyr3-Octreotate administration, patients received an amino acid solution administered as a renal protectant which was started 30 minutes prior to start of ^{177}Lu-DOTA^0-Tyr^3-Octreotate, and administered for a total of 4 hours. Patients received commercially

available amino acid solutions: in Europe patients received Vamin 18, and in the U.S., patients received AminoSynII 10%. Patients were routinely treated with anti-emetics prior to administration with the amino acid solution. Granisetron (3mg), ondansetron (8 mg), or tropisetron (5 mg) were recommended for anti-emetic use. Investigators were advised to avoid prednisone as routine anti-emetic treatment because of the potential for somatostatin receptor down-regulation. Patients on the LU arm also received 30 mg octreotide LAR intramuscularly (IM) every 4 weeks ± 3 days for clinical symptom control. Octreotide LAR was not administered within 6 weeks of the next treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Short-acting octreotide was administered subcutaneously (SQ) in the interval prior to the next scheduled ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dose but was not allowed during the 24-hour period before the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment dose. Following the final treatment dose, patients continued to receive 30 mg octreotide LAR until the time of progression or until the End of Study (Figure 10).

Figure 10: Treatment Schema for the LU Treatment Arm



* Which can be extended to 16 weeks to resolve acute toxicity
** If a patient experiences a dose modifying toxicity during 177Lu-DOTA0-Tyr3-Octreotate therapy (§ section 5.7.3), whereby the time period between two administrations is prolonged, Sandostatin LAR continues being administered every 4 weeks, however it should be stopped at least 6 weeks before the subsequent 177Lu-DOTA0-Tyr3-Octreotate treatment.
After 4 administrations of 177Lu-DOTA0-Tyr3-Octreotate at 8±1-week intervals, patients will continue to receive 30 mg Sandostatin® LAR Depot (1 i.m. injection/4 weeks), until the End of Study, unless the patient progresses or dies

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, page 48 \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf

Octreotide Treatment Arm

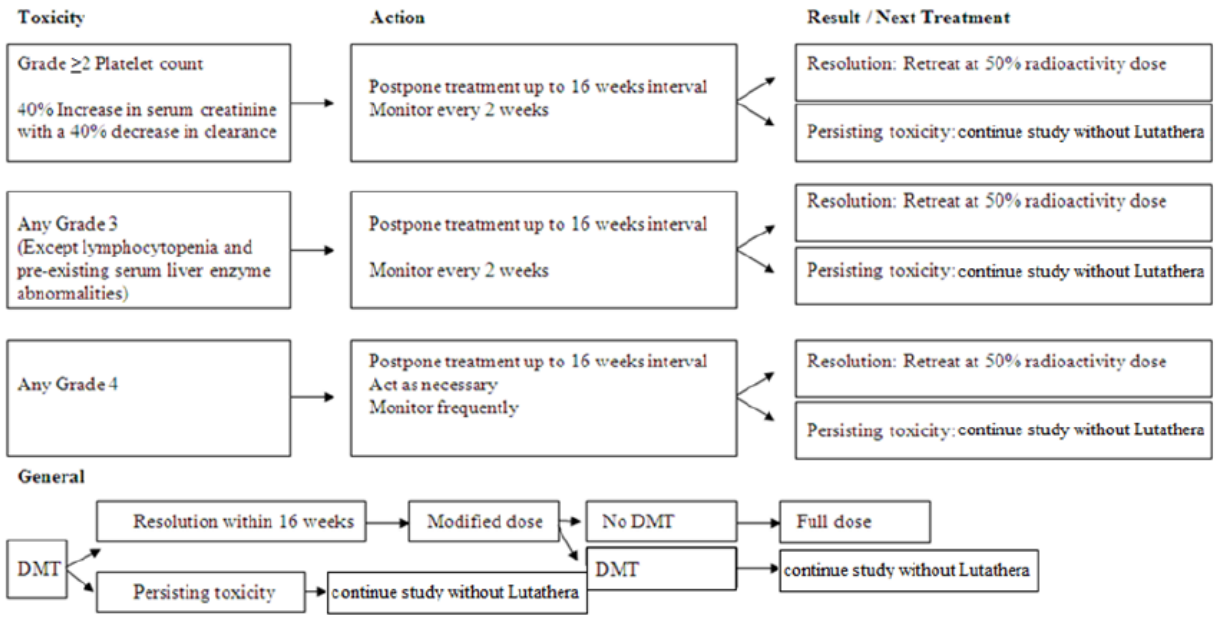
Patients in the octreotide arm received 60 mg octreotide LAR intramuscularly (IM) as two concurrent 30 mg IM injections of octreotide LAR every 4 weeks ± 3 days. Patients continued to receive 30 mg octreotide LAR until the time of progression or until the End of Study.

Dose Modifying Toxicity Guidelines

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

The clinical protocol-specified dosing modification rules for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for toxicity is shown below in Figure 11. If a dose-modifying toxicity (DMT) was observed, the next dose could be administered with a 50% dose reduction. If DMT did not recur, the next dose could be re-escalated back to the full dose level. If the DMT recurred, the patient was discontinued from ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, but could continue octreotide LAR at monthly intervals at the investigator's discursion.

Figure 11: Dose Modifying Schemes for 177Lu-DOTA0-Tyr3-Octreotate Treatment Arm



Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, page 54 \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf

Dose modifying toxicity for suspected octreotide LAR

If Grade 3 or 4 toxicity, especially abdominal symptoms and hypo- and hyperglycemia, were encountered and attributed to octreotide LAR, the dose of octreotide LAR was reduced or suspended until the event resolved. The dose could then be re-escalated to the initial dose of octreotide LAR at the investigator's discretion.

Dose modifying toxicity for nausea/vomiting suspected related to amino acid solution

If nausea and vomiting occurred concurrent with administration of amino acid solution despite premedication, reduction of the rate of infusion was recommended according to the rate schedule below:

Table 7: Modification of Amino Acid Infusion Rate for Nausea and Vomiting During Infusion

Solution	Vol (L)	Time (h)	Rate (mL/h)
AminoSynII 10% - **maximum infusion rate**	2	4	**500**
AminoSynII 10% (5h)		5	400
AminoSynII 10% (6.25h) – **minimum infusion rate***		6.25	**320**
Vamin 18 – **maximum infusion rate**	2	4	**500**
Vamin 18 (5h)		5	400
Vamin 18 (6.15h) – **minimum infusion rate***		6.15	**325**

* It was highly recommended not to reduce infusion rates below the stated minimum (e.g., 320 mL/h for Aminosyn II 10%, or 325 mL/h for Vamin 18).

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Study Assessments:

The study schedule for both arms is summarized in the tables below. Disease assessment in both arms was performed every 12±1 weeks from the time of randomization, and the IRC analyzed imaging using RECIST criteria and communicated the independent assessment to the investigator within 5 working days. Patients with progressive disease per IRC assessment discontinued therapy and proceeded to the long-term follow-up phase. Patients who had not progressed at the time of the data cut-off for the primary analysis were assessed every 12 weeks until week 76 unless they developed clinical signs/symptoms of disease progression, which led to an assessment, or died.

Table 8: Visit Schedule: 177Lu-DOTA0-Tyr3-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Study Treatment Phase																							Follow-Up Phase[7]
																								Further visits[5]		End of Study Treatment Phase Visit	Every 6 months
Week		Week -3	0	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																											
OctreoScan®	< 24 weeks																											
Histology and Ki67[1]	x																											
Diagnosis and Extent of Cancer	x																											
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																											
Demographic Data	x																											
Relevant Medical History		x																										
Prior Therapy for Carcinoid Tumour	x	x																										
Confirmation of Eligibility and Randomization		▼																										
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																										
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x														x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x		x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x		x		
Quality of Life (EORTC GI.NET21; EORTC C30)		x					x					x			x			x			x			x		x		
Hematology[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Urinalysis[2]	x	x		x	x	x	x	x	x	x	x	x	x		x			x			x			x		x	x	x
Pregnacy test[2]		x			x			x			x																	
Serum CgA[1]		x					x				x				x			x			x			x		x		
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																												
Antitumor-therapies after progression																												
Adverse Events[5]																												
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x	x	x
Survival Information																												

Investigator had to ensure that the laboratory parameters met the retreatment criteria prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Investigator had to maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

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Footnotes:

TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; 4 administrations at 8±1-week intervals

TREATMENT: 30 mg Octreotide LAR injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Octreotide LAR injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[1]Restaging was performed every 12±1 weeks since randomization. Centrally evaluated until the PFS Primary-End-Point occured; then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. This involved comparing a recent scan (withing 4 weeks of randomization) with an older scan which must be no older than 3 yrs prior to randomization. Both scans had to be obtained while the patient was receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it was acceptable if the oldest scan was obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it was acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returned to the Octreotide LAR fixed dose after the OctreoScan® had been obtained. Octreotide LAR needed to be administered continuously between the scans.

RECIST Disease Assessment during the long-term follow-up to be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test was accepted to assess protein), Pregnancy test if applicable (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment; blood pregnancy test was accepted). 5-HIAA had to be done on 24h urine collection: in case of logistic problems, the patient should have been instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam was requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests were performed within 2 weeks before and 4±1 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum:
  a. serum blood urea nitrogen and creatinine
  b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
  c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.
- If a 40% increase over the baseline serum creatinine value occured during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients had also to have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should have been through two 24-h urine collections. Total urinary protein should have also been measured

[3]During the study, symptoms were recorded in the e-CRF according to patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) were not eligible according to exclusion criterion №-12)

[5]AEs/SAEs were reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate had to be reported to the Sponsor Safety Officer

[6]Any progressive patient ceased treatment/assessment and proceeded to the 5years long-term follow-up assessment.
Any non-progressive patients continued treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:
a) Patients who had 76 weeks or more treatment/assessment stopped treatment but continued 6-monthly assessments for overall 5-years from the date of randomization of the last patient

b) Remaining randomized patients continued in the fixed 76-week treatment/assessment period unless progression occured, then continued for overall 5-year from the date of randomization of the last randomized patient

[7]Patient had to be contacted every 6 months until the moment 158 deaths had occurred, or 5 years from the date of randomization of the last randomized patient whichever occured first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), further anti-tumour treatments, SAEs suspected in relationship to the study drug, tumour progression (local evaluation after the analysis of the PFS Primary End-Point) and death were reported. In case of phone contacts, medical reports/CT-MRI images had to be provided by the patient to the Investigational Site.

– – – ▶ Information to be collected during the entire study

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Table 9: Visit Schedule: Octreotide LAR (Octreotide) Treatment Arm

Visit	Eligibility	Baseline	Study Treatment Phase																			Further visits[6]		End of Study Treatment Phase Visit	Follow-Up Phase[7]
Week		Week -3	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓			
Informed Consent	x																								
OctreoScan®	< 24 weeks																								
Histology and Ki67[1]	x																								
Diagnosis and Extent of Cancer	x																								
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																								
Demographic Data	x																								
Relevant Medical History		x																							
Prior Therapy for Carcinoid Tumour	x	x																							
Confirmation of Eligibility and Randomization		▼																							
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																							
ECG		x	x		x		x		x															x	
Physical Exam and Vital Signs		x				x			x			x			x			x			x		x	x	
Karnofsky Performance Status	x	x				x			x			x			x			x			x		x		
Quality of Life (EORTC GI.NET21; EORTC C30)		x				x			x			x			x			x			x		x		
Hematology[2]	x	x		x		x			x			x			x			x			x		x	x	x
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x		x	x	x
Urinalysis[2]	x	x		x		x			x			x			x			x			x		x	x	x
Pregnancy Test		x																							
Serum CgA[1]		x				x			x			x			x			x			x		x		
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant/Rescue Therapy																									
Anti-tumour therapies after prgression																									
Adverse Events																									
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x	x	x
Survival Information																									

Investigator was responsible to ensure that the laboratory parameters meet the retreatment criteria. Investigator had to maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

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Footnotes:

TREATMENT: 60 mg 4-week interval Octreotide LAR injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Restaging was performed every 12±1 weeks since randomization. Centrally evaluated until the analysis of the PFS Primary End-Point (74 evaluable and centrally confirmed progressions or death events), then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. . This involved comparing a recent scan (withing 4 weeks of randomization) with an older scan which must be no older than 3 yrs prior to randomization. Both scans had to be obtained while the patient was receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it was acceptable if the oldest scan was obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it was acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR had switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returned to the Octreotide LAR fixed dose after the OctreoScan® had been obtained. Octreotide LAR needed to be administered continuously between the scans. RECIST Disease Assessment during the long-term follow-up was performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter only at baseline for female of childbearing potential; blood pregnancy test is accepted). 5-HIAA had to be done on 24h urine collection: in case of logistic problems, the patient should have been instructed to collect urine the day before the scheduled visit at site. 5-HIAA exam was requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits)

[3]During the study symptoms were recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) were not eligible according to exclusion criterion №-12)

[5]AEs/SAEs were reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate had to be reported to the Sponsor Safety Officer

[6]Any progressive patient ceased treatment/assessment and proceeded to the long-term follow-up assessment.
Any non-progressive patients continued treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:
a) Patients who had 76-weeks or more treatment/assessment stopped treatment but continued assessments for overall 5-year from the date of randomization of the last patient

b) Remaining randomized patients continued in the fixed 76-week treatment/assessment period unless progression occured, then continued for overall 5-years from the date of randomization of the last randomized patient

[7]Patient had to be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), tumour progression (local evaluation after the analysis of PFS Primary End-Point, further anti-tumour treatments and death were reported. In case of phone contacts, medical reports/CT-MRI images had to be provided by the patient to the Investigational Site.

- - - - - ► Information to be collected during entire the study

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, page 40 \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf

Study Endpoints

The primary endpoint was progression-free survival (PFS). PFS was defined as the time from the date of randomization to the date of tumor progression using RECIST 1.1 criteria as assessed by the IRC or death from any cause.

Key secondary efficacy endpoints were: overall response rate (ORR), defined as the proportion of all randomized patients with the best overall response of partial response (PR) or complete response (CR), and overall survival (OS), defined as the time from randomization to the date of death from any cause, or to the last contact at the date of data cut-off, during the entire study period (treatment phase and follow-up phase).

Quality of Life (QoL) was assessed using the EORTC QLQ-C30 and the EOTC QLQ-G.I.NET21 questionnaires which were filled in by the patient prior to receiving the CT/MRI imaging results.

Statistical Analysis Plan

Based on the FDA's Complete Response letter to the original NDA submission, the applicant revised the statistical analysis plan (SAP) to V3. The SAP subsection reflects the SAP V3, ADRG, ADRG addendums, and CSR V2.0.

Sample Size Considerations

Assuming that the median PFS was 14 months in the octreotide arm and 30 months in the Lutathera arm, a total of 74 centrally confirmed PFS events per IRC assessment were needed to detect a hazard ratio of 0.47 with 90% power at a 2-sided alpha level of 5%.

The trial was also designed to test OS. Assuming the median OS was 32 months in the octreotide LAR arm and 50 months in the Lutathera arm, a total of 158 death events were needed to detect a hazard ratio of 0.64 with 80% power at a 1-sided alpha level of 2.5%. An interim analysis was planned at the time of PFS analysis. The O'Brien-Fleming (OBF) boundary method was used with respective alpha allocation of 0.000085 for the OS interim analysis. Based on a lack of number of projected OS events at the planned interim analysis, the meaning of 0.000085 is unclear. The actual end-of-study would be conducted at 158 death events or after 5 years from the randomization date of the last randomized patient, whichever occurs first.

Upon further clarification, the applicant conducted neither unplanned PFS nor OS interim analysis. At the request of the FDA, one additional updated analysis of OS, with data cut-off of June 30, 2016, was also included in this NDA resubmission with no alpha allocation penalty applied as agreed to with FDA.

Based on the actual planned and updated OS analysis, FDA calculated the alpha allocation using the OBF boundary method via the EAST 6.6.1 software (Table 10). The stopping boundaries for

the 2-sided alpha allocations are 0.00008 and 0.002 for the pre-planned OS interim analysis and updated OS analysis. The alpha for the final OS analysis is 0.049.

Table 10: NETTER-1 Trial: OS Analysis Timing and 2-Sided Stopping Boundary for OS 0n the ITT

Number of Look	Information Fraction	Cumulative Alpha Spending	Stopping Boundaries
1	48 (30%)	0.00008	0.00008
2	70 (45%)	0.002	0.002
Final	158	0.05	0.049

Major secondary endpoints include OS and ORR. A hierarchical procedure was proposed to adjust for multiplicity in testing the secondary endpoints in the order of ORR and OS.

Analysis Sets

The following analysis sets were defined:

- The primary efficacy analysis population was the intent-to-treat (ITT) study population, which was categorized by the treatment arm to which they were assigned at randomization, regardless of the actual treatment received. The ITT population was named as the Full Analysis Set (FAS) in the statistical analysis plan (SAP) and protocol.

- The per-protocol set (PPS) included all randomized patients, who had no major protocol violations.

- The safety set (SAF) included all randomized patients who received any amount of study drug. For analyses, patients were categorized by the actual treatment received.

The ITT was used for all analyses of efficacy, demographics, and baseline disease characteristics. The PPS was used for the sensitivity efficacy analyses. The SAF was used for all safety analyses.

Efficacy Analysis Methods

PFS

The analysis for PFS was to be performed using an un-stratified log-rank test. The median PFS with corresponding two-sided 95% CIs and survival curves were to be estimated using the Kaplan-Meier (KM) method. If a patient had no IRC-assessed progression and had not died at the time of the primary end-point analysis, the patient was to be regarded as censored in the context of a time to event analysis at the date of last evaluable tumor assessment. Table 11 presents the actual censoring rule for primary PFS analysis in the CSR 2.0.

Table 11: NETTER-1 Trial: Actual Censoring Rule for Priamry PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Date of randomization	Censored
Progression documented between scheduled assessment visits	Date of radiological assessment showing progression, if centrally confirmed	Event (Progressed)
No progression	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for undocumented progression and no additional scans are collected	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity or other reason with no additional scans	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Treatment discontinuation for toxicity, but with continued scanning and subsequently documented progression	Date of radiological assessment (date of the scan) showing progression, if centrally confirmed	Event (Progressed)
New anti-cancer treatment started	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored
Death before first progression assessment	Date of death	Event (Death)
Death between adequate assessment visits	Date of death	Event (Death)
Death or progression after more than one missed assessment visit during the treatment phase*	Date of last adequate radiological assessment (date of the scan) of measured lesions	Censored

(*) In this trial, more than one missed assessment visit is defined as an assessment visit not occurring within 2.5 times the length between two per protocol assessment visits (i.e. 210 days following the previous visit); Source: Adapted from ADRG Section 8.2

The applicant also conducted the following sensitivity analyses for PFS:

- Time to tumor assessment analysis between treatment arms from the date of randomization and from the date of treatment initiation
- Different censoring rules:

a. Assigning the event time to the next scheduled imaging time rather than the actual time, in case progression was documented between scheduled assessments visits, to correct for any difference in timing of scans.
b. Ignoring new anti-cancer treatments started before progressive disease, instead of censoring PFS prior to the start of any such treatments.
c. Ignoring missed assessment visits during the treatment phase, instead of censoring PFS prior to those missed visits.
d. Ignoring both missed assessments and new anti-cancer treatments.
e. Calculating the PFS times from 1) date of baseline scan and, 2) date of first investigational drug administration instead of date of randomization; this PFS sensitivity analysis would be used to assess the impact of any delay in screening process or initiation of treatment.

- PFS analysis per INV assessment.
- Stratified log rank test as well as stratified Cox regression.
- PFS analysis on the PPS.

ORR

The analysis for ORR would be the Fisher's exact test. Response rates and Binomial exact 95% CIs would be calculated for the ORR by treatment arm on the ITT with measurable disease at baseline which is a subset of the ITT population. FDA generally considers the results of the ITT population as the primary ORR analysis. Upon a further information request, the applicant provided the ORR analysis based on the ITT population.

OS

The OS analysis method is identical to that of the PFS analysis.

QoL

QoL would be assessed by comparison of the changes of the different scales and single items from baseline (i.e. pre-post randomization differences) by means of Wilcoxon's rank sum test on an alpha-level of 5%.

Protocol Amendments

The following summary of protocol amendments was provided by Dr. Joohee Sul in the review of the original NDA submission and is reproduced here for completeness.

- July 6, 2012:
    - Definition of PFS, TTP and OS were modified to be based on time from the date of randomization rather than the date of first treatment.
    - Clarified and added safety assessments for blood chemistry and urine tests for both arms.

- Added details of the DSMB responsibilities.
- Added details on the sub-study conduct and data analysis.
- Modified appendices for recommended precautions for patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, randomization procedures, and determination of administered radioactivity.

- July 24, 2013:
  - Biased coin randomization scheme replaced by stratified permuted block scheme with a balanced ratio (1:1) between the treatment arms, and stratification for specific center enrolment was deleted.
  - The method to control the family-wise type I error rate for OS and ORR was included as well as a detailed description of the statistical analysis for OS.
  - The end of study definition was modified and the description of the primary analysis adapted accordingly.
  - Patient replacement for the primary analysis was excluded and the primary analysis using the log-rank test was specified.
  - Clarifications related to study procedures (e.g. CT/MRI timelines, OctreoScan), the study population characteristics, and the allowed time-windows for the octreotide LAR injections.
  - Clarified discontinuation criteria for individual patients.
  - Further options for additional allowed amino acid solutions, details on the drug administration procedures in the octreotide arm, details about the administration procedures of rescue medication, and details about the handling of study medication were added.
  - Further details on SAE and AESI reporting were included.

- September 23, 2013:
  - Added details on the dosimetry sub-study procedures related to the performance of optional dosimetry.
  - Increased the number of sites participating in the sub-study was increased.

- March 25, 2014:
  - Adjusted the sample size and increased the follow-up period from 3 to 5 years to detect a statistically significant and clinically relevant difference in OS.
  - Specified that the primary analysis was to be conducted after 74 PFS events.
  - Added secondary endpoints: Duration of Response (DoR) and Time to Second Progression (PFS2) as exploratory objectives.
  - Specified that the End of Study (EOS) is when 158 deaths have occurred, or 5 years have elapsed since the date of randomization of the last randomized patient, whichever occurs first.
  - Added specifications regarding the use of an unstratified log-rank test in the primary analysis of PFS.
  - Added details on Dose Modifying Toxicity criteria and procedures.

- Modified the sub-study exclusion criteria regarding subsequent treatments.
- Added additional criteria for discontinuation related to screening failures, study termination, and study withdrawal.
- Added description of handling discrepancies in the evaluation of the progressive status between investigator and central assessor.
- Clarified procedures for dropouts, replacements, and deliberate treatment interruption criteria.
- Added recommendations regarding the amino acids solution infusion and regarding the use of antiemetics.
- For patients on the sub-study, additional information and clarifications included ECG assessments, physical examination and vital signs data collection procedures, timing of the exams in relation to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments, dosimetry, PK and cardiac assessments.

- June 5, 2014:
  - Specified recruitment, randomization, and data analyses details for the sub-study.

8.1.2 NETTER-1 Trial Study Results

Compliance with Good Clinical Practices

In the CSR for the NETTER-1 trial, the applicant states that the study was conducted in accordance with:

1. The principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments,
2. The International Conference on Harmonization, Good Clinical Practice (ICH GCP guidelines E6, 1996),
3. The FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50, 54, 56, 312, and
4. The Data Protection Act 1998, the 18th World Medical Assembly, Helsinki 1964 and later revisions.

The applicant also states that the investigational centers initiated the study procedures after approval has been obtained from the Radioprotection Agencies, Competent Authorities and the Ethical Committee in compliance with local laws.

Financial Disclosure

In the NDA submission, the applicant submitted PDF copies of Statement of Financial Interests for Investigators (NDA Module 1.3.4). There was no summary of the financial interests or arrangements provided, and each form was reviewed for disclosures. A request for missing documentation and clarifying information was sent to the applicant on June 9, 2016. The applicant submitted responses to the information request on June 16, 2016 and July 1, 2016. The applicant did not identify any sub-investigators or principle investigators who participated

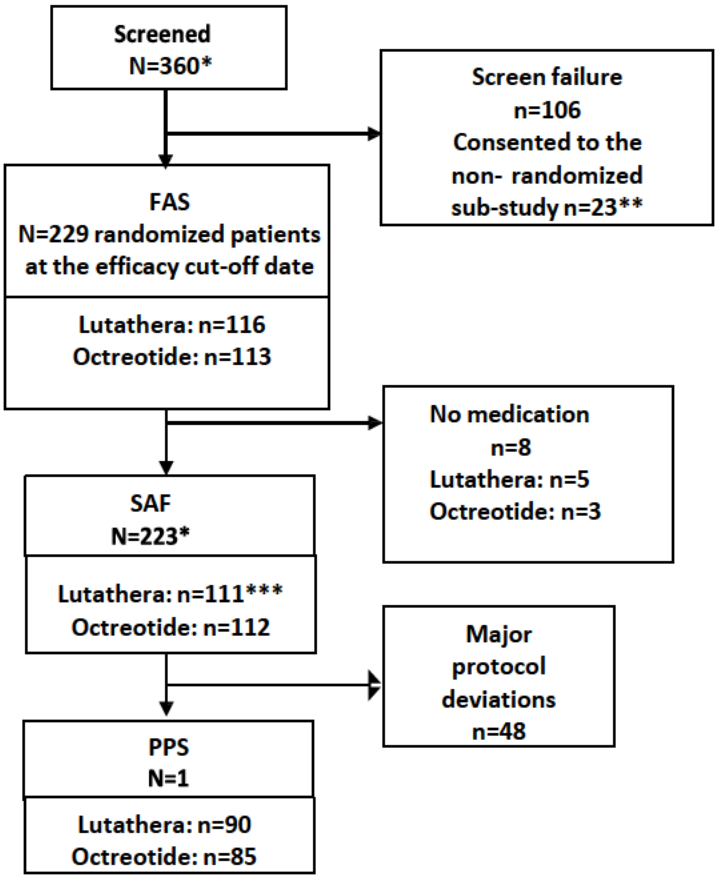
and completed their respective "Statement on Financial Interests" form as having a financial arrangement as defined in 21 CFR 54.2(a), a proprietary interest in the product or significant equity interest in the covered studies as defined in 21 CFR 54.2(b) or as the recipient of significant payments as defined in 21 CFR 54.2(f). In the resubmission, "Statement on Financial Interests" forms were provided from additional investigators (Drs. Teitelbaum, Strosberg, Almahanna, El-Haddad, and Soares), none of whom reported reportable financial interests.

Patient Disposition

At the time of the cut-off date for database lock (June 30, 2016), 360 patients had been screened at 41 study sites in Belgium, France, Germany, Italy, Portugal, Spain, U.K., and the U.S. Of these, 106 patients did not meet criteria for study entry. Twenty-three patients were selected for the PK sub-study and were not randomized. Twenty-two patients in the PK sub-study were treated. In the randomized cohort, two remaining patients were screened but were randomized after the efficacy cut-off date and were not included in the efficacy analysis. The ITT population included a total of 229 patients (Lutathera: n=116; octreotide: n=113). Figure 12 presents the populations in NETTER-1 used in the analyses.

The applicant provided reasons for disposition of the entire randomized patient population instead of on the ITT population. Table 12 summarizes FDA's summary of treatment discontinuations for patients in NETTER-1 on the ITT population. Progression of disease was the most common reason for treatment discontinuation (16% vs. 57%) in the Lutathera arm. Fewer patients on the Lutathera arm discontinued treatment for completed treatment (40% vs. 10%). The two study arms were generally comparable in the other reasons.

Figure 12: NETTER-1 Trial: Study Populations



Source: AAA-III-01(NETTER-1) Clinical Study Report (Version 2.0; Version Date: 5July2017), Figure 10-1, page 86
*Two patients were screened but randomized after the primary efficacy endpoint cut-off date and were included in the SAF.
** One patient from the sub-study was not treated.
***One patient randomized to receive Lutathera received only octreotide and was re-classified with the octreotide arm.

Table 12: NETTER-1 Trial: Disposition by Treatment on the ITT

Reason of Disposition	Lutathera + Octreotide LAR (30 mg) N=116 n (%)	Octreotide LAR (60 mg) N=113 n (%)
Discontinued	112 (97)	111 (98)
Progressive Disease	19 (16)	64 (57)
Completed Treatment	46 (40)	11 (10)
Physician Decision	16 (14)	16 (14)
Withdrawal by patients	10 (9)	10 (9)
AE	13 (11)	10 (9)
Not Compliance	2 (2)	0
Other	6 (5)	0

Protocol Violations/Deviations

Overall, 59 major protocol violations were reported in 48 (22%) (Lutathera: 23 [21%]); octreotide LAR 25 [22%]) patients. Eight additional randomized patients received no treatment, resulting in 56 (24%) patients on the ITT having major protocol violations. The breakdown of major protocol violations by study arm is shown below:

Table 13: NETTER-1 Trial: Overview of Major Protocol Deviations

Type of major protocol deviation	Lutathera + Octreotide LAR (30 mg) N=116 %	Octreotide LAR (60 mg) N=113 %
Inclusion/Exclusion criteria not met	8	7
Incorrect procedure	6	12
Out of window	12	7

Source: AAA-III-01(NETTER-1) CSR V2; Version Date: 5July2017), Table 10-2, page 89

The number of patients with Inclusion/exclusion criteria not met was comparable between arms. The number of patients assessed as having an incorrect study procedure was higher in the octreotide arm. This was largely attributable to a higher number of patients reported to have poor quality assessments in the octreotide arm (8% vs 2%).

While the overall rate of major protocol violations in the NETTER-1 trial appears high, more problematic in terms of the efficacy analysis was the discrepancy between study arms in the number of patients with a delay between the baseline tumor assessment and the first study treatment. While up to 12 weeks between baseline screening and the date of first treatment was allowed per protocol, 14% of patients on the Lutathera arm and only 1% of patients on the octreotide arm had a delay of 30 days or more between the baseline screen and the date of first treatment. The potential impact of the delay in initial treatment on the analysis of PFS is further discussed under the efficacy result for PFS subsection. Additionally, a sensitivity analysis was conducted using the per protocol analysis set (PPS) in Table 22.

Demographic Characteristics

A total of 229 patients were randomized in a 1:1 allocation (Lutathera: 116; octreotide: 113). The two trial arms were generally comparable in age, sex, race, region of enrollment, and baseline Karnofsky performance status.

Table 14: NETTER-1 Trial: Demographic Characteristics of Patients in the ITT Population

Demographic Parameters	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
ITT, n	116	113
Randomized but not treated, n	5	3
Randomized and treated[2], n	110	111
OS Update, n	117	114
Sex: male, %	54	47
Age (years), median (range)	64 (28, 84)	65 (34, 87)
≥ 65 years, %	47	50
Race, %		
White	79	85
Black or African American	4	4
Hispanic or Latino	5	2
Not Applicable[1]	10	8
Region, %		
United States	57	61
EU	43	39
Belgium	3	2
France	10	8
Germany	9	6
Italy	4	8
Portugal	<1	0
Spain	4	5
UK	11	10
Karnofsky Performance Score, %		
100	29	27
90	44	43
80	21	21
70	3	6
60	3	2
Median (range)	90 (60, 100)	90 (60, 100)

1. 21 patients' race and/or ethnicity were not collected in France because of local regulations.
2. Subject DE03-001 received octreotide LAR (30 mg) only and did not receive Lutathera. This patient was reclassified with the octreotide arm for the safety analysis.
Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, Abstracted from Table 11-2 (page 90) and Table 11-4 (Page 93) \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf verified by reviewer.

Other Baseline Characteristics

Table 15 summarizes baseline disease characteristics in the ITT population based on the efficacy analysis data cut-off. Patients in the two trial arms were generally similar with respect to baseline disease characteristics. Seventy-four percent had primary tumor in the Ileum. Most had well differentiated tumors (ENET Grade 1). Eighty-six percent had a tumor burden reported as limited. Nearly 96% of patients were reported to have metastatic disease which included metastatic disease in the liver. Based on reports of concomitant symptoms, the study groups were comparable in the number of patients with secretory tumors.

Table 15: NETTER-1 Trial: Disease Characteristics of Patients in the ITT Population

Disease Characteristics	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
Ki67, %		
ENETS G1: ≤2% positive cells	66	72
ENETS G2: 3-20% positive cells	34	28
Tumor Burden, %		
Extensive	3	2
Limited	85	87
Moderate	11	12
Disease Stage, %		
IIA-IIB	0	2
IIIB	3	8
IV	91	79
Not Assessed	6	12
Time since first diagnosis of midgut carcinoid (months)	45.7	57.8
Primary tumor site, %		
Jejunum	5	8
Ileum	74	73
Appendix	1	2
Right colon	3	1
Other	17	17
Metastatic disease present, %		
Yes	100	98
No	0	2
With Ex- Hep Metastases, %	77	71
Concomitant symptoms, %		
Hypertension	55	58
Flushing	6	13
Diarrhea	12	17
Hypothyroidism	13	14
Type 2 diabetes	11	11
Carcinoid syndrome	6	2

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, Abstracted from Tables 11-14 (page 104) and 11-15(page 105) \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf verified by reviewer.

The two trial arms were generally similar regarding prior surgical resection, ablation, and chemo-embolization for midgut carcinoid. A greater percentage of patients on the Lutathera arm were reported as having had a prior treatment other than radiotherapy, radiometabolic

therapy, or chemotherapy (37% vs 27%). This treatment arm included protein kinase inhibitors. The implication of this finding is unclear but may suggest that patients in the Lutathera arm were more heavily pretreated.

Table 16: NETTER-1 Trial: Prior Treatment for Midgut Carcinoid in Patients on the ITT

Prior Treatment for Midgut Carcinoid	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
Any prior cancer surgery, %		
Yes	80	83
Number of patients with prior, %		
Resection	78	83
Ablation	5	10
Chemo-embolization	12	10
Time since last intervention (years) Mean(SD)	3.3(3.3)	4.3(3.5)
Another other previous cancer treatment, %		
Yes	42	35
No	58	65
Type of other previous cancer treatment, % Yes		
Radiotherapy	3	5
Radiometabolic therapy	1	1
Chemotherapy	9	13
Other**	37	27

**Includes protein kinase inhibitors
Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, Abstracted from Tables 11-5 (page 95) and 11-6(page 97) \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf verified by reviewer.

Stratification Factors

The two trial arms appeared similar in terms of the pre-specified stratification factors: time on a constant dose of octreotide and the highest OctreoScan tumor uptake score (details in Table 17).

Table 17: NETTER-1 Trial: Distribution of Stratification Factors in the ITT Population

Stratification Factors	**Lutathera + Octreotide LAR (30 mg) N=116 %**	**Octreotide LAR (60 mg) N=113 %**
Length of time on constant octreotide dose		
> 6 months	73	75
<= 6 months	27	25
Highest OctreoScan tumor uptake score:		
Grade 2	12	14
Grade 3	30	30
Grade 4	58	57

The neuroendocrine marker profiles were generally similar between study arms at baseline (see Table 18).

Table 18: NETTER-1 Trial: Neuroendocrine Tumor Markers at Baseline in the ITT Population

Neuroendocrine Tumor Marker	Lutathera + Octreotide LAR (30 mg) N=116 (%)	Octreotide LAR (60 mg) N=113 (%)
Synaptophysin, % tumor cells positive		
Insufficient/Not evaluable	0	<1
0% positive cells	2	<1
1-50% positive cells	4	4
>50% positive cells	92	94
CgA, % tumor cells positive		
Insufficient/Not evaluable	2	1
0% positive cells	2	1
1-50% positive cells	4	4
>50% positive cells	92	94
NET blood/urine markers (baseline)		
CgA[µg/L]		
>2 ULN*	53	58
<=2 ULN	16	17
5-HIAA [umol/day]		
>2 ULN	47	54
<=2 ULN	29	25
Alkaline Phosphatase (AP)[U/L]		
>ULN	35	33
<=ULN	61	66

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: AAA-III-01(NETTER-1) Clinical Study Report; Version 2.0, 05July2017, Abstracted from Table 11-2 (page 90) and Table 11-4 (Page 93) \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5351-stud-rep-contr\netter-1phase3studyresubmission\phase-iii-netter-1-csr-v2-0-final.pdf verified by reviewer.
*ULN: upper limit of normal

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Efficacy Results – Primary Endpoint PFS

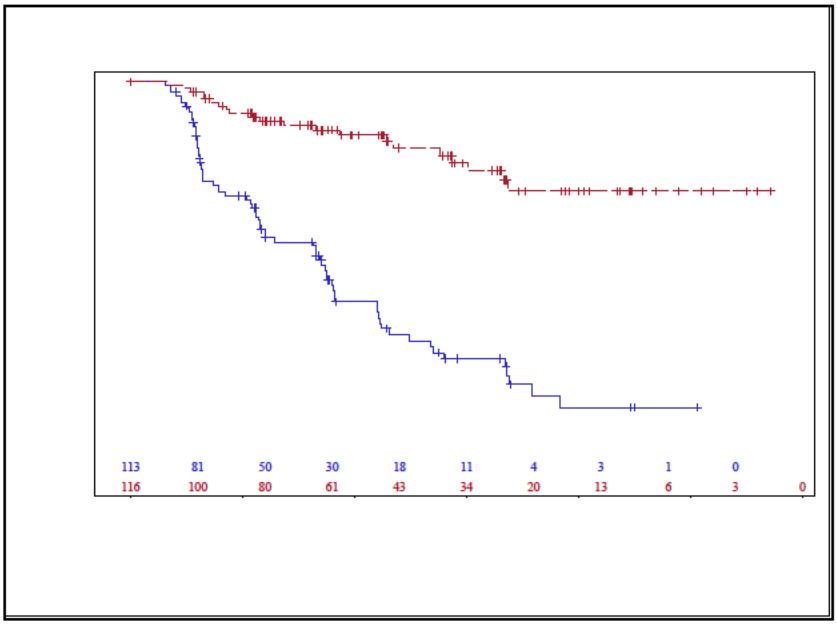
Figure 13 present the applicant's efficacy analysis results for PFS per IRC assessment which were duplicated by the statistical reviewer. The Lutathera arm demonstrated an improvement in PFS compared with the octreotide arm, based on 91 IRC-confirmed PFS events in the ITT population. The un-stratified log-rank test P value was reported to be less than 0.0001. The estimated median PFS was not reached for the Lutathera arm and 8.5 months (95% CI: 5.8, 9.1) for the octreotide arm. The corresponding un-stratified HR was reported as 0.18 (95% CI: 0.11, 0.29) in the Lutathera arm compared to the octreotide arm.

Table 19: NETTER-1 Trial: Applicant's PFS Analyses, Per IRC assessment

	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
Number of Events, n (%)	21 (18)	70 (62)
PD, n (%)	15 (13)	61 (54)
Death, n (%)	6 (5)	9 (8)
Number of Censored, n (%)	95 (82)	43 (38)
Median PFS (months), 95% CI	NR (NE, NE)	8.5 (5.8, 9.1)
Cox un-stratified HR (95% CI)	0.18 (0.11, 0.29)	
P value, unstratified log-rank test	< 0.0001	
Cox Stratified HR (95% CI)	0.18 (0.11, 0.29)	
P value, stratified log-rank	< 0.0001	

NR: Not reached; NE: Not evaluable

Figure 13: NETTER-1 Trial: Applicant's K-M Curves for PFS



There were 16 patients in the Lutathera arm and 1 patient in the octreotide LAR arm who had a treatment delay of at least 30 days after randomization. Additional patients had a treatment delay of at least 15 days: 83 (72%) patients with a median of 24 days' delay in the Lutathera arm and 15 (13%) patients with a median of 7 days' delay in the octreotide LAR arm. In the original protocol, the applicant defined the PFS start point from the treatment start date. In the 1st protocol amendment dated on July 6, 2012, definition of PFS, TTP and OS were modified to be based on the time from the date of randomization rather than the date of first treatment.

Following FDA advice received on June 23, 2017, a post-hoc assessment of time to scan

from randomization in the two arms of the NETTER-1 trial was performed to evaluate the impact of an imbalance in the time to scheduled tumor assessment on the PFS analysis. Regarding the local/investigator tumor evaluation up to the first progression of disease, the time to scan from randomization was (nominally) statistically significantly different between the two study arms at the first 8 tumor assessment visits (Table 20). However, an analysis of the time to scan from study treatment start, found no (nominally) statistically significant difference between the two study arms at all assessment visit times (Table 21).

Table 20: NETTER-1 Trial: Time from Randomization to Tumor Assessment Date as per IRC Tumor Assessment

Assessment	Median (Week)		Log Rank Test Nominal P Value
	Lutathera + Octreotide LAR (30 mg)	Octreotide LAR (60 mg)	
1st	14.6	13.0	<0.0001
2nd	26.9	25.0	<0.0001
3rd	39.1	37.1	<0.0001
4th	50.7	49.1	0.03
5th	62.4	61.1	0.02
6th	75.1	73.1	0.03
7th	87.3	85.3	0.02
8th	99.9	97.1	0.04

Table 21: NETTER-1 Trial: Time from Treatment start to Tumor Assessment Date as per IRC Tumor Assessment

Assessment	Median (Week)		Log Rank Test Nominal P Value
	Lutathera + Octreotide LAR (30 mg)	Octreotide LAR (60 mg)	
1st	12.0	12.0	0.10
2nd	24.0	24.0	0.11
3rd	36.1	36.1	0.28
4th	48.1	48.1	0.53
5th	59.6	60.0	0.86
6th	71.9	71.9	0.51
7th	85.3	84.2	0.14
8th	97.8	96.1	0.23

Time to tumor assessment analyses presented in the above show that the asymmetric tumor assessment from the randomization date is due to the time-lag in the first post randomization tumor assessment resulting from a delay in the initiation of treatment in the Lutathera arm. The asymmetric tumor assessment from the randomization date is inherited from protocol modification to follow FDA's ITT principle.

In general, pre-planned primary PFS analysis followed the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. However, the statistical reviewer noted the following review issues:

- The applicant used a 210-day gap as the threshold to calculate the flag of two continuous missing tumor assessments in the primary PFS analysis. FDA recommended that AAA use 175 [(12 * 2+1) *7] days instead. A 175-day gap as the threshold to calculate the flag of two continuous missing tumor assessments is one of the applicant's sensitivity analyses.

- There was asymmetric delayed 1st treatment post randomization between two treatment arms as well as asymmetric tumor assessments from randomization (Table 20).

- SAP V3 states that "baseline CT scan/MRI must not be older than 4 weeks before the projected randomization date. In order to provide a consistent CT/MRI scan time-point between the two arms of the study it may be necessary for the site to repeat the baseline CT/MRI scan immediately before randomization if the CT/MRI time-point is greater than 4 weeks before randomization to provide more recent and protocol-compliant lesion data." Based on the submitted SAS program and data, there were 3 patients where the post randomization date was used as their baseline tumor assessment date and 90 (39%) patients where the baseline CT scan/MRI was obtained more than 28 days prior to the randomization date. Of note, the imaging reading center (b) (4) had re-evaluated the tumor assessments. The IRC-adjudicated visit specific tumor response results were reported in the SDTM RS domain, the review could not trace back to the target lesion PD derivation, which should be based on at least 30% increase in the sum of largest lesion diameters from the pre-randomization baseline tumor assessment.

- The SAP also stated that "A radiological assessment is considered as an adequate assessment if the RECIST response (as per IRC) is CR, PR, SD or PD. A response of NE or missing will not be considered as an adequate assessment, and the visit will be considered missing for the analysis, as presented in the table above." However, NE was part of tumor response derivation as stated in the RECIST 1.1.

- As described in the ADTTE2 SAS program, the PFS censoring rule related to the last known alive date used imputed dates and used information after the efficacy data cut-off. Specifically, concomitant medication date, disposition, death date, and progress start date used imputed information. The last known alive date for the entire ITT population was derived from actual complete date, imputed complete dates, or efficacy cut date. This data manipulation occurred before applying the censoring rules. Following FDA's conventional censoring rule, the reviewer re-derived PFS data. Per FDA's sensitivity analysis, the un-stratified log-rank test P value was also reported to be less

than 0.0001. The median PFS was not reached for the Lutathera arm and 5.4 months (95% CI: 3.3, 17.9) for the octreotide arm. The corresponding un-stratified HR was reported as 0.15 (95% CI: 0.08, 0.28) in the Lutathera arm compared to the octreotide arm. The discordance between FDA's analysis and applicant's is due to the high censoring rate. Hence, FDA considers the applicant's primary PFS analysis as an exploratory analysis.

Due to above review issues, FDA assessed PFS events if a patient had disease progression or death regardless of whether the patient had missing scheduled visits, treatment discontinuation for toxicity, or new anticancer treatment started without progression. This analysis was consistent with the approach described in FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry (although the guidance is for NSCLC disease, the principle is the same); furthermore, the involved dates are not imputed or replaced. FDA's primary PFS analysis is one of applicant's sensitivity analysis, which is reported in the ADTTE2 domain in the variable PFS4.

Table 22 and Figure 14 present FDA's primary analysis results for PFS per IRC assessment. The Lutathera arm demonstrated a statistically significant improvement in PFS compared with octreotide arm based on 95 IRC confirmed PFS events in the ITT population. The un-stratified log-rank test P value was less than 0.0001. The median PFS was not reached for the Lutathera arm and 8.5 months (95% CI: 6.0, 9.1) for the octreotide arm. The corresponding un-stratified HR was reported as 0.21 (95% CI: 0.13, 0.32) in the Lutathera arm compared to the octreotide arm. The PFS sensitivity analyses using different tumor assessment (IRC vs. INV), censoring methods (imputed, start from first treatment, ignore missing, using next tumor assessment date, worst case scenario, stratified Cox model), and analysis populations (in randomized population using permuted block method and PPS population) ranged from 0.15 to 0.46, which are consistent with FDA's primary PFS analysis.

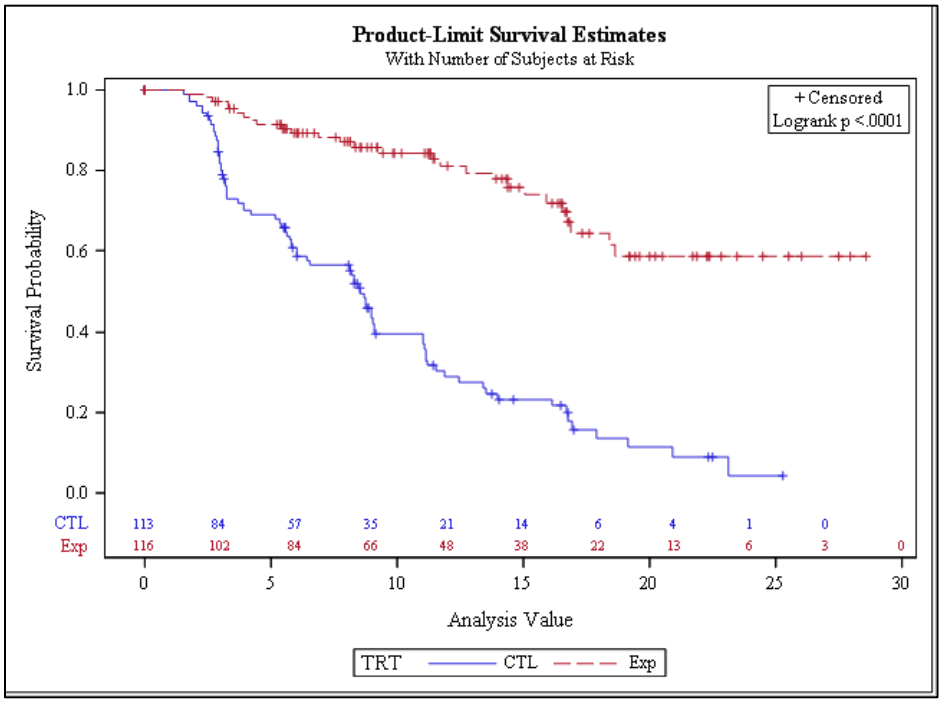
Table 22: NETTER-1 Trial: FDA's PFS Analyses, Per IRC assessment

	Lutathera + Octreotide LAR (30 mg) N=116	**Octreotide LAR (60 mg) N=113**
FDA's Primary PFS analysis		
Number of Events, n (%)	27 (23)	78 (69)
PD, n (%)	15 (13)	61 (54)
Death, n (%)	12 (10)	17 (15)
Number of Censored, n (%)	89 (77)	35 (31)
Median PFS (months), 95% CI	NR (18.4, NE)	8.5 (6.0, 9.1)
Cox un-stratified HR (95% CI)	0.21 (0.13, 0.32)	
P value, unstratified log-rank test	< 0.0001	
FDA's sensitivity Analysis		
Cox stratified HR (95% CI)	0.20 (0.13, 0.31)	
Cox un-stratified HR (95% CI) in patients	0.22 (0.13. 0.35)	

	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
randomized by Permuted Block Method		
In the PPS	0.18 (0.10. 0.31)	

NR: Not reached; NE: Not evaluable

Figure 14: NETTER-1 Trial: FDA's K-M Curves for PFS



Efficacy Results – Key Secondary Endpoint ORR

Table 23 presents the ORR and DoR analyses based on the IRC assessments in the ITT population. The Lutathera arm demonstrated an improvement in ORR compared with octreotide arm. The Fisher's exact test P value was 0.0148. The ORRs were 13% (95% CI: 6.8%, 19.0%), and 4% (95% CI: 0.1%, 6.9%) in the Lutathera arm and octreotide arm, respectively. The DoR was not reached for the Lutathera arm and was 1.9 months (95% CI: 1.9, NE) for the octreotide arm.

Table 23: NETTER-1 Trial: ORR Results Based on the IRC Measurements

	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
Overall Response	15 (12.9%)	4 (3.5%)
CR	1 (0.9%)	0

	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113
PR	14 (12.1%)	4 (3.5%)
Binomial 95% CI	(6.8%, 19.0%)	(0.1%, 6.9%)
Fisher's exact test P -value	0.0148	
DoR, median (95% CI)	NR (2.8, NE)	1.9 (1.9, NE)

NR: Not reached; NE: Not evaluable

Efficacy Results – Key Secondary Endpoint OS

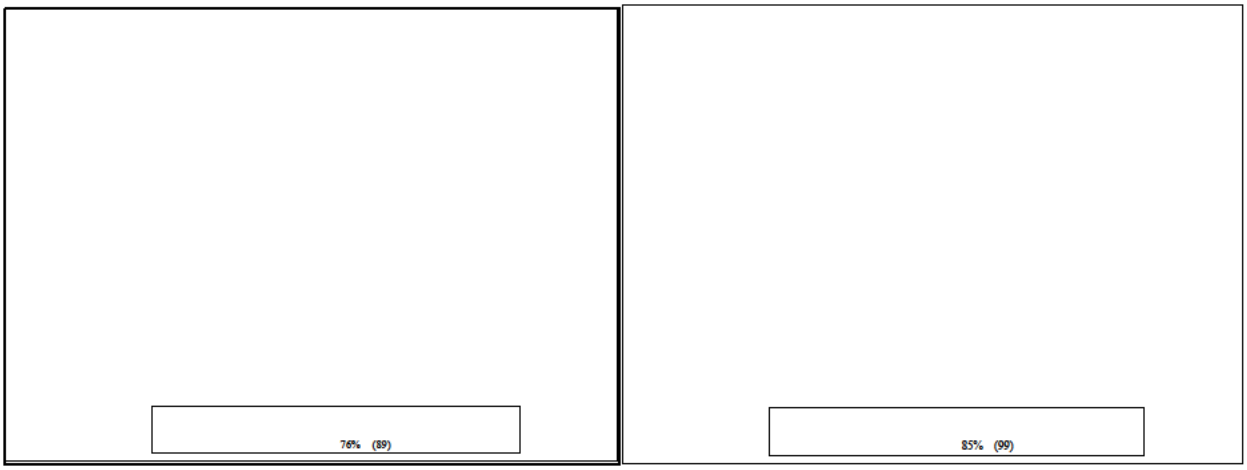
Table **24** and Figure 15 presents the applicant's OS analysis results with a total of 48 deaths at the pre-planned OS interim analysis and 71 deaths based on FDA's requested updated OS analysis. Compared to the OBF-utilized 2-sided alpha allocation of 0.00008, and 0.002 for the interim and updated OS analysis, respectively, neither analysis demonstrated a statistical significant improvement in OS. FDA noted that the applicant used imputed dates to derive OS. In the updated OS analysis, two patients who were randomized after the efficacy cut-off were included in the analysis population.

Table 24: NETTER-1 Trial: OS Analyses (CSR)

	At PFS Analysis[§]		Updated Analysis [£]	
	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113	Lutathera + Octreotide LAR (30 mg) N=117	Octreotide LAR (60 mg) N=114
Number of Deaths, n (%)	17 (14.7)	31 (27.4)	28 (23.9)	43 (37.7)
Median OS in months, (95% CI)	NR	27.4 (20.1, NE)	NR	27.4 (23.1, NE)
Cox Un-Stratified HR (95% CI)	0.46 (0.25, 0.83)		0.54 (0.33, 0.86)	
P value, Unstratified log-rank	0.0083		0.0094	

NR: Not reached; NE: Not evaluable

Figure 15: NETTER-1 Trial: K-M Curves for OS -CSR Results



a) OS Pre-Planned Interim Analysis b) OS Updated Analysis

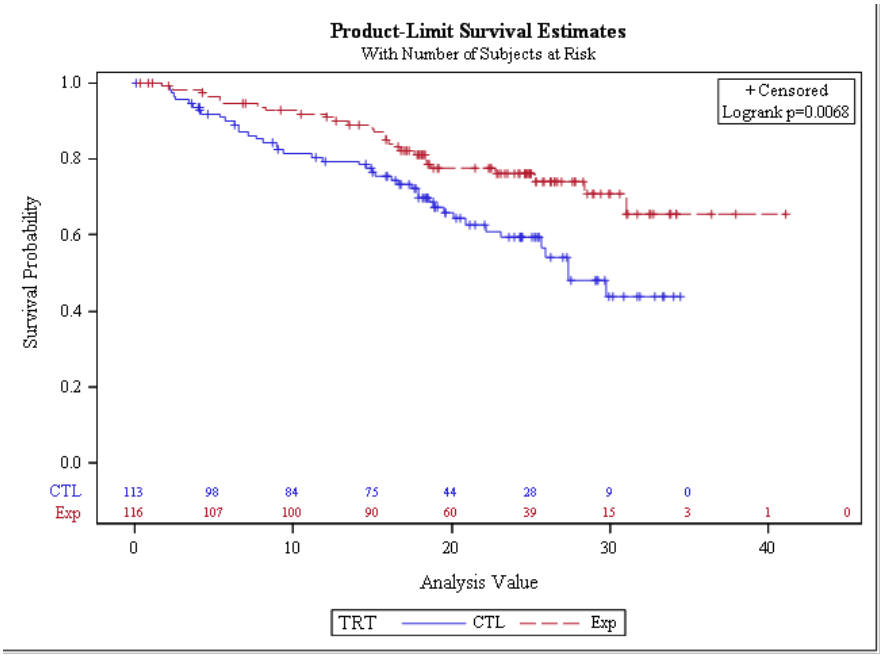
Following an FDA information request, the application amended the OS analysis using the date of randomization as the starting time in the ITT population without imputation. Table 26 and Figure 16 summarizes later amended analysis results. This analysis failed to demonstrate a statistically significant improvement in OS with a nominal un-stratified log rank test p value of 0.0068 (>0.002). The median OS was not reached in the Lutathera arm and 27.4 (95% CI: 22.2, NE) in the octreotide arm. The un-stratified HR was 0.52 with 95% CI (0.32, 0.84) for the Lutathera arm compared to the octreotide arm.

Table 25: NETTER-1 Trial: Updated OS Analyses in the ITT without Imputed Date

	Updated Analysis	
	Lutathera + Octreotide LAR (30 mg) N=116	**Octreotide LAR (60 mg) N=113**
Number of Deaths, n (%)	27 (23.3)	43 (38.1)
Median OS in months, (95% CI)	NR (31.0, NE)	27.4 (22.2, NE)
Cox Un-Stratified HR (95% CI)	0.52 (0.32, 0.84)	
P value, Unstratified log-rank	0.0068	

NR: Not reached; NE: Not evaluable

Figure 16: NETTER-1 Trial: K-M Curves for OS Updated Analysis without Imputed Date



Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Upon FDA's further IR, the applicant only provided changes for global health status from baseline in the submission. Table 26 presents a snapshot of the applicant's results as provided in the CSR 2.0.

Table 26: NETTER-1 Trial: Global Health Status QLQ changes from Baseline Between both Treatment Arms

Visit	Treatment	Nx	n (%)	Mean* (±SD)	Median
Week 12	Lutathera	106	70 (66)	0.357 ± 18.68	0.00
	Octreotide LAR	100	68 (68)	-2.941 ±18.43	0.00
Week 24	Lutathera	94	57 (61)	1.462 ± 18.10	0.00
	Octreotide LAR	68	51 (75)	-4.248 ± 26.32	0.00
Week 36	Lutathera	83	53 (64)	2.201 ± 19.21	0.00
	Octreotide LAR	54	38 (70)	-3.070 ± 21.61	0.00
Week 48	Lutathera	74	44 (60)	3.598 ±18.80	0.00
	Octreotide LAR	39	25 (64)	-2.667 ± 17.47	0.00
Week 60	Lutathera	67	39 (58)	5.769 ± 16.13	8.33
	Octreotide LAR	29	21 (72)	-2.381 ± 17.51	0.00
Week 72	Lutathera	58	33 (57)	5.556 ± 21.42	0.00
	Octreotide LAR	19	11 (58)	1.515 ± 10.42	0.00
Week 84	Lutathera	25	10 (40)	18.333 ± 19.56	12.50
	Octreotide LAR	4	2 (50)	4.167 ± 5.89	4.17
Week 96	Lutathera	19	8 (42)	14.583 ± 23.88	16.67
	Octreotide LAR	3	2 (67)	0.00 ± 23.57	0.00
Week 108	Lutathera	12	3 (25)	-11.11 ± 34.69	0.00
Week 120	Lutathera	4	2 (50)	-16.67 ± 0.00	-16.67

Source: Adapted from CSR 2.0 Table 11-51

Additional Analyses Conducted in the NETTER-1 Trial

Table **27** presents PFS subgroup analysis results by demographics, stratification factors, and important disease characteristics. No outlier subgroups were identified.

Table 27: NETTER-1 Trial: FDA's PFS Subgroup Analyses

	Sample Size (Censored/ Events)		Un-stratified HR (95% CI)
	Lutathera + Octreotide LAR (30 mg) N=116	Octreotide LAR (60 mg) N=113	
Overall	89/27	35/78	0.21 (0.13, 0.32)
Age: <=65	47/ 14	21/ 35	0.23 (0.12, 0.42)
>65	42/ 13	14/ 43	0.20 (0.11, 0.37)
Gender: Female	43/ 10	19/ 41	0.16 (0.08, 0.33)
Male	46/ 17	16/ 37	0.24 (0.13, 0.43)

	Sample Size (Censored/ Events)		Un-stratified HR
Race: White	67/ 25	30/ 66	0.25 (0.16, 0.40)
Other	22/ 2	5/ 12	0.08 (0.02, 0.34)
Region: Europe	40/ 10	13/ 31	0.17 (0.08, 0.35)
USA	49/ 17	22/ 47	0.24 (0.14, 0.42)
Length of time on constant Octreotide dose:			
> 6 months	62/ 23	28/ 57	0.25 (0.15, 0.4)
<= 6 months	27/ 4	7/ 21	0.12 (0.04, 0.34)
Highest OctreoScan tumor uptake score:			
Grade 2	10/ 4	4/ 11	0.21 (0.06, 0.68)
Grade 3	27/ 8	12/ 22	0.23 (0.10, 0.53)
Grade 4	52/ 15	19/ 45	0.20 (0.11, 0.35)
Karnofsky Performance Score, 60-80	2/ 8	6/ 2	0.22 (0.05, 1.05)
90	5/ 19	14/ 10	0.26 (0.12, 0.57)
100	28/ 51	69/ 15	0.18 (0.10, 0.32)
Disease Stage: IV	79/ 26	31/ 58	0.22 (0.14, 0.35)
Tumor Burden: Limited	75/ 24	31/ 67	0.21 (0.13, 0.34)
Moderate	11/ 2	4/ 9	0.22 (0.05, 1.06)
Extensive	3/ 1	0 / 2	0.17 (0.02, 1.93)
Ki 67 ENETS: G1 ≤2% positive cells	5/ 4	1/ 6	0.25 (0.07, 0.91)
G2 3-20% positive cells	84/ 23	34/ 72	0.20 (0.12, 0.32)
Alkaline Phosphatase <=ULN	57/ 14	27/ 48	0.19 (0.1, 0.34)
>ULN	30/ 11	8/ 29	0.18 (0.09, 0.38)
CgA Positive Tumor Cell: 0%-50%	5/ 4	1/ 6	0.25 (0.07, 0.91)
> 50%	84/ 23	34/ 72	0.20 (0.12, 0.32)
With Ex- Hep Metastases: No	23/ 4	13/ 20	0.18 (0.06, 0.53)
Yes	66/ 23	22/ 58	0.20 (0.12, 0.33)
Any prior cancer surgery: No	17/ 6	8/ 11	0.28 (0.10, 0.82)
Yes	72/ 21	27/ 67	0.19 (0.12, 0.32)
Any Prior Chemotherapy: No	81/ 25	28/ 70	0.19 (0.12, 0.30)
Yes	8/ 2	7/ 8	0.35 (0.07, 1.72)
Any Prior Radiotherapy: No	86/ 26	34/ 73	0.20 (0.13, 0.32)

	Sample Size (Censored/ Events)		Un-stratified HR
Yes	3/ 1	1/ 5	0.22 (0.03, 1.92)

8.1.3 Erasmus Medical Center (EMC) Clinical Trial (MEC127.545/1993/84)

Trial Design

Title: *"Phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumors."*

The Erasmus Medical Center trial (ERASMUS) was an investigator-sponsored, open-label, single-arm, single-institution retrospective study of 1214 patients with somatostatin receptor (SSTR) positive neuroendocrine (NEC) tumors conducted at the Erasmus Medical Center (EMC), Rotterdam, the Netherlands from January 2000 through December 2012. The Medical Ethical Committee of the EMC allowed the treatment of patients with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on a compassionate basis. Sixty-seven percent of enrolled patients were from the Netherlands (Dutch patients); the remaining 33% were referred from elsewhere (non-Dutch patients). The study population was heterogeneous with respect to primary tumor site. Most patients had gastroenteropancreatic neuroendocrine tumors (GEP-NET)—foregut, midgut and hindgut carcinoids of the digestive tract, the bronchus, and all types of pancreatic neuroendocrine tumors (PNET). However, other NETs were also included (medullary thyroid cancer, pheochromocytoma, paraganglioma, neuroblastoma and Merkel cell carcinoma). Additionally, non-NET SSRT positive tumors (melanoma, non-differentiated thyroid cancers, non-small cell lung cancer, breast cancer, lymphoma, and malignant meningioma) were also included.

Patients were treated using an institutional protocol derived from the study of other high-dose radiolabeled peptides conducted at EMC using a different commercial product. ERASMUS included no formal prespecified statistical analysis plan. The protocol for ERASMUS included in the NDA submission is described as "a protocol describing retrospectively a study with prospectively collected data that was performed between January 2000 and March 2007," which was conducted "in agreement with the declaration of Helsinki." The protocol in the NDA submission is dated November 18, 2008. Prospective collection of data on case report forms (CRFs) was limited. Data from the CRFs and patient files were prospectively entered in a master Excel database by the principal investigator for statistical analysis for publication. Follow-up data on the non-Dutch patients was less complete than on the Dutch patients. AAA employed an independent CRO (b) (4) to retrospectively verify the ERASMUS study source data and generate a SAS database for statistical analysis.

Two separate analyses were conducted on the ERASMUS data:

- The first analysis was conducted in 2011-2012 and included 615 patients who were enrolled in the study between January 2000 and March 2007 with a follow-up cut-off date of January 2010. This analysis was included in the ERASMUS Clinical Study Report dated February 8, 2012, and was submitted with the original IND submission, prior to the initiation of the NETTER-01 trial.
- AAA resumed data collection in 2015 to update follow-up data on the original 615 patients enrolled prior to 2007 and verify data from an additional 599 patients enrolled in the study between March 16, 2007 and December 2012. In total, verified data from 1214 patients were included in the final database. Among these, 47 patients were patients with GEP-NETs who were enrolled on the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate only control arm of a randomized trial comparing ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with or without capecitabine conducted at the EMC. The data analysis on these 1214 patients is included in the NDA submission.

FDA previously expressed reservations concerning the limitations of the ERASMUS trial and the adequacy of this trial to support the broader indication of GEP-NET. These concerns were summarized at the PreIND meeting held on March 8, 2011, the general advice (Type C) meeting held on August 27, 2015, the PreNDA meeting held on November 24, 2015 and the PreNDA meeting held on March 14, 2016. Please refer to the meeting minutes for additional details.

The following specific concerns about the ERASMUS trial have previously been noted:

- There was no formal clinical protocol or prespecified statistical analysis plan; a protocol which summarized the procedures followed along with a statistical analysis plan was retrospectively generated and provided with the NDA submission.
- Baseline tumor assessments were obtained for only 578/1214 (48%) EMC study patients.
- Patients were not required to have disease progression following the most recent prior therapy for NET.
- There was no central review of histology or of OctreoScan uptake at baseline
- There was no central review of response, and except for a small subset of Dutch patients (n=38), a retrospective central review was not attempted.
- There was a high loss to follow-up among non-Dutch participants and a differential reporting of serious adverse events between Dutch and non-Dutch participants, resulting in a high degree of censoring and under-reporting of safety events among non-Dutch participants.
- Prospective data collection was limited and was supplemented by retrospective medical records review and data verification in the Dutch subset of patients only.
- Follow-up assessments measured by CT or MRI were obtained less regularly and less frequently than in the NETTER-1 trial (at 6 weeks, 3-4, 6-8, 9-12 and 12-16 months after the last administered dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and every 6 months thereafter until disease progression, death, or loss to follow-up).

- A different response criteria was used. The Modified Southwest Oncology Group (SWOG) criteria was used in the assessment of patients enrolled prior to March 15, 2007. After this date, patients were assessed using RECIST criteria. To provide parity with the NETTER-1 trial, based on recorded lesion diameters, assessments were retrospectively reclassified to RECIST 1.1 criteria using a SAS program which calculated the sum of the longest diameter of each target lesion and accounted for the development of new lesions.

There were study design limitations in the version of the statistical analysis plan dated November 18, 2008. FDA's concerns were discussed with AAA during the Pre-IND and Pre-NDA meetings. A revised SAP dated November 30, 2015, for ERASMUS was submitted in the NDA resubmission. This review reported the results/analyses per the SAP in cases where discordance existed between the protocol and SAP; the SAP reflected the applicant's most recent analysis strategy. Because time-to-event analyses and patient reported outcomes are not interpretable in single arm trials, the focus of the FDA efficacy assessment was the primary endpoint of response rate and duration of response.

Objectives:

Primary Objective:

- To determine the overall response rate (ORR) in patients with SSTR positive tumors treated with *^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate assessed by investigators using RESIST 1.1 criteria*
- Evaluate the safety of treatment with *^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with SSTR positive tumors*

Secondary Objectives:

- Evaluate the progression free survival (PFS), time to progression (TTP) and Overall survival (OS) in patients with SSTR positive tumors.
- Assess the effect of treatment with *^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate on Quality of Life (QoL) as measured with the EORTC QLQC30 questionnaire and in patients enrolled in 2012 and later, the EORTC QLQC30 as well as the EOTC-QLQ-GI.NET21 questionnaire.*

Study Population:

Key eligibility criteria include:

1. Presence of somatostatin receptors on known lesions as demonstrated by OctreoScan® uptake within 6 months prior to the first dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with uptake in lesions at least as high as normal liver uptake on planar imaging.
2. Histologically confirmed (applied only to patients with GEP-NETs, including bronchial carcinoids).

3. Karnofsky Performance Score ≥ 50.
4. Laboratory:
    a. Serum creatinine ≤ 150 µmol/L and a calculated (Cockroft-Gault) or measured creatinine clearance of ≥40 ml/min.
    b. Hb ≥5.5 mmol/L; WBC≥2x10^9/L; platelets ≥ 75x10^9/L.
    c. Total bilirubin ≤3 x Upper limit of normal.
    d. Serum albumin > 30 g/L.
5. Not a candidate for surgery with curative intent.
6. No history of surgery, radiotherapy, chemotherapy or other investigational therapy within 3 months prior to the initiation of ^{177}Lu-DOTA^0-Tyr^3-Octreotate.
7. Patients with uncontrolled congestive heart failure were excluded.
8. Patients in whom short-acting somatostatin analogues could not be interrupted for 12 hours before and 12 hours after administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate or in whom long-acting somatostatin analogues could not be interrupted for at least 6 weeks before administration of ^{177}Lu-DOTA^0-Tyr^3-Octreotate were excluded unless the uptake on the OctreoScan during continued somatostatin analogue administration is at least as high as normal liver uptake on planar imaging.

Study Treatment:

Patients received ^{177}Lu-DOTA^0-Tyr^3-Octreotate as 4 intravenous administrations of 7.4 GBq (200 mCi) at 6-13 week intervals with the aim of delivering a cumulative administered dose of up to 29.6 GBq (800 mCi). Patients may have received a different dose for the following reasons:

1. Patients in the initial biodistribution and dosimetry study and in the ascending dose study may have received less than the full dose due to lower initial starting doses.
2. Patients who experienced dose limiting toxicity (DLT) may have received a dose reduction and/or discontinuation.
3. Patients may not have received the full fourth dose if the kidney dosimetry data based on planar images obtained after the first administration of 7.4 GBq ^{177}Lu-DOTA^0-Tyr^3-Octreotate indicated that the patient would exceed the 23 Gy kidney threshold dose limit.
4. Variations in the amount of ^{177}Lu delivered to the hospital radiopharmacy for the preparation of ^{177}Lu-DOTA^0-Tyr^3-Octreotate.
5. Selected patients who progressed following an initial response to ^{177}Lu-DOTA^0-Tyr^3-Octreotate could be retreated at the investigator's digression, exceeding the 29.6 GBq threshold.
6. Patient died, withdrew, or experienced other morbidity.

^{177}Lu-DOTA^0-Tyr^3-Octreotate was administered at a rate of 200 mCi over 30 minutes with a concomitant infusion of amino acids (lysine (b) (4), and arginine (b) (4)). Amino acids were administered via a separate pumping system over a 4-hour period beginning 30

minutes before the initiation of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion. Ondansetron (8 mg) was administered IV 30 minutes prior to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion as an antiemetic.

Dose Modifying Toxicity Guidelines:

The guidelines used for dose delay, modification and discontinuation were not outlined in the version of the clinical protocol submitted with the NDA.

Study Assessments:

Study assessments were obtained according to the visit schedule in Table 28 below:

Table 28: ERASMUS: Study Assessments

Evaluation	Baseline	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Follow-up				
		Week 6-13	Week 6-13	Week 6-13	Week 6-13	Week 6	Month 3	Month 6	Month 12	Month 18
Informed Consent	X									
OctreoScan®	X								X	
Relevant Medical History	X	X								
Diagnosis and Extent of Cancer	X	X								
Physical Exam	X	X	X	X	X	X	X	X	X	X
Karnofsky Performance	X	X	X	X	X	X	X	X	X	X
Quality of Life	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Therapy	X	X	X	X	X	X	X	X	X	X
Adverse Events/Side-Effects	X	X	X	X	X	X	X	X	X	X
Creatinine Clearance	X							X		X
Disease Assessment SWOG (CT,MRI)	X					X	X	X	X	X
Survival Information						X	X	X	X	X

Follow-up after 18 months continues every 6 months until the moment of documented disease progression or death, and is identical to the follow-up after 18 months. The visit schedule time lines apply on the conditions that the patient's health status permits keeping these time lines, that the patient cooperates, and that the planning of exams by the departments of radiology is according to scheme.

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: Erasmus Clinical Study Report, Appendix 5, page 30. Protocol: "A phase I/II single arm study to evaluate the efficacy of 177LuDOTA0-Tyr3-Octreotate in patients with somatostatin receptor positive tumors; Version Date: 18Nov2008
\\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5352-stud-rep-uncontr\erasmusphase12study\emcresub\appendix-16-1-1.pdf

Statistical Analysis Plan

- **Sample Size Considerations**

Due to the retrospective design, this subsection is not applicable.

- **Analysis Sets**

Safety Population (SAF): The SAF consists of all patients who entered the trial and who received at least one dose of Lutathera. This population will be used for all safety parameters and efficacy analyses.

Full Analysis Set (FAS): The FAS consists of all patients who have been enrolled and have at least one valid baseline tumor assessment.

Per Protocol Set (PPS): The PPS consists of those patients of the FAS who complied with the protocol without any major deviation.

The SAF is the primary analysis population in the provided protocol and SAP (Section 7.5.1) which is consistent for regulatory consideration for the single arm clinical trial. FAS excluded 67% of patients without baseline tumor assessment is the sensitivity analysis population.

- **Study Endpoints**

ORR

The primary efficacy endpoint was investigator-assessed objective tumor response rate (CR or PR) using RECIST 1.1. For all the ORR analyses, patients without a valid post-baseline scan were defined as non-responders. Tumors were measured using CT or MRI. Baseline tumor assessments could be obtained within 6 months prior to the start of treatment. Response assessments were done at 6 weeks, 3-4, 6-8, 9-12, and 12-16 months following the last treatment, and then every 6 months thereafter or until disease progression.

Patients included in the first data analysis (615 patients enrolled prior to March 15, 2007) were evaluated using Southwest Oncology Group (SWOG) assessment criteria. Patients enrolled after March 15, 2007 (n=599) were assessed using RECIST 1.1 criteria.

The primary difference between the SWOG and RECIST tumor grading systems was the manner in which target lesions were identified and non-target tumor lesions were handled. In RECIST, a maximum of 2 target lesions are identified per organ and 5 target lesions in total are used. In SWOG, up to 5 target lesions per organ are allowed; a maximum of 3 target lesions per organ are allowed if the patient has more than 20 measurable lesions. In that case, all other lesions in

that organ site are listed as a single evaluable lesion. To perform the conversion to RECIST, the longest diameter of each target lesion was extracted from the SWOG bi-dimensional measurements and the sum of the longest diameter of each target lesion was calculated based on the extracted longest diameters at each visit. In SWOG assessments where 3 target lesions per organ were selected at baseline, the longest diameter of all target lesions was used. The algorithm accounted for the appearance of new lesions. Non-target lesions were only indirectly assessed as they contributed to the assessment of non-measurable or evaluable disease in the determination of objective status.

For those patients enrolled after March 15, 2007, who were assessed for response using RECIST criteria, the same computer algorithm was applied to the sum of the longest diameter of the target lesions to determine the response status in the database.

DoR

DoR is defined as the time from initially meeting the criteria for response (CR or PR) until the time of progression by RECIST 1.1.

Efficacy Analysis Methods

For categorical variable, (e.g., ORR), descriptive analyses including proportion and binomial exact confidence intervals (95% CI) were planned.

Descriptive statistics for continuous variables (e.g., DoR), would be number of non-missing value, quartiles, arithmetic mean, standard deviation (sd), minimum, median, and maximum. FDA's analysis for DoR is K-M method to assess median DoR and 95% CI.

Subgroup analyses for ORR and DoR were conducted by tumor subgroup:

- Foregut NET (excluding bronchial NET and pancreatic NET)
- Midgut NET
- Hindgut NET
- Pancreatic NET (pNET)
- Bronchial NET (also known as pulmonary NET)
- Paraganglioma
- Thyroid carcinoma
- Other (including other NET and non-NET)
- GEP-NET tumors, comprising foregut NET (excluding bronchial and pancreatic NET), midgut NET, hindgut NET, pNET and bronchial NET

FDA conducted a sensitivity analysis of ORR and DoR analysis in SAF, FAS, by March 15, 2007 (the cutoff date to switch tumor assessment criteria from modified SWOG to RECIST 1.1), and tumor subgroups.

Protocol Amendments

Two protocol amendments are identified in Appendix 10 of the clinical protocol:

- As of February 2004, either 8 mg ondansetron or 3 mg granisetron was administered IV prophylactically for nausea associated with the administration of the amino acid solution.
- As of March 2002, patients who had responded to initial treatment but who progressed during follow-up were allowed to receive one or more additional administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
- Revised Statistical Analysis Plan for the February 2012 analysis \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5352-stud-rep-uncontr\erasmusphase12study\emcresub\appendix-16-1-9-1.pdf
- Statistical Analysis Plan Addendum for the 2015 analysis \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5352-stud-rep-uncontr\erasmusphase12study\emcresub\appendix-16-1-9-2.pdf

Study Results

Compliance with Good Clinical Practices

In the CSR for the ERASMUS trial, the applicant stated that the study was conducted in accordance with:

1. Ethical principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong and South Africa).
2. Principles of Good Clinical Practice (GCP) as outlined in the "Guideline for Good Clinical Practice" (ICH GCP guidelines E6, 1996).

The applicant also stated that the general study design for peptide receptor radionuclide therapy (PRRT) was approved by the Medical Ethics Committee (MEC) of Erasmus Medical center; previously called the Academisch Ziekenhuis Rotterdam, in December 1993. Detailed specifications for each studied radiopharmaceutical had to be submitted to the MEC prior to the initiation of a clinical investigation and approval from the MEC was required before starting the study. The applicant also stated that, "Written informed consent was obtained from each study participant after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study" and that, "Informed consent was to be obtained before any study-related procedure was performed."

Financial Disclosure

ERASMUS was initiated as a clinical treatment trial and was not conducted by AAA. No financial disclosure forms were submitted with the NDA for this study.

Patient Disposition

Definition of study population:

There were no pre-defined analysis sets in ERASMUS. Study endpoints were examined using the following defined sets (Figure 17):

- Safety Analysis Set (SAF): included all patients who were enrolled and who received at least one treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

- Full Analysis Set (FAS): consisted to all patients who were enrolled and who had a baseline tumor assessment recorded in the CRF/database.

Other analysis subsets were defined ad hoc included:

- Dutch Subset (Dutch): Follow-up on this subset of patients was more complete than for other international patients. This subset was used to refine estimates on response rate and safety (Figure 18).
- Midgut, Progressive NET (Midgut NET): This subset was selected to be comparable to the patient population enrolled in NETTER-1 and was limited to Dutch patients with baseline tumor assessments who were assessed to have progressed following the treatment prior to study entry. Out of 98 potential patients, only 38 had scans retrievable for independent review of ORR (Figure 18).
- GEP-NET: A subset of 433 patients (360 Dutch; 73 Non-Dutch). The Dutch subset of the GEP-NET study population was used by AAA to support a claim for an expanded indication (Figure 17).

Figure 17: ERASMUS: Safety (SAF) and Full Analysis Set (FAS) Data Analysis Sets (A)

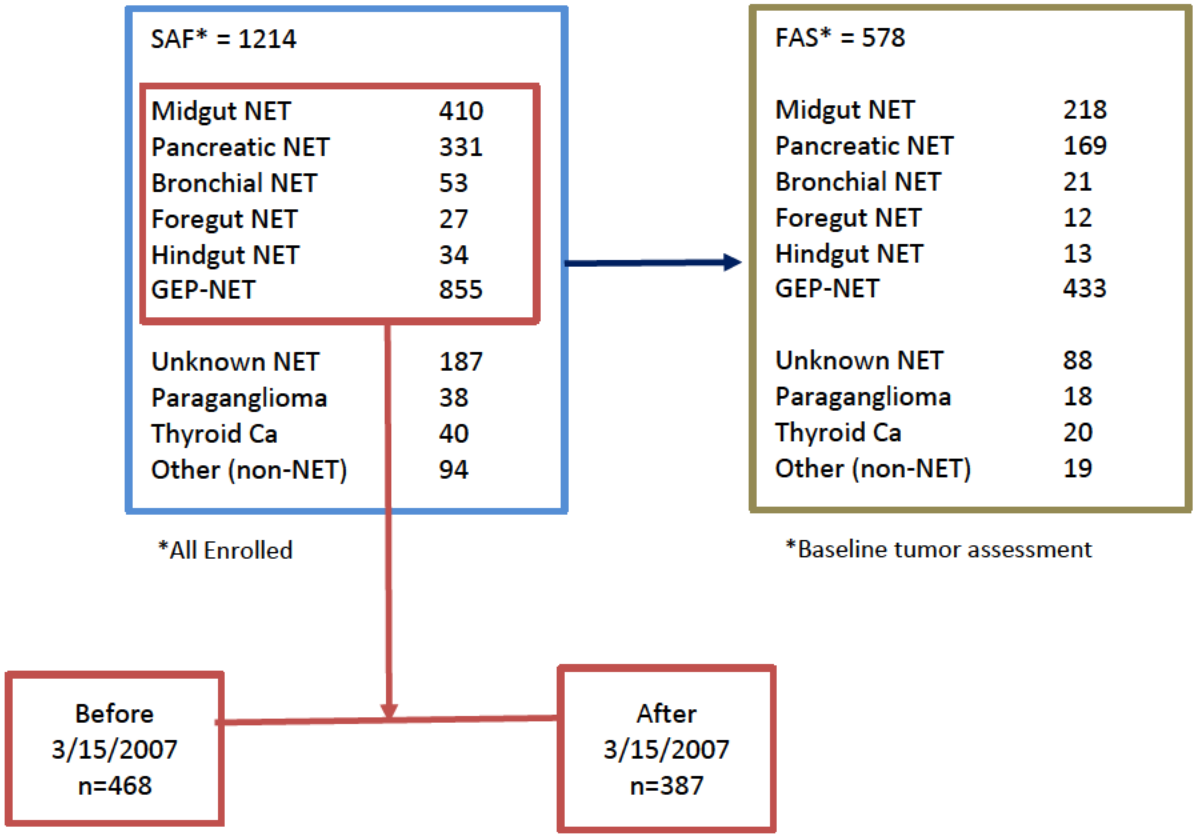
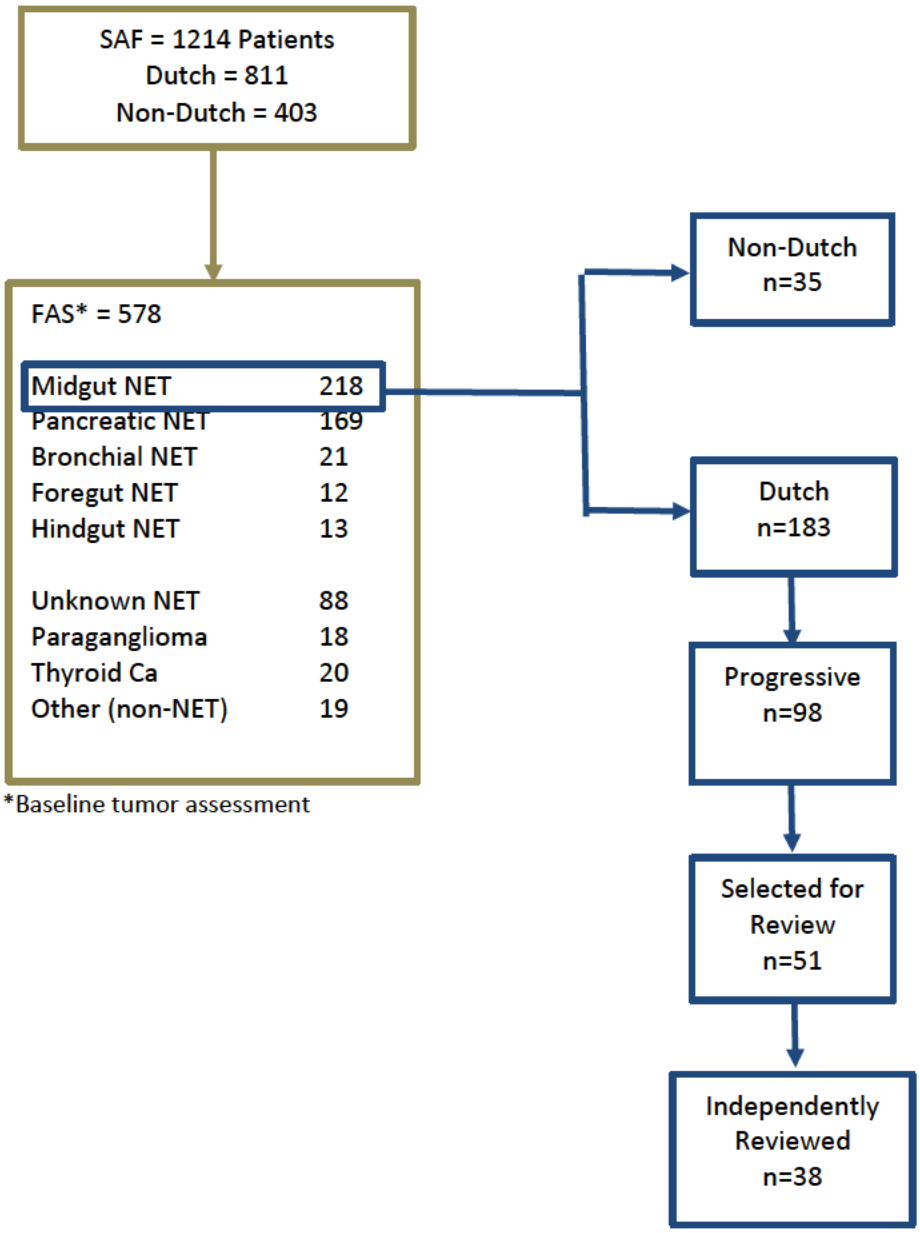


Figure 18: ERASMUS: Midgut Progressive Analyses Set (B)



Protocol Violations/Deviations

The per-protocol dataset (PSS) was reported by the applicant to contain 541 patients, 45% of

the total patient population. The number of protocol violations was assumed to be high and could not be independently verified by the clinical reviewer.

Demographic Characteristics

Demographic characteristics of the FAS and SAF analysis sets are shown below. Overall, 54% of patients in ERASMUS were male, the median age was 58 years, 67% were Dutch and 63% had a Karnofsky performance status above 90. Except for the percentage of Dutch patients which was higher in the FAS study population, the FAS and SAF analysis sets were generally similar with respect to these basic demographic characteristics.

Table 29: ERASMUS: Demographic Characteristics of the FAS and SAF Analyses Sets

Demographic Parameters	FAS N=578	SAF		
		Dutch N=811	Non-Dutch N=403	Total SAF N=1214
Sex: male, %	58	52	60	54
Age (years), median (range)	59 (16, 86)	60 (18, 90)	56 (16, 85)	58 (16, 90)
≥ 65 years, %	31	36	21	31
BMI (kg/m^2), median (range)	24 (15, 45)	24 (15, 97)	24 (15, 37)	24 (15, 97)
Region, % Dutch	85	-	-	67
Karnofsky Performance Score, %				
100	32	25	32	27
90	38	36	35	36
80	20	23	15	21
70	6	8	5	7
≤ 60	4	5	3	4
Missing	0	3	10	5
Median (range)	90 (40, 100)	90 (40, 100)	90 (40, 100)	90 (40,100)

[1] Data on race and/or ethnicity were not reported in the ERASMUS database.
Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: ERASMUS Clinical Study Report; Version 2.0, 05July2017. Abstracted from Tables 12.1.2.1 and 14.1.2.2 and verified by reviewer.
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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, 70% of patients enrolled in ERASMUS had gastroenteropancreatic-neuroendocrine (GEP-NET) or bronchial neuroendocrine tumors. Fifty-eight percent were assessed to have progressive disease at the time of enrollment. Eighty-three percent had an OctreoScan uptake score of 3-4. Nineteen percent had had prior chemotherapy as treatment for their tumors. The FAS was generally similar to the SAF with respect to these baseline disease characteristics.

Table 30: ERASMUS: Disease Characteristics

Disease Characteristics	FAS N=578 Dutch and Non-Dutch	SAF		
		Dutch N=811	Non-Dutch N=403	Total SAF No=1214
Primary tumor site GEP-NET/Bronchial, n (%)	433 (75)	559	296	855 (70)
Foregut NET	12 (2)	18	9	27 (2)
Midgut NET	218 (38)	278	132	410 (34)
Hindgut NET	13 (2)	26	8	34 (3)
Pancreatic NET	169 (29)	198	133	331 (27)
Bronchial NET	21 (4)	39	14	53 (4)
Tumor Burden, %				
Extensive	16	18	17	17
Limited	16	18	11	16
Moderate	68	62	63	62
Disease status, %				
No progression	17	18	15	17
Progression	54	56	61	58
Not known	29	25	15	22
Missing	< 1	8	9	4
Time since first diagnosis (months), median (range)	17 (<1, 419)	18 (< 1, 419)	37 (2, 256)	22 (< 1, 419)
Scan uptake, %				
0-1	1	5	10	7
2	9	13	4	10
3	61	57	61	58
4	30	25	25	25
Ascites, Yes, %	3	5	2	4
Previous chemotherapy, Yes, %	10	10	39	19
Previous radiotherapy, Yes, %	9	11	16	13
Previous surgery, Yes, %	48	45	57	49
Alkaline phosphatase (U/L) median, (range)	107 (13, 1632)	108 (8, 2106)	119 (38, 1895)	112 8, 2106)
CGA (ug/L), median, (range)	623 (48, >6x10^5)	688 (7, >6x10^5)	913 (71, >9x10^5)	751 (7, >9x10^5)
5-HIAA (mmol/mol), median (range	395 (13, 2533)	387 (11, 2910)	186 (7, 956)	360 (7, 2910)

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: ERASMUS Clinical Study Report; Version 2.0, 05July2017. Abstracted from Tables 12.1.2.1 and 14.1.2.2 and verified by reviewer.
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Efficacy Results – DoR and ORR

In ERASMUS, 247 responses (CR: 20; PR= 227) were reported among 1214 enrolled patients in the SAF population. The estimated response rate was 20% (95%CI: 18%, 23%). The median duration of response was 19.4 months (range: 0, 95 months; 95% CI: 16.6, 23.7 months). The response rate in the subset of patients with GEP-NET or bronchial neuroendocrine tumors was 198/811 (23%; 95% CI: 20.4, 26.1 months). The median duration of response was 20.1 months (range: 0, 95 months; 95% CI: 16.7, 24.4 months). The response rate in the subset of patients with pancreatic neuroendocrine tumors (PNETs) appeared at least as good as for all patients with GEP-NETs and bronchial neuroendocrine tumors, and the responses among patients with PNETs were durable. These analyses were conducted on the SAF population which included all treated patients. The 403 (33%) patients with no baseline studies and patients with no follow-up assessments were considered non-responders (generally consistent with the approach FDA has taken on other applications).

To assess the impact of the high percentage of patients missing baseline assessments, a sensitivity analysis was conducted comparing estimates of ORR based on the SAF dataset which includes all enrolled patients, with and without baseline scans, to estimates of ORR in the FAS which is limited to patients with baseline scans. As expected, ORR is consistently lower when the SAF population is used. However, since it is not possible to ascertain whether exclusion of these patients without scans resulted in a systematic bias in the estimate, this reviewer recommends the analysis using the SAF population rather than the FAS, which yields a more conservative estimate of ORR (**Table 31**).

To assess the impact of enrollment timeframe, a sensitivity analysis was conducted that stratified patients by date of enrollment (analysis population 1: enrolled prior to March 15, 2007 vs. analysis population 2: enrolled on or after March 15, 2007). This analysis demonstrates consistently higher estimates of ORR in the population enrolled during the earlier timeframe. Before March 15, 2007, responses were graded by investigators using SWOG criteria and converted algorithmically to RECIST criteria; on or after March 15, 2007, responses were assessed by investigators using RECIST (analysis population 2). Thus, limiting the analysis to patients enrolled on or after March 15, 2007, provides a more conservative estimate. A total of 387 patients with GEP-NET and bronchial carcinoid tumors were enrolled in ERASMUS after March 15, 2007 (Figure 17). There were 60 responders in this subgroup (CR: 3; PR: 57). The estimated response rate was 16% (95%CI: 12%, 20%). The median duration of response was 35 months (range: 0, 70+ months; 95% CI: 17.0, 38.0 months).

Table 31: ERASMUS: Overall Response Rate (ORR) and Duration of Response (DoR) for Overall Study Population (SAF) and Selected Subgroups

Tumor Type	Analysis Set	Study Phase*	ORR				DoR**		
			ORR, n (%)	95% CI	CR, n (%)	PR, n (%)	Median	95% CI	Range
All	FAS	All	247 (42.7)	(38.7, 46.9)	20 (3.5)	227 (39.3)	19.4	(16.6, 23.7)	(0.0+, 95.0+)
		1	162 (46.6)	(41.2, 51.9)	17 (4.9)	145 (41.7)	17.2	(14.0, 21.3)	(0.0+, 95.0+)
		2	85 (37.0)	(30.7, 43.5)	3 (1.3)	82 (35.7)	25.3	(17.0, 37.1)	(0.0+, 70.3+)
	SAF***	All	247 (20.3)	(18.1, 22.7)	20 (1.6)	227 (18.7)	19.4	(16.6, 23.7)	(0.0+, 95.0+)
		1	162 (26.3)	(22.9, 30.0)	17 (2.8)	145 (23.6)	17.2	(14.0, 21.3)	(0.0+, 95.0+)
		2	85 (14.2)	(11.5, 17.2)	3 (0.5)	82 (13.7)	25.3	(17.0, 37.1)	(0.0+, 70.3+)
GEP-NET and Bronchial	FAS	All	198 (45.7)	(41.0, 50.6)	19 (4.4)	179 (41.3)	20.1	(16.7, 24.4)	(0.0+, 95.0+)
		1	138 (48.1)	(42.2, 54.0)	16 (5.6)	122 (42.5)	17.7	(15.3, 23.0)	(0.0+, 95.0+)
		2	60 (41.1)	(33.0, 49.5)	3 (2.1)	57 (39.0)	35	(17.0, 38.0)	(0.0+, 70.3+)
	SAF	All	198 (23.2)	(20.4, 26.1)	19 (2.2)	179 (20.9)	20.1	(16.7, 24.4)	(0.0+, 95.0+)
		1	138 (29.5)	(25.4, 33.8)	16 (3.4)	122 (26.1)	17.7	(15.3, 23.0)	(0.0+, 95.0+)
		2	60 (15.5)	(12.0, 19.5)	3 (0.8)	57 (14.7)	35	(17.0, 38.0)	(0.0+, 70.3+)
P-NET	FAS	All	108 (63.9)	(56.2, 71.1)	14 (8.3)	94 (55.6)	23	(16.6, 32.6)	(0.0+, 86.4+)
		1	70 (68.6)	(58.7, 77.5)	12 (11.8)	58 (56.9)	19.4	(12.2, 24.4)	(0.0+, 86.4+)
		2	38 (56.7)	(44.0, 68.8)	2 (3.0)	36 (53.7)	35	(16.7, 38.0)	(0.0+, 70.3+)
	SAF	All	108 (32.6)	(27.6, 38.0)	14 (4.2)	94 (28.4)	23	(16.6, 32.6)	(0.0+, 86.4+)
		1	70 (40.2)	(32.9, 47.9)	12 (6.9)	58 (33.3)	19.4	(12.2, 24.4)	(0.0+, 86.4+)
		2	38 (24.2)	(17.7, 31.7)	2 (1.3)	36 (22.9)	35	(16.7, 38.0)	(0.0+, 70.3+)
Midgut	FAS	All	70 (32.1)	(26.0, 38.7)	4 (1.8)	66 (30.3)	17.2	(13.1, 23.0)	(0.0+, 95.0+)
		1	61 (36.1)	(28.9, 43.8)	4 (2.4)	57 (33.7)	17.2	(11.5, 23.0)	(0.0+, 95.0+)
		2	9 (18.4)	(8.8, 32.0)		9 (18.4)	17	(16.6, NR)	(0.0+, 39.6+)
	SAF	All	70 (17.1)	(13.6, 21.1)	4 (1.0)	66 (16.1)	17.2	(13.1, 23.0)	(0.0+, 95.0+)
		1	61 (23.1)	(18.2, 28.7)	4 (1.5)	57 (21.6)	17.2	(11.5, 23.0)	(0.0+, 95.0+)
		2	9 (6.2)	(2.9, 11.4)		9 (6.2)	17	(16.6, NR)	(0.0+, 39.6+)

*1=Enrolled before 3/15/2007; 2= Enrolled 3/15/2007 or later; ** DoR and 95% Confidence Interval estimated using Kaplan Meyer Method; ***Patients with no baseline assessments were assumed to be non-responders; SAF: All enrolled study population (N=1214); FAS: Subset of SAF with baseline tumor assessment (N=811)

As FDA stated in the pre-BLA meeting held on March 14, 2016, FDA does not view time to event analyses (TTP, PFS, and OS) to be interpretable in the context of the single arm Erasmus trial. (b) (4) With quality of life endpoints, the limited ascertainment of baseline assessments, the high drop-out rate for subsequent ascertainments, and the open-label nature of the trial limits the inference that can be drawn from the analyses of these data. (b) (4) FDA clinical/statistical reviewers did not independently review the data.

Therefore, FDA's confirmation of study endpoints in ERASMUS was restricted to ORR and DoR.

Dose/Dose Response

Please see the Clinical Pharmacology review.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The EORTC Quality of Life Questionnaire (QLQ-C30) and OLQ-GI.NET21 questionnaire were assessed during ERASMUS. However, baseline assessments were obtained on a small number of patients (EORTC QLQC30: 61%; EORTC QLQ-GI.NET21: 23%) in the FAS. Due to the open-label nature of the trial and the small number of patients completing the assessments, these results were considered uninterpretable and were not verified by FDA reviewers.

Additional Analyses Conducted on the Individual Trial

In an attempt to compare the ORR observed in ERASMUS with the ORR in NETTER-1, AAA presented an exploratory analysis using a subset of ERASMUS patients diagnosed with midgut NET with baseline scans available for review who were reported to have had progression following their most recent treatment prior to study enrollment (Figure 18). The analysis was limited to the Dutch subset to maximize the possibility of retrieving scans for independent review. Out of a subset of 51 patients with potentially retrievable scans, only 38 were retrievable. These were independently reviewed using RECIST 1.1 criteria. The result of this exploratory analysis is shown below in **Table 32**.

In the limited and highly selected subset of ERASMUS patients with progressive midgut NETs available for independent review, the response rate appears to be in the range of that observed in the NETTER-1. However, these data do not provide confirmation of the response estimates from ERASMUS, nor do they constitute justification for extrapolation of the response rates observed in other subsets for labeling purposes.

Table 32: Response Rate Following Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in Patients with Progressive Midgut Carcinoid Tumors. Comparison Between Findings in the NETTER-01 and EMC Study Subsets

Study	Year	Reader/Response Criteria	N	CR	PR	OR	95% CI ORR	
ERASMUS	2012	Independent (RECIST)	38	0%	13%	13%	4%	28%
ERASMUS	2012	Independent(RECIST)/ Computer (RECIST)**	38	0%	18%	18%	8%	34%
ERASMUS	2015	Local(SWOG)/ Computer (RECIST)**	153	1%	20%	22%	15%	29%
NETTER-1	2015	Independent (RECIST)	116	1%	12%	15%	8%	22%

*All patients without post-baseline tumor assessments were considered non-responders
** SAS program used to convert SWOG response to RECIST criteria.
Source: Table 19, page 52. 2.7.3 Summary of Clinical Efficacy, Version 2 Submitted 8/15/2017
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8.1.4 Assessment of Efficacy Across Trials

As outlined in sections 8.1.1 and 8.1.3, there were certain limitations in the interpretation of the results of NETTER-1 and ERASMUS. Furthermore, the two trials differed from each other in substantive ways as outlined below in Table 33. For this reason, an integrated efficacy analysis was not undertaken.

Table 33: Key Differences between design of NETTER and EMC

ERASMUS	NETTER-1
Study Design	
Investigator conducted, single institution, open-label, single arm	Sponsored, multicenter, open-label, stratified, randomized comparator controlled
Study Population	
Inoperable SSTR positive tumors	Inoperable, progressive, SSTR positive midgut carcinoid tumors
Sample	
Subset of 811 Dutch patients from total study population of 1214 patients which included: • Foregut: n=18 • Midgut: n=278; 153 met criteria for NETTER-01 • Hindgut: n=26 • Pancreatic: n=138 • Thyroid: n=37 • Paraganglioma: n=28 • Other: n=45 • Unknown: n=138 *Only partial data collection was performed at EMC after Dec. 2012 and only on patients previously enrolled.	229 patients with midgut tumors randomized (1:1) (Lu: n=116; octreotide: n=113)
Key Eligibility Criteria	
• SSTR positive; within 6 months with uptake in lesions ≥ uptake in normal • Only GEP-NETs, including bronchial carcinoids histologically confirmed • Karnofsky Performance Score ≥ 50. • Laboratory: a. Serum creatinine ≤ 150 µmol/L and a calculated (Cockroft-Gault) or measured creatinine clearance of ≥40 ml/min. b. Hb ≥5.5 mmol/L; WBC≥2x10^9/L; platelets ≥ 75x10^9/L. c. Total bilirubin ≤3 x Upper limit of normal d. Serum albumin > 30 g/L • No history of surgery, radiotherapy, chemotherapy or other investigational therapy within 3 months prior to start of ^{177}Lu-DOTA^0-Tyr^3-Octreotate • Patients with uncontrolled congestive heart failure were excluded Patients in whom short-acting somatostatin analogues could not be interrupted for 12 hours	• Presence of locally advanced/inoperable or metastatic, histologically proven, midgut carcinoid tumor with at least 1 measurable site of disease (centrally confirmed) • Ki67 index ≤ 20% (centrally confirmed) • Treated with octreotide LAR at a fixed dose of 20 or 30 mg at 3-4 week intervals for at least 12 weeks prior to randomization on the study • Progressive disease, assessed using RECIST Criteria (Version 1.1) while receiving an uninterrupted fixed dose of octreotide LAR (20-30 mg/at 3- week intervals (centrally confirmed) • Confirmed presence of somatostatin receptors on all target lesions, based on positive OctreoScan® imaging within 24 weeks prior to randomization • Tumor uptake observed in each target lesion using OctreoScan® should be ≥ normal liver uptake observed on planar imaging (centrally confirmed)

before and 12 hours after administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate or in whom long-acting somatostatin analogues could not be interrupted for at least 6 weeks before administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were excluded unless the uptake on the Octreoscan® during continued somatostatin analogue administration is at least as high as normal liver uptake on planar imaging	• Karnofsky Performance Score (KPS) ≥ 60. • Laboratory Exclusions: o Serum Creatinine >150 µmol/L (>1.7 mg/dL) or creatinine clearance < 50 mL/min (Cockroft Gault) o Hb concentration < 5.0 mmol/L (<8.0 g/dL); WBC <2x10^{9}/L (2000/mm^{3}; platelet count <75 x10^{9}/L (75 x10^{3}/mm^{3}). o Total bilirubin >3xULN • Prior treatment with peptide receptor radionuclide therapy (PRRT) • Prior external beam radiation therapy to more than 25% of the bone marrow.
Treatment Regimen (177Lu-DOTA0-Tyr3-Octreotate)	
• Total cumulative dose of 29.6 GBq (800 mCi) administered as 4 doses at 6-13 week intervals • Amino acid solution locally compounded • 80% of EMC patients were receiving somatostatin analogs at enrollment	• Total cumulative dose of 29.6 GBq (800 mCi) administered as 4 doses at 8 week intervals. Dosing could be delayed to 16 weeks for acute toxicity • Commercially available amino acid solution
Efficacy Assessments	
• Assessment Criteria: SWOG (assigned to RECIST using computer algorithm) • Only subset of 38 Dutch patients with progressive midgut NEC who had baseline scans and images available for review were centrally confirmed; others assessed by investigators • Tumor response assessed at baseline, 6 weeks after last treatment, 3,6 and 12 months after last treatment, then every 6 months until progression	• Assessment Criteria: RESIST • Independent, blinded assessment • Tumor response assessed every 12 weeks
Safety Assessments	
• Safety monitoring at baseline, 4 weeks after first cycle, 2 weeks before and 4 weeks after each subsequent treatment • Long-term toxicity not routinely monitored • SAEs were retrospectively conducted based on medical chart review. Only laboratory AEs were graded. • CTCAE 4.03 (laboratory events only)	• Safety monitoring within 2 weeks prior and 4 weeks following each cycle. • Safety assessments subsequently done every 12 weeks • Data prospectively collect on AEs of special interest: hematotoxicity, secondary hematologic malignancies, nephrotoxicities, cardiovascular events • CTCAE 4.03

Source: NDA 208700/SD-36/EDR-0036; Submission Date: 7/26/2017; Resubmission/Class2: Erasmus MC Clinical Study Report; Version 2.0, 30June2017, page 52 \\cdsesub1\evsprod\nda208700\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\gepnets\5352-stud-rep-uncontr\erasmusphase12study\emcresub\erasmus-csr-clean.pdf

8.2 Review of Safety

8.2.1 Safety Review Approach

The Lutathera safety database was composed of data from three sources: NETTER-1, ERASMUS, and the expanded access/compassionate use database (Figure 19).

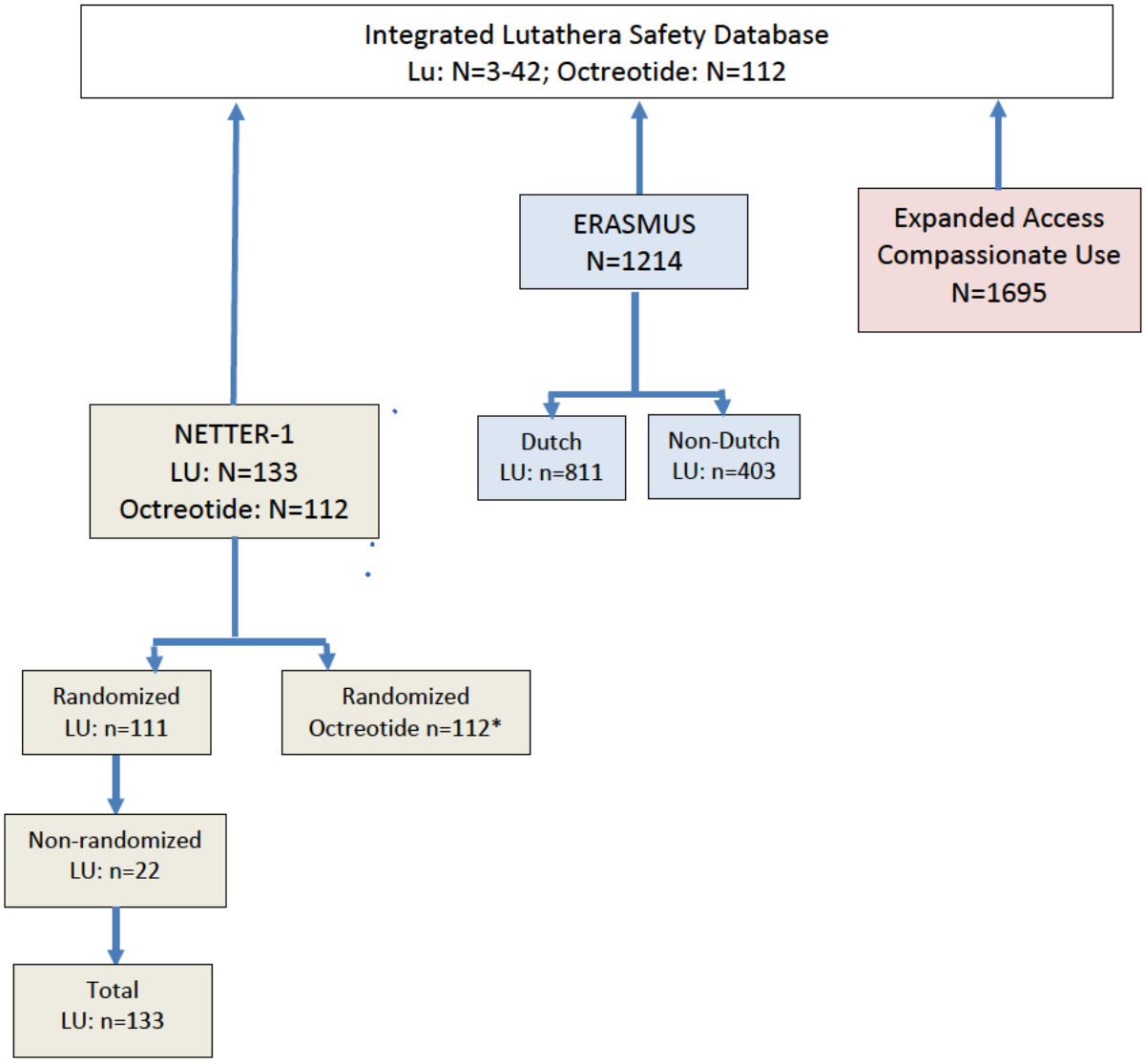
NETTER-1 provided a prospective and pre-specified safety monitoring plan for patients with locally advanced or metastatic, progressive, somatostatin receptor positive midgut neuroendocrine tumors. Patients were randomized to receive Lutathera plus standard dose octreotide LAR (30 mg q month) (n=111) or high-dose octreotide LAR (60 mg q 4 weeks) (n=112) which served as the comparator arm in this open-label trial. Twenty-two additional non-randomized patients enrolled in the NETTER-1 dosimetry sub-study were treated and followed in the same manner as were patients randomized to the Lutathera arm. Review of NETTER-1 focused on the differential analysis of deaths, serious adverse events, and adverse events of special interest occurring on study and through the duration of the follow-up period. The small number of patients enrolled on the Lutathera arm of NETTER-1 limits the potential for detection of rare adverse events. The median duration of follow-up for this study of 19 months may allow for detection of some delayed safety signals.

The Erasmus Medical Center Study (ERASMUS) was a large single institution, international, investigator initiated, open-label, single arm treatment trial. Patients were treated with Lutathera in a manner similar to that in the NETTER-1 trial. In ERASMUS, serious adverse events were not formally recorded in a case report form or reported to a dedicated Safety Officer on an ongoing basis. Therefore, AAA employed an independent Clinical Research Organization (CRO) to conduct a retrospective review of source data verification from the medical charts of all patients enrolled in the study. As part of this retrospective process, all potential SAEs were identified and listed in an Excel file. Additionally, a list of hematological and biochemical laboratory data with NCI CTCAE grade 3 and 4 toxicities was prepared by the CRO and integrated into the SAE listing. Other SAEs were not graded. The causality of all SAEs was retrospectively determined by the PI. All SAEs thought possibly or probably related to study drug treatment were graded as serious adverse reactions (SARs). Narratives were written for all SARs and narratives were written for all SAEs where death occurred within 30 days from Lutathera treatment. Differential rates of serious adverse events between the Dutch and non-Dutch patients in ERASMUS and the high rate of non-Dutch patients lost to follow-up suggested under reporting in this trial. The approach taken with ERASMUS was to review data from this trial to identify sentinel, rare adverse events and adverse events of special interest not identified in NETTER-1, acknowledging that estimates derived from this trial may underestimate the true risk.

Finally, AAA provided data on a large and diverse population of patients treated under expanded access and compassionate use programs. The follow-up time available on these patients was limited and reporting focused on serious adverse events. Review on this patient population focused on screening for sentinel acute and short term serious adverse events not identified in the NETTER-1 trial.

The review will focus on results from the NETTER-1 trial with salient observations from ERASMUS and the expanded access/compassionate use databases incorporated in the review where relevant.

Figure 19: Composition of the Integrated Lutathera Safety Database



*One patient was randomized to the LU arm but received only octreotide LAR. This patient was reclassified by the FDA reviewer with the octreotide LAR arm for purposes of the safety review.

8.2.2 Review of the Safety Database

Overall Exposure

In the NETTER-1 trial, 26% of the 111 patients in the safety analysis population (SAF) received the full recommended dose of Lutathera of 29.6 GBq (800 mCi). Seventy-nine percent received a cumulative dose of 22.2 GBq or higher (≥600 mCi) (Table 34). Seventy-six percent of patients received four doses of Lutathera with a mean total dose of 29.1 GBq. Overall, the mean total

dose administered to patients in NETTER-1 was 25.6 GBq (range: 6.5-31.8 GBq) (Table 35).

Table 34: NETTER-1: Cumulative Lutathera Exposure (GBq/mCi) in the Safety Population (n=111)

Cumulative Lutathera Exposure (mCi)	N (%)
≥ 29.6 GBq (≥800 mCi)	29 (26%)
22.2-29.6 GBq (600 – 800 mCi)	59 (53%)
14.8 – 22.2 GBq (400 – 600 mCi)	9 (8%)
7.4 – 14.8 GBq (200 – 400 mCi)	10 (9%)
0-7.4 GBq (0-200 mCi)	4 (4%)
Total	111 (100%)

Table 35: NETTER-1: Distribution of Lutathera Administrations in the Safety Population (N=111)

Number of administrations	Patients N (%)	Mean total dose (GBq)	Min total dose (GBq)	Max total dose (GBq)
1	6 (5%)	7.1	6.5	7.5
2	12 (11%)	14	11.1	15.5
3	9 (8%)	21.0	17.9	22.9
4	84 (76%)	29.1	22.4	31.8
Total	111 (100%)	25.6	6.5	31.8

The cumulative exposure in ERASMUS was higher than in the NETTER-1 trial (Table 36). In ERASMUS, over 60% of patients received a cumulative dose of 29.6 GBq (800 mCi) or higher compared to 26% of patients in the NETTER-1 trial. The mean total dose in ERASMUS was 28.4 GBq (766.5 mCi) with a range of 3.7 – 59.2 GBq (100 -1600 mCi).

A total of 216 ERASMUS patients received a dose of over 29.6 GBq (800 mCi) (range: 900, 1600) which

provides some data on patients receiving Lutathera doses in excess of the recommended dose.

Table 36: Cumulative Lutathera Exposure (GBq/mCi) in the Safety Population: Comparison of ERASMUS and NETTER-1

Cumulative Lutathera Exposure (mCi)	ERASMUS		NETTER-1
	All Patients	Dutch	
	n (%)	n (%)	n (%)
≥ 29.6 GBq (≥800 mCi)	757 (62%)	528 (65%)	29 (26%)
22.2-29.6 GBq (600 – 800 mCi)	225 (19%)	132 (16%)	59 (53%)
14.8 – 22.2 GBq (400 – 600 mCi)	125 (10%)	77 (10%)	9 (8%)
< 14.8 GBq (< 400 mCi)	107 (9%)	74 (9%)	14 (13%)
Total	1214 (100%)	811(100%)	111 (100%)

Table 37: ERASMUS: Cumulative Lutathera Exposure (GBq/mCi) in Patients Treated at Doses in Excess of 29. 6GBq (800 mCi) (n=216)

Cumulative Lutathera Exposure (mCi)	**N (%)**
> 29.6 – ≤ 37.0 GBq (>800 mCi - ≤1000)	44 (20%)
>37.0- ≤ 44.4 GBq (>1000 – ≤1200 mCi)	156 (72%)
>44.4 – ≤ 59.2 GBq (>1200 - 1600 mCi)	16 (1%)
Total	216 (100%)

Relevant characteristics of the safety population:

The demographic and baseline tumor characteristics of the safety analysis population (SAF) and the full analysis set (FAS) of the NETTER-1 were similar. Please refer to the analysis of the FAS described in Table 14, Table 15, Table 16, Table 17, and Table 18 in Section 8.1.1. In ERASMUS, the FAS was a limited subset of all treated patients. The demographic characteristics of the SAF and FAS populations of ERASMUS are described in Table 29 and Table 30 in Section 8.1.2. In ERASMUS, the SAF was generally similar to the FAS with the following exceptions:

- There were fewer Dutch patients in the SAF (67% vs 85%).
- The percent of patients with high Karnofsky Performance Score (≥ 90) was higher (70% vs 63%).

- The median time since first diagnosis (months) was higher (22 vs 17).
- The octreotide scan uptake score was lower (0-2: 17% vs 10%; 3-4: 83% vs 91%).
- The percent of patients with prior chemotherapy was higher (19% vs 10%).

These differences suggest that patients in the larger ERASMUS SAF may have had a better performance status but more pretreated disease.

Key differences in demographic and disease characteristics between the NETTER-1 and ERASMUS are summarized below.

Table 38: Key Demographic and Disease Characteristics Which Differ Between the NETTER-1 and ERASMUS Trials

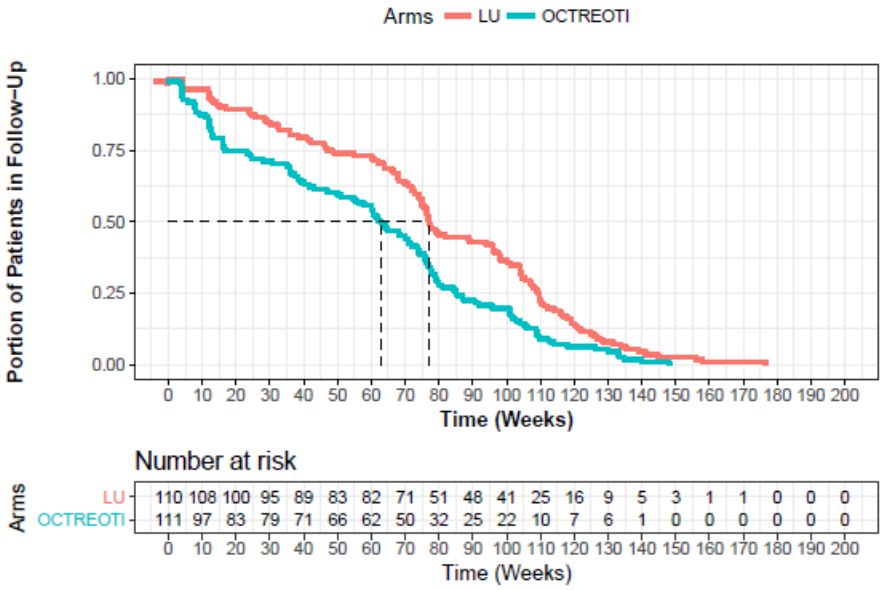
Demographic or Disease Characteristic	NETTER-1 Lutathera SAF N=111	ERASMUS SAF N=1213
Age (years), median (range)	64 (28, 84)	58 (16, 90)
≥ 65 years, %	47	31
Karnofsky Performance Score ≥ 90, %	56	63
Tumor Burden Limited, %	85	16
Tumor Octreotide Uptake Score ≥ 3	88	83
Primary tumor site midgut, %	100	34
Prior Chemotherapy Yes, %	9	19

Patients in ERASMUS were more diverse with respect to the primary tumor site, tended to be slightly younger with a better performance status, had more extensive disease, and were more pre-treated than were patients in NETTER-1.

Adequacy of the safety database:

The safety database of NETTER-1 is small, including only 111 patients; however, follow-up assessments were generally completed at protocol defined intervals and the duration of follow-up was judged to be sufficient to allow for signal detection of anticipated delayed toxicities, primarily renal toxicity and hematologic toxicity. The median time to the last laboratory assessment in Lutathera-treated patients was 19 months with a maximum time of 44 months. Figure 20 shows the time to the last follow-up assessment and the number of patients reaching each protocol-defined assessment landmark.

Figure 20: NETTER-1: Patients in Follow-up Over Time



While a large number of patients were potentially available for safety assessment in ERASMUS, only serious adverse events were reported in the safety database and no active follow-up of the non-Dutch patients was conducted at the Erasmus Medical Center. Furthermore, only data from the Dutch subset was verified against source documents in the retrospective review. Thus, for estimation of the risk of serious adverse events, the Dutch subset of ERASMUS is likely to more accurately reflect the true risk. Reports in the non-Dutch subset, while informative, are likely to under estimate the true risk due to under reporting. Erasmus, however, provides an opportunity to assess risks at dose ranges above the proposed indicated dose. The median follow-up time for the Dutch Subset was 35 months (SD: 26.7).

Overall, the safety database for Lutathera was considered adequate in size to assess the safety profile for common adverse events occurring during treatment. The duration of follow-up is likely to be adequate to provide a signal for delayed adverse events but not likely to allow for estimation of the magnitude of the risk.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, data quality for this the Lutathera safety database was considered adequate. Case report forms (CRFs) for NETTER-1 were reviewed and compared to the datasets and clinical narratives reviewed. Case narratives from ERASMUS were reviewed and compared to the datasets. No major data integrity issues were noted with data from NETTER-1 or ERASMUS.

Categorization of Adverse Events

In the NETTER-1, adverse events were graded according to the CTCAE, v 4.03. Verbatim terms were captured and classified across the MedDRA hierarchy using Version 18.0. In ERASMUS, verbatim event terms for serious adverse events were collected and mapped across the MedDRA hierarchy (version: 18.0). Adverse events were originally graded by investigators using the World Health Organization (WHO) toxicity grading criteria (The Chemotherapy Source Book 1992: Williams and Wilkens). Because of this discrepancy, and the retrospective nature of adverse event data collection, adverse event grades were not provided in the ERASMUS database with the exception of available laboratory data which was graded using CTCAE.

Routine Clinical Tests

In NETTER-1, routine laboratory tests, including serum blood urea nitrogen and creatinine, serum total bilirubin, aspartate aminotransferase and alanine aminotransferase, hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count were assessed at minimum at baseline, within 2 weeks before and 4 ± 1 weeks after each treatment and then monthly through week 72. Patients were then assessed every 6 months thereafter through the end of the 5-year follow-up phase (Table 8). Since patients on the Lutathera arm could be treated with dosing delays following the initial dose, there was a discrepancy in the timing of routine laboratory assessments since few patients on the high-dose octreotide arm experienced dosing delays (Table 9).

In ERASMUS, routine laboratory tests were obtained for hematology, blood chemistry, and uranalysis. Studies were to be obtained prior to and four weeks following each treatment cycle and 6 weeks, 3-4 months, 6-8 months, 9-12 months, and 12-16 months following the last treatment cycle and every 6 months thereafter until disease progression or death. Creatinine clearance was assessed at baseline and at the end of the follow-up period only (Table 28).

8.2.4 Safety Results

Deaths

In NETTER-1, 16 deaths occurred on treatment or within 30 days following the last treatment in randomized patients (7%); 7 deaths (6%) occurred on the Lutathera arm and 9 (8%) occurred on the octreotide arm. Based on a review of the clinical narratives of these events, none were considered related to study drug. No additional deaths occurred among non-randomized patients in the NETTER-1 sub-study.

In ERASMUS, over the course of the study, deaths were reported in 446/1214 (37%) patients 397/811 (49%) in the Dutch subset and 49/403 (12%) in the non-Dutch subset. In the Dutch

subset, sixteen deaths (2%) occurred on treatment or within 30 days following the last treatment within the Dutch subset. Based on a review of the clinical narratives of these events, none of these deaths were considered related to study drug.

Serious Adverse Events

In the initial version of the NETTER-1 clinical protocol (AAA-III-01/Version 1.0) and through all amendments, a serious adverse event (SAE) was defined as:

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
  Note: "life-threatening" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly or birth defect;
- Requires in-patient hospitalization or leads to prolongation of hospitalization, except for elective pre-planned hospitalizations.

Serious adverse events occurred in 37 (33%) of patients randomized to receive Lutathera and in 30 (27%) patients randomized to receive high-dose octreotide. Table 39 below lists serious adverse events occurring with an incidence of two percent or higher in the Lutathera arm and occurring more frequently in the Lutathera arm than in the control arm.

Table 39 NETTER-1: Per-patient Incidence of Serious Adverse Events Occurring More Frequently in Lutathera Treated Patient with an Incidence of ≥ 2%

SOC/PT	Lutathera (n=111) (%)	Octreotide LAR (n=112) (%)
Blood and lymphatic system disorders		
Lymphopenia	2	0
Infections and infestations		
Sepsis	3	0
Injury, poisoning and procedural complications		
Femur fracture	2	0
Renal and urinary disorders		
Acute kidney injury	4	1
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	2	0

After review of the clinical narratives associated with the SAEs occurring in excess in Lutathera-treated patients, only two were assessed to be likely related to Lutathera and to be of clinical significance. One patient developed protracted G4 lymphopenia which may have been a predisposing factor to pneumocystis jirovicii pneumonia and one patient developed acute renal failure attributed to Lutathera-related nephrotoxicity and pre-renal azotemia.

Only serious adverse events (SAEs) were captured in the ERASMUS safety database. Events were captured using a retrospective medical record review to identify events judged to be potentially serious in nature and possibly or probably related to study drug. An analysis of the per-patient incidence of SAEs was conducted for the entire safety population and for the Dutch subset in which reporting was thought to be more complete. Although the per-patient incidence of SAEs was slightly higher in the Dutch sub-set compared to the total SAF, the pattern of SAEs reported was similar to the SAF.

The most commonly reported SAEs in ERASMUS were pancytopenia (10%), diarrhea (6%), abdominal pain (6%), anemia (5%); nausea, vomiting, and pyrexia (4% each); thrombocytopenia, constipation, pneumonia, dehydration, and dyspnea (3% each).

Table 40: ERASMUS: Per-Patient Incidence of Serious Adverse Events (SAEs) Occurring in ≥ 2% of Patients in the SAF

SOC/PT	SAF	Dutch Subset
	N=1214	N=811
	(%)	(%)
Blood and lymphatic system disorders		
Pancytopenia	8	10
Anemia	4	5
Thrombocytopenia	3	3
Gastrointestinal disorders		
Diarrhea	5	6
Abdominal pain	4	6
Vomiting	4	4
Nausea	3	4
Constipation	2	3
Ascites	2	2
General disorders and administration site conditions		
Pyrexia	3	4
Malaise	2	3
Pain	2	2
Infections and infestations		
Pneumonia	2	3
Metabolism and nutrition disorders		
Dehydration	3	3
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2	3
Surgical and medical procedures		
Cholecystectomy	2	2
Abdominal cavity drainage	2	2

In ERASMUS, patients who were thought to have benefited from Lutathera treatment but who relapsed could receive additional treatment cycles at the discretion of the investigator. A total of 216 patients in ERASMUS received Lutathera doses in excess of the proposed indicated treatment dose. In an attempt to assess the toxicity associated with higher dose exposures, patients in ERASMUS who received doses in excess of 29.6 GBq (>800 mCi) were compared to those receiving up to the maximum recommended dose of 29.6 GBq (800 mCi). The results are shown below in Table 41. The incidence of hematologic and gastrointestinal toxicities appears to be higher in patient treated at doses above 29.6 GBq. However, interpretation of these findings is confounded by the fact that patients who progressed and required additional treatment likely had complications due to end stage disease.

Table 41: ERASMUS: Per-patient Incidence of Serious Adverse Events Occurring in ≥ 2% of Patients receiving >800 mCi Lutathera and Occurring More Frequently* than in Patients Receiving ≤ 800 mCi by Lutathera Dose Level (SAF)

	SAF-Total		SAF-Dutch
	Lutathera Dose		
	≤ 29.6 GBq (800 mCi)	> 29.6 GBq (> 800 mCi)	> 29.6 GBq (> 800 mCi)
	n = 998 (%)	n = 216 (%)	N=178 (%)
Blood and lymphatic system disorders			
Pancytopenia	8	9	10
Anemia	4	6	7
Thrombocytopenia	3	3	3
Gastrointestinal disorders			
Diarrhea	4	10	11
Abdominal pain, abdominal pain upper	5	9	20
Vomiting	3	7	6
Nausea	3	6	6
Melena	0	3	3
Ascites	1	2	3
Ileus	1	2	3
General disorders and administration site conditions			
Pyrexia	3	6	6
Pain	1	4	4
Chest pain	0	2	4
Hepatobiliary disorders			
Cholelithiasis	1	2	2
Infections and infestations			
Urinary tract infection	0	3	3
Pneumonia	2	4	4
Metabolism and nutrition disorders			
Dehydration	2	5	6
Respiratory, thoracic and mediastinal disorders			
Dyspnea	2	3	3
Surgical and medical procedures			
Cholecystectomy	1	5	5
High frequency ablation	1	3	3
Stent placement	1	2	3

*Difference between high- and low-dose groups 2% or more.

Narratives of serious adverse events were reviewed to identify rare and/or unusual events assessed by the reviewer to be of potential clinical significance. In addition to the identified

adverse events of special interest (AESI) discussed below in Section 8.2.5, two other types of events which were not identified in an assessment of common events were noteworthy. These included neuroendocrine release syndrome and hepatic toxicity. A discussion of these events is included in Section 8.2.5.

Dropouts and/or Discontinuations Due to Adverse Effects

In NETTER-1, 7 (6%) patients experienced a treatment emergent adverse event (TEAE) which required a dose reduction, all due to thrombocytopenia, and 14 (13%) patients discontinued Lutathera due to a TEAE. Three patients discontinued Lutathera due to hematologic toxicity, 5 patients due to a renal-related event, 2 related to disease progression, 2 due to underlying disease or a disease-related procedural complication, and 2 for events not clearly related to Lutathera. On the high-dose octreotide arm, 12 (11%) patients experienced a TEAE resulting in study discontinuation.

Significant Adverse Events

Treatment Emergent Adverse Events and Adverse Reactions

In NETTER-1, the most common adverse events (any grade) occurring with a frequency of > 10% include: nausea (65%), vomiting (53%), fatigue (38%), diarrhea and abdominal pain (26% each), decreased appetite (21%), lymphopenia (18%), headaches and dizziness (17% each), peripheral edema and anemia (16% each), flushing (14%), back pain (13%), renal failure, hypertension, anxiety and alopecia (12% each) and cough and extremity pain (11% each). The most common grade 3-4 adverse events occurring with a frequency of ≥ 2% include: lymphopenia (12%), vomiting (7%), nausea (5%), renal failure, abdominal pain and diarrhea (3% each), and femur fracture, back pain and hypertension (2% each). AAA attributed GI symptoms to the co-administration of the amino acid solution used as a renal protectant. Per protocol, an antiemetic was administered concurrent with the start of the amino acid infusion. Musculoskeletal and connective tissue disorders also appeared in excess in the Lutathera treatment arm.

Table 42: NETTER-1: Per-Patient Incidence of Treatment Emergent Adverse EVENTS Occurring at a Higher Incidence in Patients Treated with Lutathera [Between Arm Difference of ≥ 5% (all Grades) or ≥ 2% (Grades 3-4)]

SOC/PT	Lutathera (n=111)		Octreotide LAR (n=112)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Blood and lymphatic system disorders				
Lymphopenia	18	12	0	0
Anemia	16	0	8	0
Thrombocytopenia	14	3	0	0
Neutropenia	5	1	1	0
Leukopenia	5	1	0	0
Cardiac disorders				
Atrial fibrillation	5	1	0	0
Gastrointestinal disorders				
Nausea	65	5	12	2
Vomiting	53	7	9	0
Abdominal pain	26	3	19	3
Diarrhea	26	3	18	1
Constipation	10	0	5	0
General disorders and administration site conditions				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	0
Injury, poisoning and procedural complications				
Femur fracture	2	2	0	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	11	3
Musculoskeletal and connective tissue disorders				
Back pain	13	2	10	0
Pain in extremity	11	0	5	0
Muscle spasms	6	0	2	0
Myalgia	5	0	0	0
Neck pain	5	0	0	0
Nervous system disorders				
Dizziness	17	0	8	0
Headache	17	0	5	0
Dysgeusia	8	0	2	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure*	12	3	2	1
Radiation nephritis**	9	0	3	0
Hematuria	6	0	2	0
Respiratory, thoracic and mediastinal disorders				

Cough	11	1	6	0
Skin and subcutaneous tissue disorders				
Alopecia	12	0	2	0
Vascular disorders				
Flushing	14	1	9	0
Hypertension	12	2	7	2

*Includes the terms: Glomerular filtration rate decreased, Acute kidney injury, Acute prerenal failure, Azotaemia, Renal disorder, Renal failure, Renal impairment
**Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain and urinary incontinence

Laboratory Findings

The per-patient incident laboratory abnormalities reported by highest reported grade is shown below.

Table 43: Per-Patient Incidence of Selected Laboratory Abnormalities Occurring in Study 1 at a Higher Incidence in Lutathera-Treated Patients [Between Arm Difference of ≥5% (All Grades)[1] or ≥2% (Grades 3-4)]*

Laboratory Abnormality	Lutathera (N = 111)		Octreotide LAR (N = 112)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	%	%	%	%
Hematology				
Lymphopenia	90	44	39	4
Anemia	81	0	54	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/metabolic				
Hyperglycemia	82	4	67	2
Hypoglycemia	15	0	8	0
Hypocalcemia	32	0	14	0
Hyperuricemia	34	6	29	6
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Creatinine increased	85	1	73	0
Hypernatremia	17	0	7	0
Gastrointestinal				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	54	9
ASAT increased	50	5	35	0
ALAT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization; N = number of patients
[1]National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

Hematologic toxicities were common among Lutathera-treated patients; however, with the exception of Grade 3-4 lymphopenia which occurred in 44% of Lutathera-treated patients, Grade 3-4 hematologic toxicities were uncommon, with Grade 3-4 neutropenia, leukopenia and thrombocytopenia occurring in 3%, 2% and 1% of patients, respectively. Metabolic and renal laboratory abnormalities (all grades) were more common among Lutathera-treated patients than among patients treated with high-dose octreotide. The between arm difference was at least 2-fold higher in the Lutathera arm for hyper- and hypoglycemia, hypocalcemia, and hypernatremia. However, Grade 3-4 metabolic and renal laboratory abnormalities were uncommon in both study arms and rates of Grade 3-4 abnormalities were generally similar between study arms. The clinical significance of this observation is not immediately clear and

could be related to neuroendocrine hormonal release, but could also be confounded by the imbalance in the number of patients with functional neuroendocrine tumors as manifest by a higher number of Lutathera-treated patients with diabetes and carcinoid symptoms at baseline. The observed increase in all grade toxicity could also result from a differential follow-up of Lutathera treated patients in this open-label trial. Increased creatinine/renal failure, which occurred with a between arm difference of > 10%, was an adverse event of special interest and is further examined in Section 8.2.5 (page 129).

Vital Signs

Overall, there were no clinically meaningful changes in temperature, blood pressure (systolic or diastolic), pulse rate, respiration rate, BMI, or weight over the course of the study.

Electrocardiograms (ECGs)

ECGs were obtained at baseline, immediately after each Lutathera administration and at the last treatment visit. ECGs were also taken at the same time intervals (before the octreotide injection) at the same time points. There were 82 patients in the Lutathera arm and 85 patients in the high dose octreotide arm with baseline assessments. There were no differences between arms in the number of patients with clinically relevant ECG abnormalities over time.

QT

The ability of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to prolong the QTc interval at the therapeutic dose was assessed in an open label study in the NETTER-1 clinical pharmacology sub-study of 20 patients. No large changes in the mean QTc interval (i.e., >20 ms) were detected in the study.

Immunogenicity

Not applicable.

8.2.5 Analysis of Submission-Specific Safety Issues

The NETTER-1 clinical protocol defined the following adverse events of special interest (AESI):

- Hematotoxicity: Grade 2 or higher thrombocytopenia or Grade 3 or 4 of any other hematotoxicity,
- Secondary hematological malignancies: Including myelodysplastic syndrome and acute myeloid leukemia,
- Nephrotoxicity: Including renal failure, suspected radiation nephropathy (increased frequency and urgency of urination, nocturia, dysuria, bladder spasm, bladder obstruction, genitourinary ulceration, or necrosis), and
- Cardiovascular events: including changes on electrocardiogram or echocardiogram.

Based on a review of the case narratives of patients with SAEs identified in ERASMUS, the following additional submission-specific events were assessed:

- Neuroendocrine Hormonal Crises
- Radiation-induced Hepatotoxicity

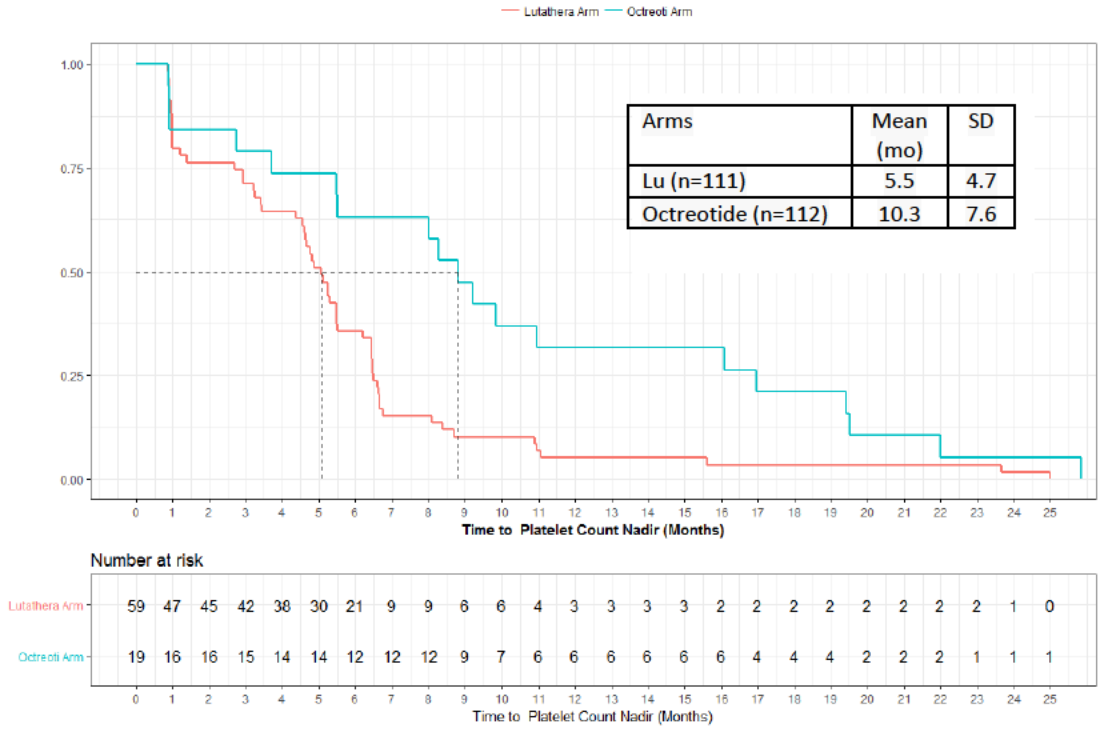
Hematotoxicity

Hematologic toxicity was anticipated based on the estimated cumulative radiation absorbed dose to the red marrow (Gy: mean=1.0; SD=0.8) for 4 treatment cycles of Lutathera in Netter-1. In NETTER-1, lymphopenia (all grades) was the most frequent hematologic toxicity, present in 90% of Lutathera treated patients. In at least one SAE, lymphopenia may have contributed to susceptibility to an opportunistic infection (pneumocystis jirovicii pneumonia). Grade 3-4 lymphopenia was seen in 44% of Lutathera treated patients. Anemia, leukopenia, thrombocytopenia, and neutropenia were also common, occurring in 81%, 55%, 53%, and 26% of Lutathera treated patients, respectively (all grades). However, with the exception of lymphopenia, Grade 3-4 hematologic toxicity was rare in NETTER-1, with Grade 3-4 neutropenia, leukopenia and thrombocytopenia occurring in 3%, 2%, and 1% or Lutathera treated patients, respectively.

Thrombocytopenia

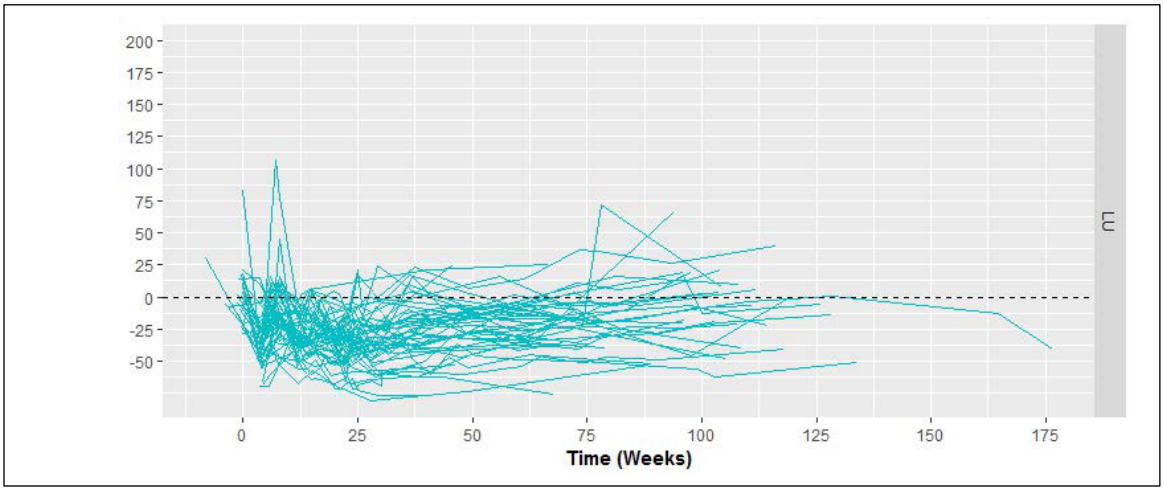
The time to platelet count nadir is shown in Figure 21 below. The mean time to platelet count nadir in Lutathera treated patients was 5.5 months.

Figure 21: NETTER-1: Time to Platelet Count Nadir by Treatment Group, SAF (N= 123)



Among Lutathera-treated patients who developed thrombocytopenia, 19/59 (32%) recovered to baseline platelet counts or higher during the duration of follow-up. Of the patients who did not recover to baseline platelet counts, all but one patient who remained at Grade 3, recovered to Grade 2 platelet counts or higher. These observations suggest that while Lutathera-treated patients were not at increased risk of bleeding due to thrombocytopenia following treatment, some residual impairment of hematopoietic function remained.

Figure 22: NETTER-1 Platelet Count Change from Baseline (%) in Patients with Thrombocytopenia Following Lutathera Treatment (N=59)



Secondary hematological malignancies

In NETTER-1, one patient was identified with a diffuse large B-cell lymphoma 14 months after the initial Lutathera dose. This patient had a prior diagnosis of breast cancer, and although prior treatment with alkylator therapy and/or radiation therapy was not documented, such therapy may have represented antecedent risk factors. Three patients (3%) were identified with a possible diagnosis of myelodysplastic syndrome (MDS). The date of diagnosis ranged from 8 to 15 months following the initial Lutathera dose. In one case, the patient had a history of breast cancer with alkylator therapy administered 20 years prior to the diagnosis of MDS. In the other two cases, patients had underlying hematologic changes.

Table 44: NETTER-1: Patients in the SAF Identified to have Hematologic Malignancies/MDS

Subject ID	PT	Onset (mo) following initial Lutathera dose	Possible Confounding Factors
75YOF	Diffuse large B-cell lymphoma	14	Prior history of breast cancer. Prior alkylator exposure and/or radiation not documented.
76YOM	MDS: Refractory cytopenia with unilineage dysplasia	9	SF3B1 mutation predated PRRT but developed MDS while on PRRT
71YOF	MDS: Refractory cytopenia with multilineage dysplasia	15	History of breast cancer with prior alkylator therapy 20 years prior to dx of MDS. Rapid Heme Panel: SH2B3 and TP53 mutations; Cytogenetics: 13/20 metaphases included del 5q, del 7q, 17p deletion, and trisomy 8
70YOM	MDS (?) Insufficient information to characterize	8	Low prevalence of myeloblasts. Pre-existing MGUS

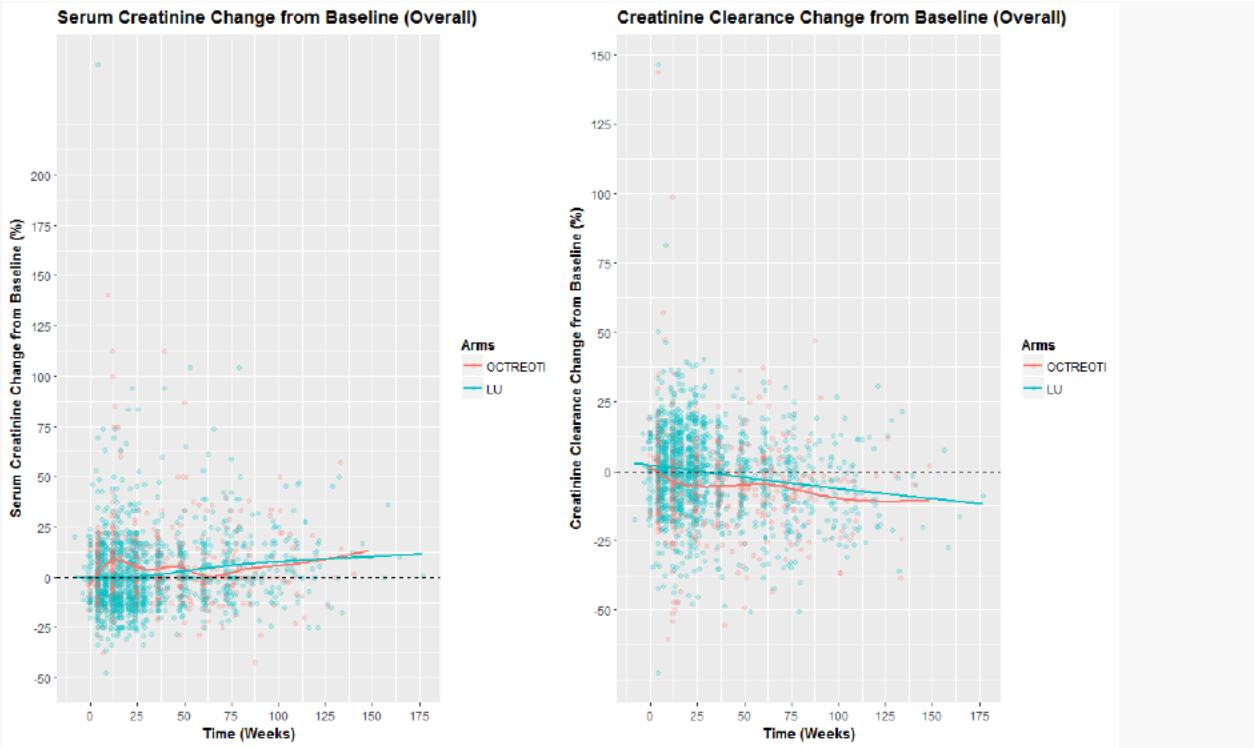
In the Dutch sub-set of ERASMUS (n=811), four patients developed acute leukemia (< 1%). The time of onset from the initial Lutathera dose ranged from 30 to 120 months. One of these events occurred in a patient with a history of treatment with FOLFIRI and a hepatic transplant for P-NET. A second patient had a history of prior external beam radiotherapy for the treatment of breast cancer. Sixteen Dutch patients (2%) were reported to have MDS. The median time of onset was 24 (Range: 10 -60) months following the initial Lutathera treatment.

Based on the available data from NETTER-1 and ERASMUS, with a median duration of follow-up of 19 months in NETTER-1 and 35 months in the Dutch sub-set of ERASMUS, the risk of acute leukemia appears to be less than 1% and the risk of MDS appears to be in the range of 2-3%.

Nephrotoxicity

Since Lutathera is primarily excreted by the kidneys, nephrotoxicity related to radiation exposure was of concern, despite the prophylactic co-administration of an amino acid solution as a renal protectant. During the treatment phase, increased creatinine (all grades) was noted in 85% of Lutathera-treated patients compared to 73% of patients receiving high-dose octreotide. However, Grade 3-4 increased creatinine was reported in only 1% of Lutathera treated patients compared to no control patients. With a median duration of follow-up of 19 months, no clinically meaningful difference was noted between study arm over time in either creatinine or creatinine clearance.

Figure 23: NETTER-1: Change in Creatinine and Creatinine Clearance Over Time by Study Arm, SAF



Adverse events occurring in the NETTER-1 safety database were examined to look for patterns of MedDRA primary terms (PTs) that might constitute radiation-related renal events. A composite term related to urinary tract events was created which included event terms defined in the NETTER-1 clinical protocol used for screening radiation-related nephrotoxicity as an adverse event of special interest. MedDRA PTs grouped for exploratory analysis are shown in Table 45. The composite terms of "radiation-related urinary tract toxicity" and "renal failure" were reported in excess among Lutathera treated patients and were included as composite events in **Table 42**. This exploratory analysis provides suggestive evidence for renal/urinary toxicity related to Lutathera which is not apparent based on screening of MedDRA PTs. This increased risk is also suggested in the exploratory MedDRA Adverse Event Diagnosis (MAED) analysis at the HLGT, SOC and SMQ levels (see Table 48 and Table 49 for SOC and HLGT analyses).

Table 45: NETTER-1: Exploration of MedDRA Primary Terms (MedDRA PT) Potentially Related to Radiation Effects on the Kidney

Reclassification	MedDRA PT	Lutathera (n=111)		Octreotide (n=112)	
		G1-4 n	G3-4 n	G1-4 n	G3-4 n
-	Malignant neoplasm of renal pelvis	0	0	1	0
Radiation-related urinary tract toxicity	Dysuria	2	0	0	0
	Micturition urgency	1	0	0	0
	Nocturia	1	0	1	0
	Pollakiuria	1	0	0	0
	Renal colic	1	0	0	0
	Renal pain	1	0	0	0
	Urinary incontinence	3	0	1	0
	Urinary tract pain	0	0	1	0
Total		10 (9%)	0	3 (3%)	0
Hematuria	Hematuria	7	0	2	0
	Hemoglobinuria	0	0	1	0
Total		7 (6%)	0	3 (3%)	0
Nephrolithiasis	Calculus ureteric	2	0	0	0
	Nephrolithiasis	2	0	0	0
Total		4 (%)	0	0	0
Renal Failure	Glomerular filtration rate decreased	2	0	1	0
	Acute kidney injury	4	1	0	0
	Acute prerenal failure	1	1	0	0
	Azotaemia	1	0	0	0
	Renal disorder	1	0	0	0
	Renal failure	3	1	0	0
	Renal impairment	1	0	2	1
Total		13 (12%)	3 (3%)	2 (2%)	1 (1%)
Urine Protein	Protein urine	1	0	0	0
	Protein urine present	2	0	0	0
	Proteinuria	3	0	4	1
Total		6 (5%)	0	4 (3%)	1 (1%)
Urine WBC	Urine leukocyte esterase positive	0	0	1	0
	Leukocyturia	1	0	0	0
Total		1 (5%)	0	1 (1%)	1 (1%)
UTI	Urinary tract infection	7	0	7	0
	Urinary tract infection bacterial	0	0	1	1
Total		7 (6%)	0	8 (7%)	1 (1%)

In ERASMUS, the incidence of renal failure (including PTs of renal failure and renal impairment) was 2%.

Cardiovascular events

Cardiovascular events were a predefined adverse event of special interest in NETTER-1 and in ERASUS. However, no cardiac signal was observed in either trial. An exploratory MedDRA Adverse Event Diagnosis (MAED) analysis did not suggest a strong cardiovascular signal at any MedDRA level (see Section 19.5.1, page 164).

In ERASMUS, cardiac failure was reported in 2% of the study population and myocardial infarction in 1%.

Neuroendocrine hormonal crises

Neuroendocrine hormonal crises manifesting with flushing, intractable diarrhea, bronchospasm and hypotension was reported in 8 (1%) patients in the Dutch subset of ERASMUS. Hypotension as a PT was reported in 1%. The onset of symptoms typically occurred while on or within 24-48 hours after Lutathera administration. In 5 cases, symptoms were severe and required administration of intravenous octreotide and steroids. No cases of neuroendocrine hormonal crises were reported in NETTER-1; however, it is possible that less severe episodes of neuroendocrine hormonal crises were undetected. Monitoring of vital signs in the peri-infusional time-period was not submitted in a manner that allowed analysis.

Radiation-induced hepatotoxicity

Since Lutathera is primarily excreted by the kidneys rather than through hepatic metabolism, drug induced liver disease would not be expected. Two cases, both on the Lutathera arm met the laboratory criteria only for Hy's Law (BE01-005 at weeks 4 and 6; FR06-007 at week 24); however, both patients had confounding factors (i.e., biliary stint dysfunction; ascites and disease progression with a history of chronic liver disease). The pattern of liver test elevation seen in NETTER-1 was non-specific. The medical reviewer hypothesizes that liver damage may be related to radiation exposure to the liver and may be related to the hepatic tumor burden. However, since there was no quantitative or qualitative assessment of liver involvement in NETTER-1, this hypothesis could not be further explored. Hepatotoxicity with 177-Lu has not been previously reported.

In ERASMUS, the following events were of interest:

- 1045 – A 50-year-old Asian female with neuroendocrine tumor of unknown origin with hepatic metastases received 1 infusion of 7.5 GBq Lutathera and presented approximately 6 weeks later with pancytopenia, decreased fibrinogen, and prothrombin time > 120 sec with a slightly prolonged PTT. Gross hepatomegaly and elevated liver function was reported. Disseminated intravascular coagulation was diagnosed. Two weeks later, the patient had a subdural hematoma requiring craniotomy for clot evacuation. At that time, liver function was improving and there were no signs of DIC.

One month later, a CT scan showed massive liver in a 65-year-old female with a neuroendocrine tumor in the terminal ileum metastatic to liver and lymph nodes was hospitalized for cholestasis approximately 6 weeks following the initial Lutathera administration. An echo of the liver showed intrahepatic congestion secondary to edema or necrosis of hepatic metastases. The patient was also suffering from abdominal complaints which were thought to be related to high-dose octreotide. The dose was decreased and the patient improved and was discharged. Approximately 1 month later, the patient was again admitted due to cholestasis due to distal choledochal stenosis and a stent was placed.

- 946 – A 66-year-old female with peritoneal carcinoid with liver metastases and carcinoid syndrome developed increasing abdominal pain in the liver area 3 days after the first Lutathera dose.
- 182 – A 29-year-old female with atypical carcinoid with liver and peritoneal metastases developed a diffuse pattern of Grade 3 hepatic enzyme elevation one month following the initial Lutathera dose:

Time	Activity mCi	ALAT (SGPT) U/L	ASAT (SGOT) U/L	GGT U/L	Alkaline phosphatase U/L
16Feb2005 Baseline	.	9	21	22	72
07Mar2005 Visit post Trt1(1)	200	363	512	211	362
09Mar2005 Visit post Trt1(2)	.	NA	106	NA	NA
11Mar2005 Visit post Trt1(3)	.	NA	41	NA	NA
21Feb2005 Visit post Trt1(4)	.	NA	16	NA	NA
25Apr2005 Visit post Trt1	.	13	19	33	132
16Jun2005 Visit post Trt2	100	9	20	20	64
17Aug2005	100	8	16	17	63

The available information is not adequate to fully characterize the risk to patients due to radiation-related hepatotoxicity. Such events may be idiosyncratic and depend not only on the hepatic tumor burden but on the response to therapy.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Health related Quality of Life (QoL) was assessed using the EOTC QLQ-30 and QLQ G.I.NET21 questionnaires in NETTER-1. The limited ascertainment of baseline assessments, the high drop-out rate for subsequent ascertainments, and the open-label nature of the trial limited the inferences that can be drawn from the analyses of these data (b) (4)

(b) (4) they were not independently reviewed by FDA clinical/statistical reviewers.

8.2.7 Safety Analyses by Demographic Subgroups

In NETTER-1, the rate of SAEs overall was similar by age group (< 65 years vs ≥ 65 years) (31% vs 37%). The small sample size did not permit an analysis of other demographic subgroups. In the Dutch subset of ERASMUS, the overall rate of SAEs and the rate of renal events were similar in both age groups (overall: 64% vs 60%; renal: 4% vs 5%).

8.2.8 Specific Safety Studies/Clinical Trials

No specific safety studies are currently underway with Lutathera. Besides the ongoing EAP study, NCT02705313, clinical trials are currently underway in the following indications (reference, clinicaltrials.gov):

Table 46: Clinical Trials of Lutathera

NCT#	Drug	Sponsor	Study Population
NCT03325816	Nivolumab Lutathera	MEDSTAR GEORGETOWN CANCER NETWORK	Extensive-stage small cell lung cancer
NCT03206060	Lutathera	CENTER FOR CANCER RESEARCH, NCI NIH	Inoperable, SSTR positive pheochromocytoma/paraganglioma

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review

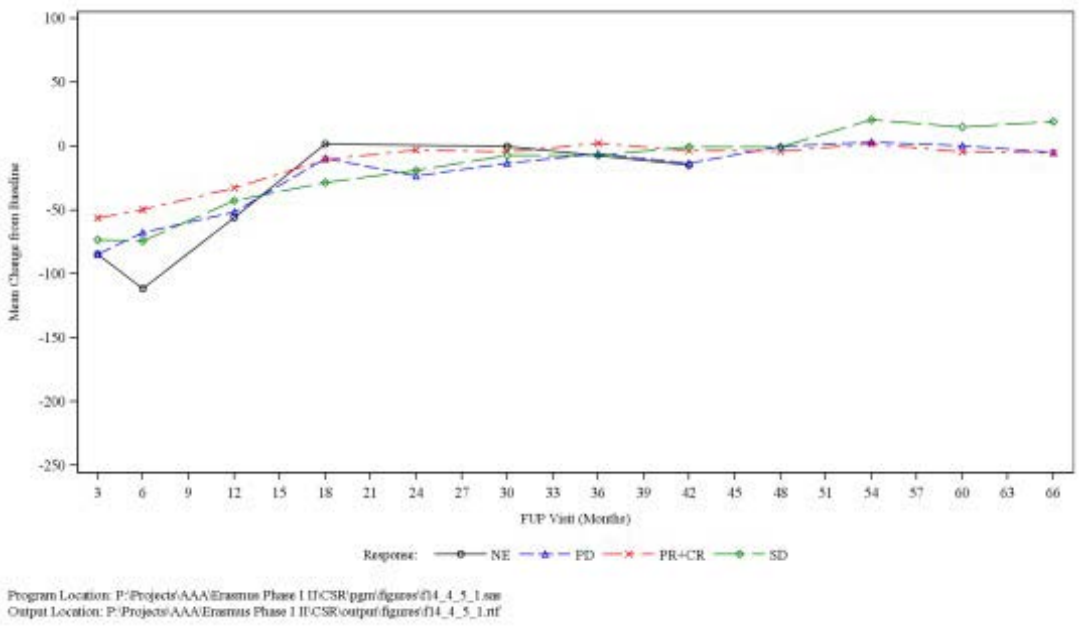
Human Reproduction and Pregnancy

See Pharmacology/Toxicology and Clinical Pharmacology Reviews.

A serial assessment of tumor markers and other biomarkers was conducted in a sub-study of Dutch ERASMUS patients. Included in this assessment was inhibin B and FSH. Baseline assessments were obtained on approximately 80 patients. Inhibin-B was found to decrease and FSH increase following Lutathera treatment suggesting the potential for impaired fertility in males and females following Lutathera treatment (See Figure 24) (data not shown for FSH). The dosimetry studies conducted by the applicant suggest that cumulative Lutathera exposure would result in a radiation absorbed dose to the testis or ovaries within the range where temporary or permanent infertility could be expected following external beam radiotherapy. A warning concerning the risk of infertility should be included in the label. Furthermore, based on

the mechanism of action, Lutathera would be expected to cause fetal harm. A warning concerning the risk of embryo-fetal toxicity is also warranted.

Figure 24: ERASMUS: Change from Baseline in Inhibin B (ng/l) by Visit and Response. (n=84) (Dutch Subset, SAF)



Source: Table 14.3.4.1.1 and Appendix 16.2.8.5

Pediatrics and Assessment of Effects on Growth

Lutathera was not studied in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no data available on the potential for abuse or dependence with Lutathera.

8.2.10 Safety in the Postmarket Setting

Not applicable. Lutathera has not previously been approved in the US.

Expectations on Safety in the Postmarket Setting

Not applicable.

8.2.11 Integrated Assessment of Safety

Because the ascertainment of adverse events differed between studies, data from the two studies was not combined for an integrated assessment of safety.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

Although the design and analysis of Trial NETTER-1 had limitations, ultimately, the large effect size observed in the trial was enough to overcome those limitations. After Complete Response to the original NDA submission on Dec 2017, the applicant resubmitted this NDA in CDISC format and conducted efficacy analysis more rigorously following FDA agreed upon SAP V3. However, some statistically related issues were inherited from the design and data collection.

The major statistical issues are:

1) this study used coin toss randomization method for the first 28 patients and permuted block randomization method for the rest of ITT population;
2) applicant's PFS and OS derivation used imputed dates which will not provide a reliable estimate;
3) Asymmetric delay of the first dose in the Lutathera arm caused asymmetric time to tumor assessment from randomization;
4) Per protocol, the PFS would be performed when the planned 74 PFS evaluable events was observed. At the same efficacy cut-off date, the resubmission has 91 PFS events; FDA's analysis has 105 PFS events.

The PFS analysis results (HR = 0.21 [95% CI: 0.13, 0.32]; p-value <0.0001) and ORR results (12.9 in the Lutathera arm and 3.5% in the octreotide arm; Fisher's exact p-value 0.0068)] demonstrated statistically significant improvement in the Lutathera arm and fit the protocol's pre-specified group sequential criteria. Regardless of the limitation in the study design and data collection, the PFS sensitivity analyses' HR ranged from 0.15-0.46 which supported FDA's PFS analysis results.

At the pre-planned OS analysis with 48 (30%) out of 158 required events for final OS analysis, the study and data did not demonstrate a statistically significant improvement in OS for the Lutathera arm relative to the octreotide arm. To get more mature OS analysis results, FDA requested the applicant conduct an updated OS analysis with 70 OS events, the HR for OS was

0.52 (95% CI: 0.32, 0.84) with a nominal p-value of 0.0068 which is larger than the OBF stopping boundary 0.002. The median OS in the experimental arm is not reached.

FDA has previously expressed reservations concerning the limitations of the ERASMUS trial and the adequacy of this trial to support expansion of the proposed indication to include GEP-NET (b) (4) tumors:

- There was no formal clinical protocol or prespecified statistical analysis plan.
- Baseline tumor assessments were obtained for only 811/1214 (67%) patients.
- Patients were not required to have disease progression following the most recent prior therapy for NET.
- There was no central review of histology or of OctreoScan uptake at baseline or response
- Prospective data collection was limited and was supplemented by retrospective medical records review and data verification in the Dutch subset of patients only.
- Follow-up assessments measured by CT or MRI were obtained less regularly and less frequently than in the NETTER-1 trial.
- Two different response criteria were used during the study.

The above limitations concerning ERASMUS suggest that despite its size, the conclusions drawn from this trial concerning the efficacy and safety of Lutathera must be interpreted with caution.

8.4 Conclusions and Recommendations

Efficacy:

NETTER-1 was an international, open-label trial which randomized 229 patients with histologically confirmed, advanced/inoperable or metastatic, somatostatin receptor (SSTR)-positive midgut carcinoid tumors that had progressed while on octreotide LAR. Patients received either LUTATHERA (7.4 GBq [200 mCi] every 8 weeks for up to 4 administrations; maximum cumulative dose of 29.6 GBq) with octreotide LAR (30 mg by intramuscular injection every 4 weeks) or octreotide LAR (60 mg by intramuscular injection every 4 weeks) alone.

Randomization was stratified by OctreoScan tumor uptake score (Grade 2, 3 or 4) and the length of time that patients had been on the most recent constant dose of octreotide prior to randomization (≤ 6 or > 6 months) through coin toss method for the first 28 patients and a permuted block minimization method for the rest 201 patients. The primary endpoint of NETTER-1 was PFS per IRC assessment and was designed with 90% power at a 2-sided alpha level of 5%. ORR and OS were major secondary measurements and test in the hierarchical order as appeared to adjust for multiplicity of the secondary endpoints.

The trial randomized 229 patients (116 to Lutathera and 113 to octreotide). Treatment with Lutathera resulted in a clinically meaningful and statistically significant treatment effect in PFS compared to treatment with octreotide LAR. The median PFS was not reached in the Lutathera arm compared to 8.5 months (95% CI: 5.8, 9.1) in the octreotide LAR arm; un-stratified HR 0.21 (95% CI: 0.13, 0.32); p-value <0.0001. Treatment with Lutathera also resulted in a statistically significant improvement in ORR as assessed by the IRC compared to treatment with octreotide LAR. The ORR was 12.9% (95% CI: 7%, 19%) in the Lutathera arm and 3.5% (95% CI: 0.1%, 7%) in the octreotide LAR arm; Fisher's exact test p-value is 0.0148. The median OS for the updated analysis was not reached in the in Lutathera arm and 27.4 months (95% CI: 22.2, not evaluable) in the octreotide LAR arm, stratified HR 0.52 (95% CI: 0.32, 0.84), p-value 0.0068.

Despite the limitations in trial design and data collection in NETTER-1, a substantial, statistically significant and clinically meaningful improvement in both PFS and ORR were observed in this trial for Lutathera-treated patients who had histologically confirmed, advanced/inoperable or metastatic, somatostatin receptor (SSTR) positive midgut carcinoid tumors and had progressed while on octreotide LAR.

Therefore, we recommend the approval of Lutathera for the treatment of patients with histologically confirmed, (b) (4) somatostatin receptor (SSTR) positive midgut (b) (4) tumors (b) (4).

ERASMUS was an investigator-sponsored, open-label, single-arm, single-institution study of 1214 patients with somatostatin receptor (SSTR) positive neuroendocrine (NET) and other SSTR positive tumors. The study population was heterogeneous. The study population included 855patients with GEP-NETs and bronchial carcinoid tumors (b) (4)

In ERASMUS, patients were treated with a regimen similar to that used in NETTER-1 using an institutional protocol derived from the study of other high dose radiolabeled peptides. There was no formal protocol or prespecified statistical analysis plan. The primary study endpoint was investigator assessed overall response rate. There were many design issues with this study. There was no central review and confirmation of pathology, SSTR uptake at baseline or response. No baseline tumor assessments were obtained on 33% of the treated population. Different response assessments were used during the study (N=1214; prior to 3/15/2007: SWOG: n= 615; after 3/15/2007: RECIST: n=599).

The flaws in the design and implementation of ERASMUS make it impossible to precisely define a response rate for patients with GEP-NETs and bronchial carcinoid tumors. However, the most conservative estimates suggest some benefit with durable responses demonstrated (and were generally consistent with effects observed in NETTER-1). (b) (4)

Safety:

An assessment of the safety of Lutathera was based on an assessment of patients treated with Lutathera with octreotide LAR (30 mg IM q4 weeks) (n=111) or octreotide LAR (60 mg IM q4 weeks) (n=112) in NETTER-1. The two treatment arms were similar with respect to major demographic, tumor, and prognostic characteristics. Among patients receiving Lutathera with octreotide LAR, 79% received a cumulative dose of greater than 22.2 GBq (> 600 mCi) and 76% of patients received all four planned doses. Six percent (6%) of patients required a dose reduction and 13% of patients discontinued Lutathera. Five patients discontinued due to renal-related events, 3 patients discontinued due to hematological toxicities, and 6 discontinued for disease- or procedure-related reasons, or other reasons. The median duration of follow-up was 24 months for patients receiving Lutathera with octreotide LAR and 20 months for patients receiving octreotide LAR alone.

The most common Grade 3-4 adverse reactions occurring with a greater frequency (≥ 2%) among patients treated with Lutathera with octreotide LAR than octreotide LAR alone include: lymphopenia (44%), increased GGT (20%) vomiting (7%), nausea and elevated AST (5% each), increased ALT, hyperglycemia, and hypokalemia (4% each).

Safety data is available from a subset of 811 patients in ERASMUS, an international, single-institution, single-arm, open-label trial of patients with SSTR positive tumors (neuroendocrine and other primaries). Retrospective medical record review was conducted to document serious adverse events. Patients received Lutathera 7.4 GBq (200 mCi) administered every 6 to 13 weeks. Eighty-one percent of patients received a cumulative dose ≥ 22.2 GBq (600 mCi). With a median follow-up time of more than 4 years, the following rate of serious adverse events was

reported: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure and impaired renal failure and renal impairment (1% and 1.2%, respectively), hypotension (1%) cardiac failure (1.5%), myocardial infarction (1.1%) and neuroendocrine hormonal crisis (1%). Several patients with hepatic metastases were reported to have severe upper abdominal pain concurrent or within 24-48 hours following Lutathera administration, hepatic necrosis and/or hemorrhage and cholecystitis weeks to months following Lutathera administration and non-specific hepatic enzyme elevation. Such events may be idiosyncratic based on hepatic tumor burden or location of metastatic disease within the liver or may be related to the underlying disease.

It is recommended that the following Warnings and Precautions be included in the Lutathera label:

- Risk of radiation exposure to medical personnel and household contacts
- Myelosuppression
- Secondary myelodysplastic syndrome and acute leukemia
- Renal toxicity
- Hepatic toxicity
- Neuroendocrine hormonal crises
- Embryo-fetal toxicity
- Risk of infertility

X

Kun He, Ph.D.
Primary Statistical Reviewer and Statistical Team Leader

X X

Ruthann Giusti	Suzanne Demko
Primary Clinical Reviewer	Clinical Team Leader

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was convened for this application, as there were no public health issues raised that would benefit from a public discussion or that required the expert opinions of the Committee. In addition, the safety profile of the drug is deemed acceptable for the indicated population of patients.

The Division attempted to solicit the advice of three Special Government Employees (SGEs) who have expertise in the treatment of patients with GEP-NETs and one patient advocate. Because of clearance issues for all SGEs identified and contacted, as well as time limitations precluding the completion of applications for waivers, no external consultations were conducted.

10. Pediatrics

This application is exempt from the requirements under the Pediatric Research Equity Act. Lutetium Lu 177 Dotatate (Lutathera) received orphan designation for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in January 2009.

11. Labeling Recommendations

11.1 Prescription Drug Labeling

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for LUTATHERA (lutetium Lu 177 dotatate) accompanying the approval letter for more information.

Labeling referencing the ERASMUS study describes different populations in different sections. For safety (e.g., Sections 5 and 6), labeling primarily references the subgroup of 811 patients from the Netherlands because of the difference in long term safety follow-up among Dutch versus non-Dutch patients (who received Lutathera in the Netherlands and then traveled back to their home countries). For efficacy (Section 14), labeling describes the subgroup of 360 patients who (1) were prospectively assessed using RECIST criteria and (2) had a GEP-NET tumor.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
General	Employed inconsistent names used to refer to drug product and drug substance. Included cross references with capitalization.	• Revised labeling to use LUTATHERA to refer to drug product, lutetium Lu 177 dotatate to refer to drug substance and non-radioactive form lutetium Lu 175 dotatate in clinical pharmacology and pharmacology/toxicology sections where applicable. • Revised cross references to use the appropriate format • Where appropriate, revised to reflect active voice when describing instructions regarding dosage & administration or storage & handling.
Highlights of Prescribing Information		
Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations	…	See revisions to Full Prescribing Information, Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations. Corrected product title.
Full Prescribing Information		

Boxed Warning	(b) (4)	Moved relevant information to Dosage and Administration and Warnings and Precautions. This product will de-facto be under restricted distribution as a radiopharmaceutical (and will be administered by physicians trained in the administration of this class of drugs)
Indications and Usage	Included (b) (4) in indication and usage statement.	Removed (b) (4) from indication and usage statement.
Dosage and Administration	Included the following subsections: Important (b) (4) Safety Instructions, Recommended (b) (4), (b) (4) and Concomitant Medications, Dose Modification, (b) (4) Preparation, and Radiation Dosimetry.	• Added recommendation to verify pregnancy status prior to initiating LUTATHERA. • Restructured to include the following subsections: Important Safety Instructions, Recommended Dosage, Premedication and Concomitant Medications, Dose Modification, Preparation and Administration, and Radiation Dosimetry. • Provided additional details regarding infusion procedure. • Consolidated the tables in Dose Modification section to provide a single table with prescriptive instructions for dose interruption, dose reduction and permanent discontinuation.
Contraindications	Included (b) (4)	Moved the relevant information to Warnings and Precautions, Adverse Reactions and Use in Specific Populations.
Warnings and Precautions	Included (b) (4) (b) (4) renal toxicity, hepatic toxicity, (b) (4) myelosuppression, (b) (4), neuroendocrine hormonal crisis and embryo-fetal toxicity (b) (4). Include (b) (4)	• Omitted (b) (4) (incidence described in Section 6); reordered the subsections in order of decreasing risk or severity; and included mitigation strategies where applicable. • Renamed (b) (4) to Risk from Radiation Exposure. Included specific information about nature and duration of risk to household contacts and

		medical personnel. • Eliminated (b) (4) . Incorporated the data about risk factors under relevant subsections. • Renamed (b) (4) to Secondary Myelodysplastic Syndrome and Leukemia. Included specific information concerning estimated risks. • Renamed (b) (4) to risk of infertility based on radiation absorbed dose to testis and ovaries and added data regarding risk of infertility to females.
Adverse Reactions	Included in the table for Adverse Reactions and Laboratory Abnormalities (b) (4)	• Added subsections for NETTER-1 and ERASMUS with an appropriate description of adverse reactions and risks. • Modified table for adverse reactions to remove (b) (4) , reorder in decreasing frequency in each category, and add adverse reactions. • Omitted (b) (4) and included relevant information in subsections for the two trials.
Use in Specific Populations	Include risk summary (b) (4) for Pregnancy, Lactation and Females and Males of Reproductive Potential. Included sections for Renal and Hepatic Impairment.	• Omitted (b) (4) for these subsections. Created a subsection in Pregnancy for Pregnancy Testing and added information to Dosage and Administration. • Modified language for Geriatric Use, Renal Impairment, and Hepatic Impairment; language for Geriatric Use based on 21 CFR 201.57 and language for organ impairment based on individual guidances.
Over dosage	(b) (4)	Recommended omitting (b) (4)
Description	…	Modified to include EPC and route

		of administration.
Clinical Pharmacology	Included pharmacodynamic section to include (b) (4)	Omitted the proposed language and described exposure-response relationships and effect on cardiac electrophysiology.
Nonclinical Toxicology	Included Carcinogenesis, Mutagenesis, Impairment of Fertility (b) (4) Animal Toxicology and/or Pharmacology sections.	Modified to include description of primary target organ.
Clinical Studies	…	• Added NCT registry number per OND Policy since 9/2015 which recommends inclusion of NCT # and trial name to ease identification of trials in labeling. • Added subsections to describe NETTER-1 and ERASMUS independently.
Patient Counseling Information	Included bulleted list for advice to patients.	Formatted to be consistent with guidance – Patient Counseling Section of Labeling and revised Warnings and Precautions.

12. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategy was deemed necessary for Lutathera. Lutathera will be administered by health care professionals with experience in managing radiolabeled products in settings where these products are handled and administered routinely (i.e., licensed centers). None of the safety signals identified during the review require a Risk Evaluation and Mitigation Strategy. The USPI as well as all controlling regulations for the shipping and handling of radiolabeled products include sufficient information and requirements for safety.

13. Postmarketing Requirements and Commitment

The following post marketing requirements (PMRs) under 505(o) are recommended:

CLINICAL

1. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors, and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

   Proposed PMR Milestone Dates:

Final Analysis Plan:	June 2018
Interim Safety Report:	September 2021
Final Report:	December 2025

2. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors, and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

   Proposed PMR Milestone Dates:

Final Analysis Plan:	June 2018
Interim Safety Report:	September 2021
Final Report:	December 2025

One additional PMC was recommended to further characterize the efficacy of Lutathera. The OS analysis of NETTER-1 was considered immature (see Efficacy Section above) and therefore the review team is recommending that AAA provide the final results of the OS analysis. Furthermore, if the pre-specified analysis is statistically significant, the potential exists for the sponsor to make a labeling claim for OS. The following is the proposed language of the PMC:

1. Submit the final clinical report and datasets at the time of the final analysis for overall survival (OS) for Trial NETTER-1, entitled "A Multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostin Receptor Positive, Midgut Carcinoid Tumors", to revise product labeling with

mature OS data.

Proposed Milestone Date:

Final report submission: May 2021

14. Division Director (DHOT)

X

15. Division Director (OCP)

X

16. Division Director (OB)

X

17. Division Director (Clinical)

I recommend approval of NDA 207800, as amended, pending final agreement on labeling and post-marketing requirements.

Approval of this application is based on the results of the randomized NETTER-1 trial with support provided by the single-arm ERASMUS study. As described above, NETTER-1 was an international, open-label trial that randomly allocated 229 patients with histologically confirmed, advanced/inoperable or metastatic, somatostatin receptor (SSTR)-positive midgut carcinoid tumors that had progressed while on long-acting octreotide. The primary endpoint of NETTER-1 was PFS per IRC assessment. Two hundred and twenty-nine patients were randomized: 116 to Lutathera and 113 to the [high dose] long-acting octreotide arm. The ERASMUS study represented a single center's experience with Lutathera in the Netherlands. Lutathera in ERASMUS was initially administered in the compassionate use setting under a general umbrella peptide radiotherapy protocol and therefore was not a traditional trial with a pre-defined sample size and analysis plan. Monitoring was variable because some patients traveled to the Netherlands for treatment and then returned to their home countries outside of the Netherlands.

In NETTER-1, treatment with Lutathera resulted in a clinically meaningful and statistically significant treatment effect on PFS compared to treatment with long-acting octreotide. The median PFS was not reached in the Lutathera arm compared to 8.5 months (95% CI: 5.8, 9.1) in the long-acting octreotide arm; unstratified HR 0.21 (95% CI: 0.13, 0.32); p-value < 0.0001. Although a statistically significant improvement in OS was not demonstrated (did not cross the conservative statistical boundary set for the interim analysis), the OS analysis was immature and alpha is available to test for a final OS analysis (to be tested post-approval and submitted as part of a post-approval commitment). The median OS for the updated analysis submitted within the NDA was not reached in the Lutathera arm and 27.4 months (95% CI: 22.2, not evaluable) in the long-acting octreotide arm, stratified HR 0.52 favoring the Lutathera arm (95% CI: 0.32, 0.84), nominal p-value = 0.0068.

The clinical and statistical review described certain limitations of the NETTER-1 trial. Nevertheless, approval based on this trial should be granted because of the large treatment effect that overcame these limitations. Given the large effect size (both in terms of statistical significance and in terms of the clinical relevance of the long delay in progression of the underling malignancy), a second trial should not be required to replicate this effect. Such a requirement would unnecessarily delay this effective treatment for patients with advanced or inoperable SSTR-positive neuroendocrine tumors (many of these patients also have symptomatic disease). Furthermore, the preliminary OS results appear favorable; however, the ultimate effect should be assessed as part of the pre-specified OS analysis plan.

Approval for the broader GEP-NET population is supported by the results of the NETTER-1 trial, underlying biology (indication is limited to patients with SSTR-positive tumors), *and* results from

the ERASMUS trial. Considering the underlying biology, FDA previously approved Lanreotide (a long-acting octreotide formulation) for the treatment of patients with *both* functional and non-functional GEP-NETS based on the results of a clinical trial that limited enrollment to patients with non-functional tumors. Such extrapolation *may* be appropriate for certain octreotide-based therapies based on the underlying biology; however, such extrapolation would not necessarily be appropriate for other therapeutic classes given differences in treatment effects observed with certain drugs (e.g., everolimus) in different groups of patients with GEP-NETs. Although I will not restate the ERASMUS results in this section, the most conservative results (i.e., FDA's analysis of ORR) in the global GEP-NET population were consistent with the results obtained in NETTER-1 (suggesting a similar effect) in patients with mid-gut tumors. The applicant submitted data describing higher-response rates; however, due to limitations in ERASMUS (described above), the clinical review team had low confidence regarding the (quantitative) reproducibility of those results.

Although Lutathera can cause severe or life-threatening adverse reactions, approval is warranted given the context of the life-threatening disease that Lutathera will treat. Adverse reactions are generally consistent with the expected effects of a radiopharmaceutical. Such adverse reactions including hematologic toxicity (e.g., cytopenias and myelodysplastic syndrome) and gastrointestinal toxicity are described in labeling. Although Lutathera is not subject to a REMS, Lutathera can only be administered by qualified and licensed medical practitioners and pharmacies that are trained in the handling and administration of radiopharmaceutical drugs.

X _____

18. Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature also represents an approval recommendation of the application under CDER.

19. Appendices

19.1 References

1. Yao, J. C., M. Hassan, A. Phan, C. Dagohoy, C. Leary, J. E. Mares, E. K. Abdalla, J. B. Fleming, J. N. Vauthey, A. Rashid and D. B. Evans (2008). "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States." J Clin Oncol 26(18): 3063-3072.
2. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. Lyon: IARC Press; 2010
3. Rindi, G., G. Kloppel, H. Alhman, M. Caplin, A. Couvelard, W. W. de Herder, B. Erikssson, A. Falchetti, M. Falconi, P. Komminoth, M. Korner, J. M. Lopes, A. M. McNicol, O. Nilsson, A. Perren, A. Scarpa, J. Y. Scoazec, B. Wiedenmann, p. all other Frascati Consensus Conference and S. European Neuroendocrine Tumor (2006). "TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system." Virchows Arch 449(4): 395-401.
4. Rindi, G., G. Kloppel, A. Couvelard, P. Komminoth, M. Korner, J. M. Lopes, A. M. McNicol, O. Nilsson, A. Perren, A. Scarpa, J. Y. Scoazec and B. Wiedenmann (2007). "TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system."
5. Storsberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. Pancreas. 2009; 38:255-8.
6. Ter-Minassian M, Chan JA, Hooshmand SM, et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. Endocrine-related cancer 2013;20:187-96.
7. Hobday, T. J., J. Rubin, K. Holen, J. Picus, R. Donehower, R. Marschke, W. Maples, R. Lloyd, M. Mahoney, and C. Erlichman. "MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study." In ASCO Annual Meeting Proceedings, vol. 25, no. 18_suppl, p. 4504. 2007.
8. Phan, A. T., J. C. Yao, D. R. Fogelman, K. R. Hess, C. S. Ng, S. A. Bullock, P. Malinowski, E. Regan, and M. Kulke. "A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC)." In ASCO Annual Meeting Proceedings, vol. 28, no. 15_suppl, p. 4001. 2010.
9. Robins JM, Tsiatis AA Correcting For Non-Compliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Commun. Statist.-Theory Meth. 1991;20(8):2609-2631.
10. FDA Mapp 6025.4 available at http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm370948.htm
11. FDA *Data Standards Catalog* available at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

12. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.
13. FDA Guidance for Industry: *Providing Regulatory Submissions In Electronic Format — Standardized Study Data* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334
14. FDA Guidance for Industry: *Study Data Technical Conformance Guide: Technical Specifications Document*, available at http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
15. FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf
16. Reubi JC, JC Schär, B Waser, S Wenger, A Heppeler, JS Schmitt, and HR Mäcke, 2000, Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use, Eur J Nucl Med, 27(3):273-82.
17. Rollerman EJ, EP Krenning, BF Bernard, M de Visser, M Bijster, TJ Visser, M Vermeij, J Lindemans, and M deJong, 2007. Long-term toxicity of [177Lu-DOTAO, Tyr3] octreotate in rats, Eur J Nucl Med Mol Imag, 34(2):219-27.

19.2 Financial Disclosure

See Sections 8.1.1 (page 70) and 8.1.3 (page 90).

Covered Clinical Study (Name and/or Number): NETTER-1 (NCT 01578239)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 271		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

None

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

None

19.5 Additional Clinical Outcome Assessment Analyses

None

19.5.1 MedDRA Adverse Event Diagnosis (MAED) Tool Analysis

The MedDRA-Based Adverse Event Diagnostic (MAED) Service is a server-based **adverse event (AE) analysis tool** that enables reviewers at the Center for Drug Evaluation and Research (CDER) to quickly generate AE analyses on datasets submitted to the U.S. Food and Drug Administration (FDA). This tool enables reviewers to conduct analyses in a batched manner, using standard medical terms or codes from the Medical Dictionary for Regulatory Activities (MedDRA). This tool allows the user to conduct analyses for all levels of the MedDRA hierarchy, as well as create Standardized MedDRA Queries (SMQs)—narrow, broad, and algorithm.

MedDRA Adverse Event Diagnostic System, Enterprise Performance and Lifecycle System Design, v3.1, 2013.

Medical Dictionary for Regulatory Activities (MedDRA), Maintenance and Support Services Organization (MSSO), http://www.meddra.org

Table 48 Exploratory MedDRA -Based Adverse Event Diagnostic (MAED) Service Analysis of Lutathera by MedDRA SOC Classification

All Grades *SOC*	*LU (N=134)*		*Octreotide (N=112)*		*OR*
	n	*(%)*	*n*	*(%)*	
Blood and lymphatic system disorders	58	43.61	12	10.71	6.444
Gastrointestinal disorders	121	90.98	77	68.75	4.583
Renal and urinary disorders	41	30.83	13	11.61	3.394
Nervous system disorders	57	42.86	28	25	2.25
Psychiatric disorders	40	30.08	17	15.18	2.404
Investigations	69	51.88	41	36.61	1.867
General disorders and administration site conditions	87	65.41	57	50.89	1.825
Metabolism and nutrition disorders	63	47.37	38	33.93	1.753
Respiratory, thoracic and mediastinal disorders	43	32.33	23	20.54	1.849

Table 49 Exploratory MedDRA -Based Adverse Event Diagnostic (MAED) Service Analysis of Lutathera by MedDRA HLGT Classification

All Grades	*LU (N=133)*		*Octreotide (N=112)*		
HLGT	*n*	*(%)*	*n*	*(%)*	*OR*
Gastrointestinal signs and symptoms	110	82.71	52	46.43	5.518
White blood cell disorders	37	27.82	4	3.57	10.406
Platelet disorders	20	15.04	1	0.89	19.646
Haematology investigations (incl blood groups)	33	24.81	8	7.14	4.29
Headaches	31	23.31	7	6.25	4.559
Anaemias nonhaemolytic and marrow depression	32	24.06	11	9.82	2.909
Respiratory disorders NEC	40	30.08	17	15.18	2.404
Renal disorders (excl nephropathies)	16	12.03	3	2.68	4.969
Protein and chemistry analyses NEC	0	0	6	5.36	**0.061**
General system disorders NEC	83	62.41	51	45.54	1.985
Muscle disorders	17	12.78	4	3.57	3.957
Neurological disorders NEC	42	31.58	19	16.96	2.259
Skin appendage conditions	20	15.04	6	5.36	3.127
Urinary tract signs and symptoms	28	21.05	11	9.82	2.448
Anxiety disorders and symptoms	20	15.04	7	6.25	2.655
Injuries NEC	18	13.53	6	5.36	2.765
Appetite and general nutritional disorders	27	20.3	12	10.71	2.123
Body temperature conditions	12	9.02	3	2.68	3.603
Depressed mood disorders and disturbances	9	6.77	2	1.79	

Table 50 Exploratory MedDRA -Based Adverse Event Diagnostic (MAED) Service Analysis of Lutathera by MedDRA HLT Classification

All Grades	*LU (N=133)*		*Octreotide (N=112)*		*OR*
HLT	*n*	*(%)*	*n*	*(%)*	
Nausea and vomiting symptoms	99	74.44	19	16.96	14.252
Leukopenias NEC	33	24.81	0	0	**75**
Thrombocytopenias	20	15.04	0	0	**40.639**
Headaches NEC	31	23.31	7	6.25	4.559
White blood cell analyses	21	15.79	4	3.57	5.063
Bladder and urethral symptoms	14	10.53	1	0.89	13.059
Alopecias	15	11.28	2	1.79	6.992
Accelerated and malignant hypertension	0	0	6	5.36	**0.061**
Protein analyses NEC	0	0	6	5.36	**0.061**
Platelet analyses	15	11.28	3	2.68	4.619
Anaemias NEC	7	5.26	0	0	**13.34**
Asthenic conditions	28	21.05	11	9.82	2.448
Disturbances in consciousness NEC	63	47.37	38	33.93	1.753
Appetite disorders	14	10.53	4	3.57	3.176
Febrile disorders	27	20.3	12	10.71	2.123
Muscle related signs and symptoms	12	9.02	3	2.68	3.603

Table 51 Exploratory MedDRA -Based Adverse Event Diagnostic (MAED) Service Analysis of Lutathera by MedDRA PT Classification

All Grades	*LU (N=133)*		*Octreotide (N=112)*		*OR*
PT	*n*	*(%)*	*n*	*(%)*	
Nausea	86	64.66	16	14.29	10.979
Vomiting	68	51.13	12	10.71	8.718
Lymphopenia	31	23.31	0	0	**69.146**
Thrombocytopenia	20	15.04	0	0	**40.639**
Headache	30	22.56	7	6.25	4.369
Alopecia	15	11.28	2	1.79	6.992
Leukopenia	9	6.77	0	0	**17.169**
Platelet count decreased	15	11.28	2	1.79	6.992
White blood cell count decreased	11	8.27	1	0.89	10.008
Hypertensive crisis	0	0	6	5.36	**0.061**
Lymphocyte count decreased	13	9.77	2	1.79	5.958
Myalgia	7	5.26	0	0	**13.34**
Blood albumin decreased	0	0	5	4.46	**0.073**
Anaemia	27	20.3	11	9.82	2.339
Fatigue	55	41.35	32	28.57	1.763
Decreased appetite	27	20.3	12	10.71	2.123
Oedema peripheral	27	20.3	12	10.71	2.123
Pyrexia	12	9.02	3	2.68	3.603
Atrial fibrillation	5	3.76	0	0	**9.63**
Haemoglobin decreased	5	3.76	0	0	**9.63**
Neck pain	5	3.76	0	0	**9.63**
Muscle spasms	9	6.77	2	1.79	3.992

19.5.2 Analysis of Patient Reported Outcomes

Health related Quality of Life (QoL) was assessed using the EOTC QLQ-30 and QLQ G.I.NET21 questionnaires in the NETTER-1. The limited ascertainment of baseline assessments, the high drop-out rate for subsequent ascertainments, and the open-label nature of the trial limits the inference that can be drawn from the analyses of these data (b) (4) the data was not independently reviewed by FDA clinical/statistical reviewers.

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/s/

NATALIYA N FESENKO
01/23/2018

M A GOHEER
01/24/2018

WHITNEY S HELMS
01/24/2018

JOHN K LEIGHTON
01/24/2018

RUBY LEONG
01/24/2018
Signing on behalf of Dr. Brian Furmanski.

PENGFEI SONG on behalf of HONG ZHAO
01/24/2018

BRIAN P BOOTH
01/24/2018

KUN HE
01/24/2018

RAJESHWARI SRIDHARA
01/24/2018

SUZANNE G DEMKO
01/24/2018
Additionally, signing by proxy for Ruthann Giusti, M.D. Please see the Primary Clinical Review memo filed herein on December 15, 2017 for her original signature that refers to this review.

STEVEN J LEMERY
01/25/2018

RICHARD PAZDUR
01/25/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Hematology and Oncology Products
Division of Oncology Products 2

DIVISION DIRECTOR MEMO

NDA:	208700
Drug Name:	LUTATHERA ® (177Lu-DOTA0-Tyr3-Octreotate)
Indication:	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors
Applicant:	Advanced Accelerator Applications USA, Inc.
Receipt Date	July 26, 2017 (resubmission)
PDUFA Goal Date:	January 26, 2018
Review Priority:	Priority
Project Manager:	Nataliya Fesenko, Pharm.D.

The Division Director review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-Disciplinary Review and Evaluation for additional details. The NDA is acceptable to support approval provided that the Applicant and the FDA reach agreement regarding labeling and post-marketing requirements.

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/s/

STEVEN J LEMERY
01/04/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translation Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES- MEMO

NDA:	208700
Drug Name:	LUTATHERA ® (177Lu-DOTA0-Tyr3-Octreotate)
Indication:	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors
Applicant:	Advanced Accelerator Applications USA, Inc.
Receipt Date:	July 26, 2017
PDUFA Goal Date:	January 26, 2018
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Primary Reviewers:	Kun He, Ph.D.
Concurring Reviewers:	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Office of Hematology and Oncology Products, Division of Oncology Products 2
Clinical Team:	Ruthann Giusti, M.D., Clinical Reviewer Suzanne Demko, PA-C, Clinical Team Leader Steven Lemery, M.D., M.H.S., Associate Director
Project Manager:	Nataliya Fesenko, Pharm.D.

The statistical review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-Disciplinary Review and Evaluation for additional details. From a statistical standpoint, the NDA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

KUN HE
01/03/2018

RAJESHWARI SRIDHARA
01/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 15, 2017

To: File for NDA #208700: 177Lu-DOTA0-Tyr3-Octreotate (Lutathera)

Through: Suzanne Demko, Clinical Team Leader, DOP 2, OHOP
From: Ruthann Giusti, MD, Medical Officer, DOP 2, OHOP

Subject: Approval

The clinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. This reviewer recommends approval of this application with the following post-marketing requirements (PRMs) under 505(o):

CLINICAL

1. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

   Proposed PMR Milestone Dates:
   Interim Safety Report: June, 2023
   Final Report: June, 2028

2. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

   Proposed PMR Milestone Dates:
   Interim Safety Report: June, 2023
   Final Report: June, 2028

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/s/

RUTHANN M GIUSTI
12/15/2017

SUZANNE G DEMKO
12/15/2017
I have read the clinical review referenced in the memo attached and agree with its content and the conclusion for approval of this NDA.

MEMORANDUM

Date: December 14, 2017
From: M. Anwar Goheer, PhD
Pharmacology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
Through: Whitney S. Helms, Ph.D.
Supervisory Toxicologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA #208700
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (LUTATHERA)
Re: Approvability of Pharmacology and Toxicology

Advanced Accelerator Applications USA submitted NDA 208700 for 177Lu-DOTA-Tyr-Octreotate (Lutathera) for the treatment of patients with (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut and hindgut (neuroendocrine tumors (b) (4)). Lutathera is a radiolabeled somatostatin analogue. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

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/s/

M A GOHEER
12/14/2017

WHITNEY S HELMS
12/14/2017
I concur with Dr. Goheer's conclusion that there are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

Office of Clinical Pharmacology Memo

NDA	208700
Link to EDR	Application 208700 - Sequence 0036 - 0036 (36) 07/26/2017 ORIG-1 /Resubmission/Class 2
Submission Date	July 24, 2017
Submission Type	Complete Response Resubmission
Brand Name	LUTATHERA
Generic Name	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
Dosage Form and Strength	7.4 GBq every 8 weeks for a total of four doses
Route of Administration	Intravenous
Proposed Indication	Treatment of adult patients with (b) (4) somatostatin receptor positive, neuroendocrine (b) (4) tumors of the midgut (b) (4)
Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Associated INDs	IND (b) (4)
OCP Review Team	Brian D. Furmanski., Hong Zhao, Ph.D.,
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for details. The proposed ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate dosing regimen is supported by the pharmacokinetics (PK) and biodistribution studies, and the efficacy and safety data from the registration trial (NETTER-1). From a Clinical Pharmacology standpoint, the NDA is approvable provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

BRIAN D FURMANSKI
12/08/2017

HONG ZHAO
12/08/2017
I concur.

NAM ATIQUR RAHMAN
12/08/2017

Office of Clinical Pharmacology Review

Application Number	NDA208700 (SDN 34)
Letter Date of Submission	1/9/2017
Product Name (Trade and generic, code)	177Lu-DOTA0-Tyr3-Octreotate (Lutathera)
Route of Administration	IV infusion
Proposed Indication	Gastroenteropancreatic neuroendocrine tumors
Submission Type	Type A
Related Applications	IND 077219
Sponsor	Advanced Accelerator Applications (AAA)

Introduction

This meeting package includes information to address items for which Advanced Accelerator Applications (AAA) seeks additional clarity or for items not mentioned in either the Discipline Review Letter (DRL) or to the Complete Response Letter (CRL). Among the 11 questions raised by the sponsor, questions 10 and 11 are partially clinical pharmacology pertinent. A complete list of questions can be found in appendix 1.

Question 11) AAA proposes to provide an SDTM dataset for the NETTER-1 dosimetry sub-study which includes both the raw pixel count data, as well as the %IA time-course data; and a SDTM dataset for the Erasmus MC dosimetry sub-study which includes only %IA time-course data.

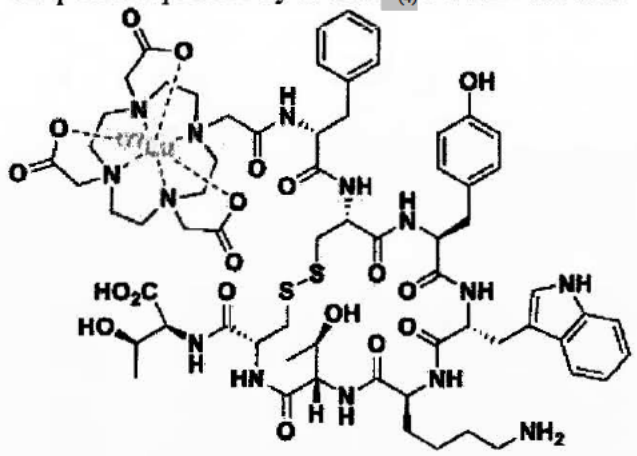
Is this approach acceptable to the Agency?

Regulatory History

On April 28, 2016 AAA submitted an NDA for the use of ^{177}Lu-DOTA0-Tyr3-Octreotate in the treatment of patients with gastroenteropancreatic neuroendocrine tumors. On December 19, 2016 FDA issued a complete response for this application due to issues in the datasets used to generate the Clinical Study Report and tables, listings, and figures submitted to FDA for review.

Background

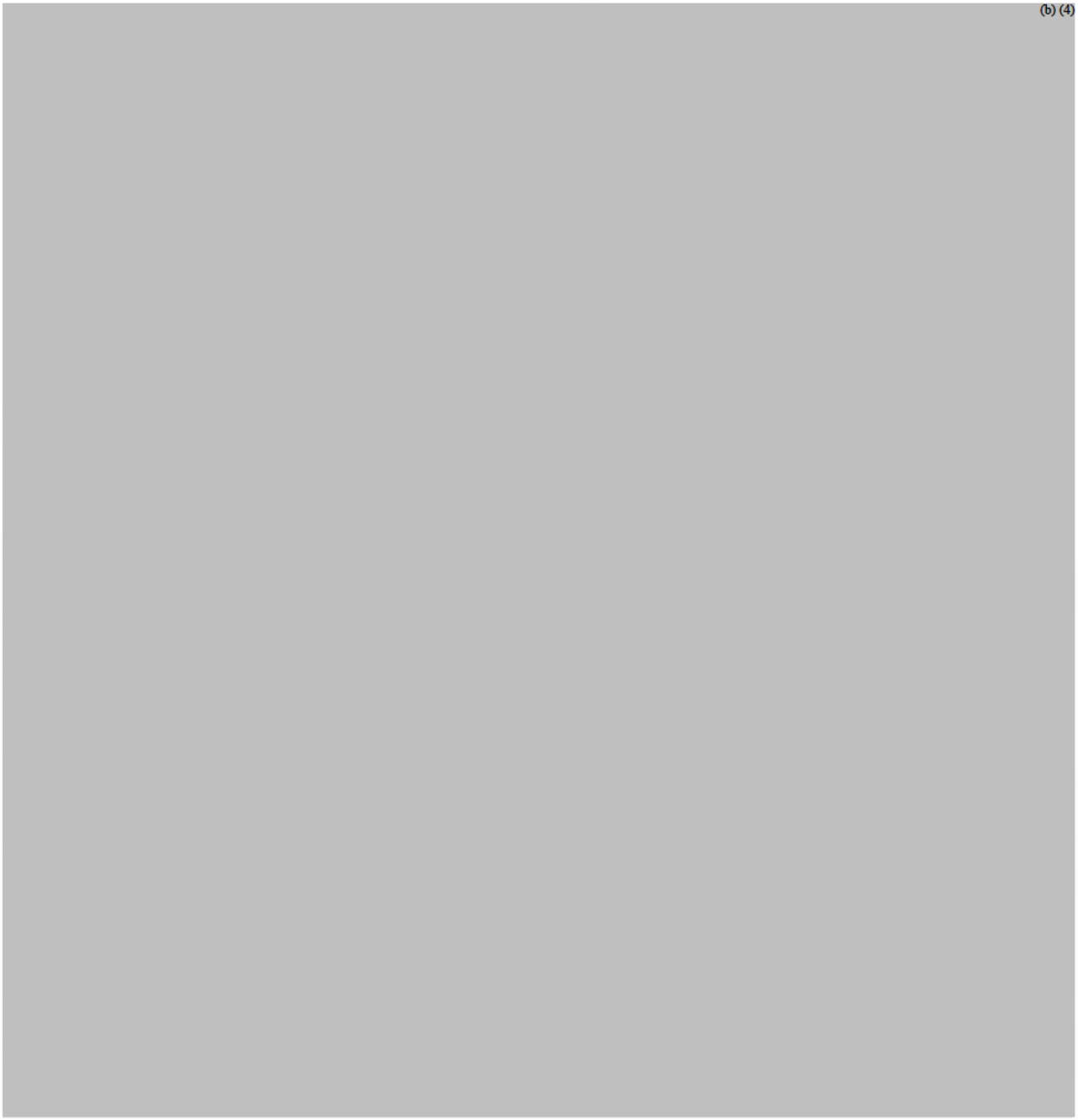
177Lu-DOTA0-Tyr3-Octreotate is a radiolabeled somatostatin analog (SSA) that binds to the somatostatin subtype 2 receptors (sstr2) and subsequently internalizes where it emits medium energy beta radiation to the tumor. 177Lu-DOTA0-Tyr3-Octreotate is comprised of the somatostatin peptide analogue Octreotate (Tyr->Phe substitution), coupled to the metal-ion chelating moiety DOTA and Lutetium-177 (^{177}Lu). 177Lu-DOTA0-Tyr3-Octreotate is provided as a single-use sterile vialed, ready-to-use 370 MBq/mL solution for infusion (at date and time of calibration) planned within a maximum 72 hours (shelf life) after the date and time of manufacturing. 177Lu-DOTA0-Tyr3-Octreotate is intended to be administered at a cumulative dose of 29.6 GBq, divided into 4 administrations via IV infusion over (b) (4) 30 minutes of 7.4 GBq each separated by at least (b) (4) 8 week intervals.



Total MW: 1609.6
^{177}Lu MW: 283.358

Rationale provided by AAA to support question 10

(b) (4)



Rationale provided by AAA to support question 11
AAA proposes to provide an SDTM dataset for the NETTER-1 dosimetry sub-study which includes both the raw pixel count data, as well as the %IA time-course data; and a SDTM dataset for the Erasmus MC dosimetry sub-study which includes only %IA time-course data. Per AAA, dosimetry assessments are based on radioactivity concentration data derived from regions of interests in scintigraphic images. In this case, the rawest measurement would be expressed as counts per pixel (or counts per region of interest), before normalization to percent injected activity (%IA). In the Erasmus MC Phase I/II study, most of the raw data derived from scintigraphs was recorded by the investigators only as %IA, so pixel count data is not available.

Sponsor proposed clinical pharmacology pertinent questions

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Question 11) Typically, dosimetry assessments are based on radioactivity concentration data derived from regions of interests in scintigraphic images. In this case, the rawest measurement would be expressed as counts per pixel (or counts per region of interest), before normalization to percent injected activity (%IA). In the Erasmus MC Phase I/II study, most of the raw data derived from scintigraphs was recorded by the investigators only as %IA, so pixel count data is not available.

Therefore, for the next submission the Sponsor proposes to provide an SDTM dataset for the NETTER-1 dosimetry sub-study which includes both the raw pixel count data, as well as the %IA time-course data; and a SDTM dataset for the Erasmus MC dosimetry sub- study which includes only %IA time-course data. *Is this approach acceptable to the Agency?*

FDA Response: Yes; however, provide both the raw pixel count data, as well as the %IA time-course data for patients in which this data exists from the Erasmus MC dosimetry sub-study.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Action: No action necessary as the above comments were conveyed to the sponsor through the meeting minutes.

Signatures:

Brian D. Furmanski., Ph.D.
Reviewer

Hong Zhao., Ph.D.
Team Leader

Division of Clinical Pharmacology V Division of Clinical Pharmacology V

Cc: OHOP: RPM –S Truitt; MTL – S Deminko; MO – J Sul
DCP-V: Deputy DD - **B Booth**; DD - **A Rahman**

Appendix 1) Complete list of sponsor proposed questions

Question 1) Is Interim Lock Procedure procedure acceptable to the Agency?

Question 2) Does the Agency agree with the above proposal for correcting scans used in the progression free survival (PFS) analysis?

Question 3) Does the Agency accept the submission of the DSUR in February 2017 to respond to the request of a safety update?

Question 4) All DSURs are included into the drafting of the main LUTATHERA DSUR which will be provided to the Agency. Does the agency wish to receive the DSURs from other sponsors as well?

Question 5) Is the presentation of the information regarding the European Compassionate Use Program, (b) (4) acceptable for the Agency?

Question 6) AAA will provide narratives for patients who experienced a serious adverse event regardless of its causality, an adverse event which led to treatment discontinuation, or death due to any cause during treatment phase, as well as patients who experienced adverse events of special interest. The narratives will be provided for the aforementioned patients who were randomized to the experimental arm.

a) Does the agency require narratives to be written for patients who developed other non-hematological malignancies?

b) Does the agency require narratives to be written for patients experiencing events described above but randomized to the control arm?

c) Are there any other group of patients the Agency will require narratives to be written?

Question 7) Would the Agency agree on the principle that a test submission of a draft electronic data package be conducted prior to the official resubmission of the complete final data package, in order to check the full technical compliance and reviewability status of the new structure and content the Sponsor offers?

Question 8) With the postponement of the PDUFA date for LUTATHERA and the NDA resubmission as planned, AAA is proposing to continue and expand the current access programs in Europe and in the United States. To date, 42 patients have received at least one dose of LUTATHERA as part of the EAP in the United States. While still considered an intermediate sized EAP, would the Agency support additional clinical sites and possibly smaller hospitals, if the nuclear medicine department is appropriately qualified?

Question 9) The compassionate use programs in Europe include pulmonary NETs. In the US, there are many centers with patients with NETs who do not meet the inclusion criteria for the EAP, would the Agency support amending the inclusion criteria of the protocol to include all NETs?

Question 11) AAA proposes to provide an SDTM dataset for the NETTER-1 dosimetry sub-study which includes both the raw pixel count data, as well as the %IA time-course data; and a SDTM dataset for the Erasmus MC dosimetry sub-study which includes only %IA time-course data.

Is this approach acceptable to the Agency?

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

/s/

BRIAN D FURMANSKI
03/28/2017

HONG ZHAO
03/28/2017
I concur.

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application/New Molecular Entity
Application Number(s)	208700
Priority or Standard	Priority review
Submit Date(s)	March 31, 2016; April 18, 2016; April 28, 2016; October 18, 2016; October 19, 2016
Received Date(s)	March 31, 2016; April 18, 2016; April 28, 2016; October 18, 2016; October 19, 2016
PDUFA Goal Date	December 28, 2016
Division/Office	Division of Oncology Products 2/OHOP
Review Completion Date	
Established Name	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
(Proposed) Trade Name	LUTATHERA
Pharmacologic Class	Peptide receptor radionuclide therapy
Code name	
Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Formulation(s)	Intravenous
Dosing Regimen	7.4 GBq every 8 weeks for four doses
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

DPMH=Division of Pediatric and Maternal Health
DMI=Division of Medical Imaging

Glossary

AC	advisory committee
ADaM	analysis data model
ADME	absorption, distribution, metabolism, excretion
ADRG	analysis Data Reviewer's Guide
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	clinical data interchange standards consortium
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OBF	O'Brien-Fleming
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SDRG	study data reviewer's guide
SDTM	study data tabulation model
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Advanced Accelerator Applications, S.A. (AAA) submitted a New Drug Application (NDA) under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lutathera (^{177}Lu-DOTA0-Tyr3-Octreotate) solution for intravenous infusion, a new molecular entity and ready-to-use radiolabeled somatostatin analogue (SSA). The drug formulation has a concentration of 370 MBq/mL, and is intended to be administered at a cumulative dose of 29.6 GBq divided into four separate administrations (b) (4) eight (b) (4) weeks apart. The proposed indication is treatment of adult patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including those of the foregut, midgut, and hindgut.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Complete, accurate, reviewable, transparent, traceable, and robust data are the foundations of any successful NDA. The amount of confidence reviewers have in these data attributes is the amount of confidence reviewers are able to have in the strength of the application. The information provided in NDA 208700 is of insufficient quality and integrity to be able to confirm the effectiveness of Lutathera for the proposed treatment population. A complete review of the data submitted in support of this NDA demonstrates that the data are materially incomplete, inaccurate, untraceable, and inconsistent. As a result, approval is not recommended for this application; rather, a complete response letter (CR) will be issued to the Applicant to include a list of the deficiencies in the application as identified by multiple review disciplines. The decision to take this action was reached after considerable efforts were made to resolve the issues with the applicant. A timeline of the post-filing interactions FDA has had with AAA with regard to the issues in the application are discussed below in section 7.1.2 of this review.

The Nonclinical, Office of Scientific Investigations, CMC, and Clinical Microbiology review teams were able to complete their reviews without identifying unresolvable issues with the application. The remaining review disciplines identified significant issues with the application to the extent that many relevant parts of the application were unreviewable as submitted originally and even as revised and re-submitted. For a summary of the product manufacturing issues contained in the application, please refer to the FDA OPQ Integrated Quality Assessment under separate cover. A discussion of the review issues encountered by the Clinical Pharmacology review team is found in section 6 of this review. The specific Clinical and Statistical review deficiencies observed in the application are delineated in section 7.1.2 of this review.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

A statistically significant increase in PFS, if supported by verifiable data that are of unquestionable quality and integrity, would represent a clinically meaningful advance for a neuroendocrine tumor subpopulation of patients who have an unmet medical need. Given the issues with the data submitted to support this application, there are no available data to confirm the findings of safety and effectiveness set forth by the applicant in any of their submissions to this application. A benefit-risk assessment of this application cannot be made. The specific data below were reported by the applicant in their initial NDA submission, and are provided as summary data here for illustrative purposes. None of the benefit and risk data provided in the table below could be confirmed by FDA reviewers and it is expected that once the applicant addresses and corrects all of the issues identified in the application, these data will change.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neuroendocrine tumors (NETs) are a heterogenous group of tumors sharing a common origin, neuroendocrine cells of the embryological gut. • NETs are rare epithelial malignancies that are clinically diverse, and include both functional and non-functional tumors; they originate most commonly from the gastrointestinal tract and pancreas [gastroenteropancreatic neuroendocrine tumors (GEP-NETs)]. • GEP-NETs are grouped by location and include tumors of the lung, thymus, stomach, duodenum and pancreas, considered foregut tumors, tumors of the ileum, cecum and proximal colon, considered midgut tumors, and tumors of the distal colon and rectum, considered hindgut tumors. They are also grouped by whether the tumor is functional, i.e. they secrete peptide hormones that result in clinical symptoms, or not. • Treatment of functional GEP-NETs requires management of clinical symptoms in addition to anti-cancer therapy.	**Patients with inoperable, progressive, SSTR positive midgut carcinoid tumors represent a subgroup of patients with an unmet medical need. These patients would not only benefit from alternative therapies to treat their tumors; but the efforts to control the multiple hormone-related co-morbid conditions associated with these tumor types is lacking.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The majority of well-differentiated GEP-NETs express somatostatin receptors (SSTRs) and can be imaged using a radiolabeled form of the somatostatin analog octreotide (e.g. 111-In pentetreotide). • Initial treatment of GEP-NET consists of wide surgical resection for limited or locally advanced disease, if feasible, and treatment of hormone-related symptoms with somatostatin analogs (SSAs), if present. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option. • The prognosis for patients with metastatic well-differentiated GEP-NETs is highly variable. Based on retrospective analyses of large databases, the median OS for patients with metastatic pancreatic NETs has been reported to range from 2-5.8 years, while the median OS for small bowel NET has been reported as 7.9 years.	
Current Treatment Options	• Systemic therapy options for well-differentiated, metastatic GEP-NETs include SSAs (e.g., octreotide, lanreotide), targeted therapies and chemotherapy. • SSAs are primarily used to manage the hormonal symptoms related to NETs, anti-proliferative activity has also been demonstrated by prolonged PFS in patients with NETs treated with octreotide and lanreotide. • Chemotherapeutic agents are streptozotocin in combination with 5-fluorouracil or doxorubicin. Temozolomide, capecitabine and oxaliplatin alone or in combination therapy have also demonstrated anti-tumor activity. • Sunitinib is approved in the US for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. Everliolimus is approved in the US for the treatment of progressive	A statistically significant increase in PFS, if supported by verifiable data that are of unquestionable quality and integrity, would represent a clinically meaningful advance for a tumor subpopulation with an unmet medical need. Given the issues with the data submitted to support this application, there are no available data to confirm the findings set forth by the applicant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pNET and progressive, well-differentiated, non-functional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. • Peptide receptor radioligand therapy (PRRT) is a targeted approach using radiolabeled SSAs in patients with tumors that are determined to be SSTR-positive. The most commonly used radionuclides include yttrium-90 (90Y) and lutetium-177 (177Lu).	
Benefit	• Trial NETTER-1 was a randomized (1:1), open-label, multi-national, and parallel-group Phase III trial comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate plus best supportive care to treatment with high dose Octreotide LAR in patients with inoperable, SSTR positive, histologically proven midgut carcinoid tumors, who exhibited progressive disease while on Octreotide LAR. • Based on the clinical study report submitted by the applicant, the trial met its primary endpoint demonstrating an improvement in independent review committee confirmed PFS compared to the control arm based on 74 PFS events in the intent-to-treat (ITT) population. The un-stratified log-rank test P value was reported to be less than 0.0001. The median PFS was not reached for the experimental arm and was 8.4 months (95% CI: 5.8, 9.1) for the control arm. The corresponding un-stratified hazard ration (HR) was reported as 0.21 (95% CI: 0.13, 0.33) in the experimental arm compared to the control arm. The estimated HRs for sensitivity analyses using different censoring methods range from 0.12 to 0.57. • NETTER-1 demonstrated ORRs of 18% (95% CI: 10.4%, 25.3%) and 3% (95% CI: 0%, 6.3%) in the experimental arm and control arm respectively. The Fisher exact test p value was 0.0008. Note that CSR reported ORR results were on a subpopulation of ITT which	Because of the issues associated with the data submitted with this application, the benefit reported by the applicant cannot be verified. No benefit is confirmed for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	included patients with non-missing central response. • The experimental arm for the NETTER-1 trial did not demonstrate an improvement in OS compared with the control arm based on 40 OS events from the ITT population. These OS events were immature at the clinical data cut-off. The un-stratified log-rank test P value of 0.0043 was greater than pre-planned two sided significance level of 0.0085% at the planned OS interim analysis. The median OS was not reached for both arms. The corresponding un-stratified HR was 0.40 (95% CI: 0.21, 0.77) in the experimental arm compared to the control arm.	
Risk	• As reported by the applicant in the clinical study report submitted with the original application, the greatest risks arising from treatment with Lutathera are radiation toxicities affecting either bone marrow or kidney function. Kidney function risks are reduced by the use of an amino acid solution co-infusion during administration of 177Lu-DOTA0-Tyr3-Octreotate, which decreases radiation doses to the kidney by approximately 45%. Bone marrow toxicity occurs both acutely and chronically. The most frequent AEs with 177Lu-DOTA0-Tyr3-Octreotate were nausea (65 patients, 59%), and vomiting (52 patients 47%), the majority related to the co-infusion of the commercial amino acids solution used for kidney protection. Other adverse events in the 177Lu-DOTA0-Tyr3-Octreotate arm included fatigue, diarrhea and abdominal pain; the large majority (≥97%) were grade 1 or 2 in severity. Among patients who received Octreotide LAR, the most common AEs were gastrointestinal disorders and fatigue. Grade 3/4 AEs occurred at a similar frequency between the two arms; however, grade 3/4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%,	Because of the issues associated with the data submitted with this application, the safety profile reported by the applicant cannot be verified. The risks associated with ^{177}Lu-DOTA0-Tyr3-Octreotate in the patient population studied cannot be confirmed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2% and 9% of patients in 177Lu-DOTA0-Tyr3-Octreotate arm versus none in controls.	
Risk Management	• 177Lu-DOTA0-Tyr3-Octreotate is intended to be administered by physicians who have expertise in the administration of radiolabeled drugs and in concert with physicians having expertise in radio-imaging. • Because of the mechanism of clearance for this drug, there is radioactivity retention in the kidneys. Concomitant administration of amino acids reduces renal uptake of radioactivity (by about half) without altering tumor uptake. Amino acids co-infusion is mandatory during treatment. Before each administration and during the treatment biological tests are required to re-assess the kidney and bone marrow function. • To avoid treatment-related nausea and vomiting, an intravenous bolus of an antiemetic drug is recommended 30 minutes before the start of the treatment. • It could be necessary to suspend treatment, adapt the dose after the first administration or even definitively discontinue the treatment. The criteria for these scenarios will be described in product labeling. • Patients with certain risk factors could be prone to develop adverse events, and in certain instances, e.g. previous external beam radiotherapy involving more than 25% of the bone marrow, treatment is not recommended. The criteria for these scenarios will be described in product labeling. • Crises due to excessive release of hormones or bioactive substances may occur following treatment. • Because this drug contains a radionuclide, patients will be informed of	The adequacy of the risk management plan for ^{177}Lu-DOTA0-Tyr3-Octreotate cannot be confirmed. A Risk Evaluation and Mitigation Strategy (REMS), however, is not needed to ensure the benefits of this drug outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	all specific measures they should adopt to minimize radiation exposure to others.	

X_____

Suzanne Demko, Cross-Discipline Team Leader

2 Therapeutic Context

Analysis of Condition

Neuroendocrine tumors (NETs) are a relatively rare, clinically diverse group of epithelial malignancies that originate most commonly from the gastrointestinal tract and pancreas [gastroenteropancreatic neuroendocrine tumors (GEP-NETs)]. In the U.S., an analysis of the Surveillance, Epidemiology, and End Results (SEER) data indicates a rise in the age-adjusted incidence of NETs from 1.9 to 5.25 cases per 100,000 people between 1973 and 2004[1]. These tumors can arise in the setting of inherited genetic syndromes such as multiple endocrine neoplasia (MEN) 1 and 2; however, most occur sporadically and are generally classified by site of origin, stage, ability to cause clinical symptoms and tumor differentiation.

These tumors are principally divided into those that are well-differentiated and poorly-differentiated, with the distinction made based on the degree of cell differentiation, tumor architecture, and tumor grade. The World Health Organization (WHO) classifies GEP-NETs into low-grade (G1), intermediate grade (G2), and high grade (G3) categories, based upon mitotic count, assessment for necrosis, and proliferative index or Ki-67[2]. The European Neuroendocrine Tumour Society (ENETS) stratifies tumors by grade and stage,[3,4] and both organizations combine grading with staging using the tumor-node-metastasis (TNM) system. GEP-NETs are also described by the tissue of origin with tumors of the lung, thymus, stomach, duodenum and pancreas considered foregut tumors; tumors of the ileum, cecum and proximal colon are midgut tumors, and tumors of the distal colon and rectum are hindgut tumors.

GEP-NETs may be further characterized as functional or non-functional, depending on whether or not they secrete peptide hormones that result in clinical symptoms. Functional GEP-NETs are generally well-differentiated, and these tumors are codified to reflect the hypersecreted hormone (e.g. insulinoma, gastrinoma). The most commonly produced hormone is serotonin, which results in “carcinoid syndrome” that is characterized by flushing and diarrhea. The clinical symptoms associated with functional tumors frequently lead to their diagnosis at an earlier stage compared with non-functional tumors that often present with symptoms related to mass effect or metastatic disease. The majority of well-differentiated GEP-NETs express somatostatin receptors (SSTRs) and can be imaged using a radiolabeled form of the somatostatin analog octreotide (e.g. 111-In pentetreotide). Treatment of functional GEP-NETs requires management of clinical symptoms in addition to anti-cancer therapy.

The natural history of GEP-NET varies considerably and appears to be affected by the primary site of disease, degree of differentiation, expression of SSTRs and presence of metastases at diagnosis. Tumors of the gastrointestinal tract and pancreas have similar histologic appearances, but pancreatic NETs (pNET) tend to have a more aggressive course, albeit with higher responses to systemic therapy. The approach to initial treatment of GEP-NET consists of wide surgical resection for limited or locally advanced disease, if feasible, and treatment of

hormone-related symptoms. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option, while somatostatin analogs (SSAs) such as octreotide are used for patients with hormone-related symptoms. Although SSAs were primarily used to manage the hormonal symptoms related to NETs, in vitro studies demonstrated the potential for SSAs to exert anti-proliferative activity and clinical studies have demonstrated prolonged PFS in patients with NETs treated with octreotide and lanreotide.

The prognosis for patients with metastatic well-differentiated GEP-NETs is highly variable. Based on retrospective analyses of large databases, the median OS for patients with metastatic pancreatic NETs has been reported to range from 2-5.8 years[1,5] while the median OS for small bowel NET has been reported as 7.9 years[6].

2.2. Analysis of Current Treatment Options

Systemic therapy options for well-differentiated, metastatic GEP-NETs include SSAs (e.g., octreotide, lanreotide), targeted therapies and chemotherapy.

Somatostatin Analogs (SSAs):
Although SSAs are primarily used to manage the hormonal symptoms related to NETs, in vitro studies demonstrated the potential for SSAs to exert anti-proliferative activity and clinical studies have demonstrated prolonged PFS in patients with NETs treated with octreotide and lanreotide. SSAs exert their effects through binding to SSTRs and the presence of these receptors, determined using radionuclide scintigraphy, is generally predictive of response to these agents. Octreotide may be administered as a short acting formulation or longer active depot formulation. Octreotide is approved for the symptomatic treatment of patients with GEP-NETs. Lanreotide is another long-acting depot formulation that is approved in the U.S. for the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic GEP-NETs, to improve progression-free survival.

Chemotherapy:
Traditional chemotherapeutic agents are streptozotocin in combination with 5-fluorouracil or doxorubicin. Temozolomide, capecitabine and oxaliplatin alone or in combination therapy have demonstrated anti-tumor activity as well. Streptozocin is approved in the U.S. for the treatment of metastatic pancreatic islet cell cancer, and has been the backbone of combination treatment regimens with 5-fluorouracil and doxorubicin; however, toxicity related to renal dysfunction has limited its use.

Targeted Therapy:
Sunitinib is approved in the U.S. for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease. Everliolimus is approved in the U.S. for the treatment of progressive pNET and progressive, well-differentiated, non-functional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic.

Sorafenib and pazopanib are tyrosine kinase inhibitors [redacted] (b) (4)

Peptide Receptor Radioligand Therapy

Peptide receptor radioligand therapy (PRRT) is a targeted approach using radiolabeled SSAs in patients with tumors that are determined to be SSTR-positive. The most commonly used radionuclides include yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu). Toxicities associated with PRRT include renal dysfunction, pancytopenia, and myelodysplastic syndrome.

Table 1: Summary of FDA approved treatments for GEP-NETS

Product Name	Relevant Indication	Efficacy Information
Streptozocin (Zanosar)	Metastatic pancreatic islet cell cancer	Streptozocin + doxorubicin resulted in RR 69%, Median OS 2.2 years Used alone or with other antineoplastic agents
Octreotide acetate (Sandostatin)	Symptomatic treatment of metastatic carcinoid tumors	Similar control of symptoms and reduction of urinary 5-HIAA levels among 67 patients treated with sandostatin LAR and 26 patients with sandostatin injection.
Everolimus (Afinitor)	Progressive pNET and well-differentiated, non-functional NET of GI or lung origin that is unresectable, locally advanced or metastatic.	Results of a randomized, double-blind trial demonstrating a statistically significant improvement in PFS [median 11.0 vs 4.6 months, HR 0.35 (95% CI: 0.27, 0.45); p 0.001].
Sunitinib (Sutent)	Unresectable or metastatic, well differentiated pNETS with disease progression	Results of a randomized, double-blind, placebo-controlled study demonstrating a statistically significant improvement in PFS [median 10.2 vs 5.4 months, HR 0.43 (95% CI: 0.27, 0.67); p 0.001]
Lanreotide acetate (Somatuline Depot)	Metastatic, well differentiated, non-functional GEP-NETs	Results of a randomized, double-blind, placebo-controlled study demonstrating a statistically significant improvement in PFS [median >22.1 vs 16.6 months, HR 0.47 (95% CI: 0.30, 0.73); p 0.001]

RR: response rate, OS: overall survival, pNET: pancreatic neuroendocrine tumor, HR: hazard ratio, CI: confidence interval

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a New Molecular Entity (NME) and is not a marketed drug in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

June 14, 2007: A pre-IND meeting was held with BioSynthema Inc. and FDA under IND 77219, to discuss the development program for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for patients with somatostatin receptor positive NETs.

- January 2009: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was designated as an orphan drug for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

- March 8, 2011: A pre-IND parallel scientific advice meeting was held with FDA and EMA to discuss the acceptability of a proposed trial comparing the ORR observed in patients with inoperable midgut carcinoid tumors who experienced progressive disease while being treated with octreotide LAR randomized to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with those randomized to Sandostatin LAR Depot. FDA stated that while the subpopulation of midgut carcinoid tumors was an acceptable population for study, given the biological and clinical heterogeneity of GEP-NETs, it would be unlikely that an indication for the treatment of (b) (4) somatostatin receptor positive GEP-NETs would be granted based upon data derived from the proposed trial.

- April 23, 2012: The IND-enabling study (NETTER-1) was submitted to IND 77219.

- September 3, 2014: FDA acknowledged change in the sponsorship of IND 77219 from Biosynthema to AAA.

- October 22, 2014: AAA informed FDA of the DSMB recommendation to stop enrolment and cross over all patients to the Lutathera arm due to observed PFS benefit. AAA followed FDA and EMA advice to continue the trial per protocol.

- April 2015: Fast Track Designation was granted for the investigation of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the treatment of patients with inoperable, progressive, well-differentiated, octreoscan positive, carcinoid tumors of the mid-gut.

- August 27, 2015: AAA provided the top-line results of the PFS analysis from NETTER-1, which demonstrated an improvement in PFS; median PFS was 8.4 months in the control (Sandostatin LAR Depot 60 mg) arm and had not been reached in the ^{177}Lu-DOTA^{0}-. Tyr^{3}-

Octreotate arm [HR 0.21 (95% CI 0.13, 0.34); p<0.001]. The following key issues were discussed at this meeting:

- A potential broader indication for patients with GEP-NET would require demonstration of a clinically meaningful anti-tumor effect (i.e. ORR by RECIST) as determined by independent review that is of sufficient magnitude and duration to be likely to predict clinical benefit and demonstrate an advance over available therapy in an adequate number of patients with progressive and inoperable bronchial NET or pancreatic NET treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at the dose and schedule employed in the NETTER-1 study, in one or more adequate and well-controlled trials.
- The adequacy of the data from the EMC study to support the broader indication cannot be determined until the data is reviewed at the time of the NDA submission.
- Possible approaches to developing an expanded access program were discussed.

- November 24, 2015: A pre-NDA meeting was scheduled. The pre-meeting package did not include completed analysis of safety data from NETTER-1; therefore, it was determined there was insufficient information to reach agreement on the content of an NDA under the PDUFA V program. The following key issues were discussed at the meeting:

  - FDA reiterated that a potential indication for patients with GEP-NET will require demonstration of a clinically meaningful anti-tumor effect as described above.
  - FDA requested additional information on the results of the EMC trial.
  - FDA did not object to AAA's proposal to open an expanded access trial at NETTER-1 study sites and to allow patients in the NETTER-1 study who progress during treatment with Sandostatin LAR 60 mg to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
  - FDA discouraged AAA from submitting the interim analysis of OS as the final analysis in the NDA and encouraged AAA to conduct additional analyses at later time points when a greater number of events have occurred. FDA emphasized that for the OS results to be included in the label, an effect on OS must meet the criteria for substantial evidence of efficacy.

- March 14, 2016: A pre-NDA meeting was held with FDA to discuss the submission of the NDA.

- April 28, 2016: The NDA rolling submission was completed.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 2 (DOP2) consulted the OSI to perform an audit of four clinical sites in the US for the NETTER-1 trial:

SITE	Principal Investigator
US08	Dr. Matthew Kulke
US12	Dr. James C. Yao
US13	Dr. Jonathan R. Strosberg
US14	Dr. Andrew E. Hendifar

In addition, two Contract Research Organizations (CROs) were selected for audit:

- (b) (4): responsible for national and international clinical project management, data management, medical review, medical coding, statistical analysis and report writing, under the direction of AAA
- (b) (4): independent Imaging Reading Center (IRC)

OSI inspections revealed the following:

- US08: No significant deficiencies; the final classification for this inspection is No Action Indicated (NAI).
- US12: No significant deficiencies; the final classification for this inspection is NAI.
- US13 and US14: European Medicines Agency (EMA) inspections, independent of FDA inspections, found discrepancies between source records and data listings submitted. However, these discrepancies did not appear to impact overall safety or efficacy outcomes.
- (b) (4) No significant deficiencies; the final classification for this inspection is NAI.
- (b) (4) No significant deficiencies; the final classification for this inspection is NAI.

The OSI report indicated that the data used in the CSR from Study AAA-III-01 in support of the NDA 208700 accurately reflects the clinical database at the data cutoff date.

4.2. Product Quality

Please see FDA CMC review.

4.3. Clinical Microbiology

Please see FDA product quality microbiology reviews

4.4. Devices and Companion Diagnostic Issues

There is no device or companion diagnostic test for review in support of this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radiolabelled somatostatin analog intended for use in the treatment of patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors. Limited nonclinical studies were conducted with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Instead, many nonclinical studies were conducted using ^{175}Lu-DOTA^{0}-TYR^{3}-Octreotate. As the only difference between the ^{177}Lu and ^{175}Lu is the radiolabel, the use of the cold construct is applicable for evaluating the non-radioactivity-mediated toxicity of the intended clinical product. In addition, the Applicant submitted pharmacology studies using ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to help support the activity of the drug in the intended patient population.

Somatostatin receptor 2 (SSTR2) is commonly over-expressed in neuroendocrine tumors. In vitro binding data showed that DOTA^{0}-Tyr^{3}-Octreotate has high affinity for somatostatin receptor 2 (SSTR2) compared to somatostatin receptors 1, 3, 4, and 5, blocking binding of somatostatin to SSTR2 with an IC_{50} of 0.98 nM. The Applicant also demonstrated cellular internalization of the construct following binding using an SSTR2-expressing pancreatic tumor cell line. In a series of in vivo studies examining the anti-tumor activity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in pancreatic tumor implanted male Lewis rats, the Applicant demonstrated that repeated treatment with the construct resulted in SSTR2-dependent tumor regression at radioactive doses ≥ 2.5 mCi (approximately 92 MBq), but that long-term survival of effectively treated animals was impacted by renal damage characterized by increased creatinine and urinary protein levels as well as histopathological lesions. Administration of lysine along with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate offered a limited degree of kidney protection in these studies. Longer dosing intervals also resulted in an improvement in renal damage scores.

Safety pharmacology and toxicology studies submitted to support the safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were reviewed in depth by Dr. Ronald Honchel under NDA 208547. In vivo animal studies demonstrated high uptake of the radiolabeled peptide in the pancreas (high SSTR2 expressing organ). This finding correlated with observations of pancreatic acinar apoptosis at doses ≥ 5 mg/kg of ^{175}Lu-DOTA^{0}-TYR3-Octreoate in repeat dose toxicology studies in rats. Pancreatic acinar cell atrophy also occurred in repeat dose toxicology studies in dogs at doses ≥ 500 mg/kg. There were no other significant test-article related findings in the general toxicology studies of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate given by intravenous injection in either species. High levels of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were also present in both the bone and kidney. Distribution to the kidney, the main excretory organ for the peptide, was consistent with findings of long term renal damage in tumor implantation experiments. Renal damage is a common acute and long term toxicity associated with administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate clinically as well. Hematological toxicity is also a major clinical toxicity.

In rats intravenous administration of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate at doses ≥ 1250 µg/kg had no effects on neurobehavioral endpoints (motor activity, behavior, co-ordination, somatic sensory/motor reflex responses and autonomic responses such as piloerection, pupil size, lachrymation, and salivation), or effects on overt cardiovascular and gastrointestinal function or body temperature in rats. Further support for the cardiovascular safety of the cold compound included its lack of effect on ECG parameters in the repeat dose toxicology study in dogs at single doses up to 3.2 mg/kg and an IC_{50} of > 100 µM in the in vitro hERG assay, though mild dose-independent effects (≤ 22% increases) on systolic, diastolic, and mean arterial blood pressure with concomitant decreases in heart rate did occur at doses as low as 40 µg/kg. At the highest dose of 20 mg/kg ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate acted as a respiratory stimulant (increased respiratory rate, peak inspiratory and peak expiratory flows, inspiration and expiration times and minute volume). The no-observed-effect level (NOEL) of ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate on respiratory parameters in conscious rats was 1250 µg/kg, when administered by the intravenous route.

The assessment of the potential for ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate to inhibit or induce human CYP450 enzymes showed that the compound does not act as an inhibitor or an inducer of the tested enzymes in the concentration range tested. ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not show any potential for P-gp specific interaction, either as a substrate or as an inhibitor. In general toxicology studies the exposure to the test items increased in a dose-proportional manner without any accumulation in terms of exposure and peak concentration.

The Applicant did not conduct carcinogenicity studies and these studies are not required to support the marketing application for a drug intended to treat advanced cancer. The cold product, ^{175}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate, was non-mutagenic in the Ames bacterial mutagenicity assay and negative in mouse lymphoma cells in vitro. As ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive product, it is considered to be genotoxic. Consistent with the ICH S9 Guidance, because ^{177}Lutetium-DOTA^{0}-Tyr^{3}-Octreotate is a genotoxic drug, no reproductive toxicology studies were conducted or required to support the registration of the drug. The risk of radiopharmaceuticals to a developing fetus is well-established in the scientific literature. The nonclinical team recommends a warning for the potential for embryo-fetal toxicity.

5.2. Referenced NDAs, BLAs, DMFs

NDA 208547 for ^{68}Gallium-DOTA^{0}-Tyr^{3}-Octreotate

5.3. Pharmacology

Primary pharmacology

To support the receptor binding specificity of DOTA-Tyr^{3}- Octreotate, the Applicant referenced Reubi et al., (Eur J Nucl Med 2000, 27:273-282). Membrane sections from CHO-K1 cells engineered to stably express somatostatin receptors (SSTRs) 1 or 5 and CCL39 cells engineered

to express SSTRs 2, 3, or 4 were mounted on slides. Affinity profiles for various somatostatin analogs were determined based on displacement of radiolabelled somatostatin 28. The DOTA-Tyr^{3}- Octreotate-based products bound to SSTR2 with high affinity and showed far more limited affinity for SSTR4 and SSTR5. There was no binding to SSTRs 1 or 3.

Table 2: IC_{50s} (nM) For Displacement of Somatostatin

Peptide	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
SS-28	8.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3
DOTA-Tyr^{3}-Octreotate	>10000	1.5±0.4	>10000	453±176	547±160
Y-DOTA-Tyr^{3}-Octreotate	>10000	1.6±0.4	>10000	523±239	187±50

Adapted from Reubi et al., 2000

The Applicant determined the IC_{50} for competitive binding of for several somatostatin analogs for somatostatin receptors (unspecified) using cell membranes from CA20948 pancreatic tumor cells (Study #20000801). The DOTA-TYR^{3}-Octreotate construct inhibited binding to the cell membranes at IC_{50}s below those determined for some other somatostatin analogs, including the approved somatostatin OctreoScan product.

Table 3: Binding Activity of Somatostatin Analog Constructs

Compound	MP #	IC50 (nM)	SE
TYR^{3}-octreotide	2249	0.48	0.03
OctreoScan (DPTA-octreotide)	1661	2.50	0.15
CMDTPA-TYR^{3}-octreotate	2148	2.16	0.21
DOTA-TYR^{3}-octreatate	2325	0.98	0.03

The Applicant investigated the internalization of labelled-DOTA^{0}-Tyr^{3}-Octreotate using somatostatin receptor (SST2R) expressing rat pancreatic ascinar tumor cells (AR42J) (Study 20000420). Cells were maintained in F-12K medium and incubated at 37°C in triplicate with approximately 0.5 nM (0.1 to 0.25 µCi) of radiolabeled peptide for 4 hours, after which cellular uptake was terminated by removing medium from the cells and washing wells with 2 ml of PBS. The combined wash and media was counted to determine free activity at 4 hours. Fresh media was added to the cells and incubation was continued. At 16 hours the wash cycle was repeated and the remaining cells were scrapped into PBS for determination of retained activity. Free and internalized radioactivity levels were determined using a Packard Cobra Gamma counter (Picker International, USA). Pancreatic acinar tumor cells showed similar uptake for both compounds.

Table 4: Summary of Internalization and Retention of Radiolabeled Compounds in AR42J Cells

Compound	Total CPM added to well	% Internalized at 4 hours	% of Activity in cells at 16 hours	% of 4 hours Activity Retained at 16 Hours	Recovery (%)
^{111}Ln-DTPA-Tyr3-Octreotate	316837	27.7	21.1	71.3	102
^{177}Lu-DOTA-Tyr^{3}-Octreotate	19939	30.7	27.2	77.9	104

Internalized activity = total counts in well at t_0 minus counts in wash 1 plus counts in incubation media; %Activity in cells at 16 h = total count in cells at 16 h divided by total counts in well at 16h.

To study the biodistribution and activity of ^{177}Lu-DOTA-Y^{3}-Octreotate, the Applicant treated CA20948 pancreatic tumor implanted Lewis rats with the compound (Study 2000701). Rats received single or multiple doses of ^{177}Lu-DOTA-Y^{3}-Octreotate administered at 30 day intervals by intravenous injection. In addition to tumors, organs with the highest exposure to ^{177}Lu-DOTA-Y^{3}-Octreotate included the pancreas, kidneys, and bone.

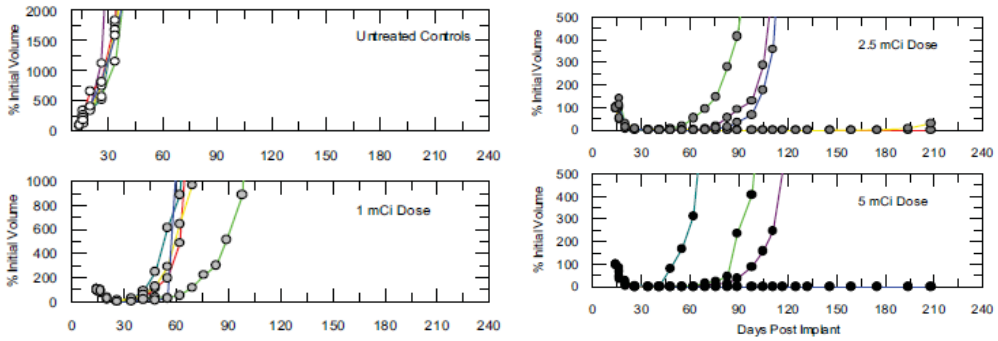
Table 5: Biodistribution of [177Lu]-DOTA-Y3-Octreotate in CA20948 Tumor Bearing Lewis Rats

	Time Post Injection (*hours*)					
Tissue Sample	***1***	***4***	***12***	***24***	***48***	***72***
Blood	0.777 ± 0.039	0.059 ± 0.001	0.030 ± 0.004	0.020 ± 0.004	0.012 ± 0.000	0.012 ± 0.000
Liver	0.500 ± 0.021	0.358 ± 0.015	0.348 ± 0.008	0.335 ± 0.008	0.304 ± 0.010	0.343 ± 0.024
Kidneys	2.606 ± 0.018	2.706 ± 0.077	3.609 ± 0.099	2.778 ± 0.123	2.672 ± 0.139	2.564 ± 0.088
Skeletal Muscle	1.651 ± 0.190	0.394 ± 0.077	0.311 ± 0.001	0.258 ± 0.037	0.218 ± 0.006	0.219 ± 0.005
Spleen	0.025 ± 0.002	0.016 ± 0.001	0.017 ± 0.002	0.017 ± 0.001	0.015 ± 0.001	0.015 ± 0.001
Heart	0.035 ± 0.001	0.011 ± 0.001	0.005 ± 0.000	0.005 ± 0.000	0.004 ± 0.000	0.004 ± 0.001
Pancreas	6.415 ± 0.403	7.964 ± 0.272	2.454 ± 0.144	2.666 ± 0.140	2.126 ± 0.123	2.207 ± 0.171
Stomach & Contents	2.573 ± 0.031	2.268 ± 0.117	3.432 ± 0.287	0.851 ± 0.237	0.922 ± 0.005	0.871 ± 0.030
Bone	6.547 ± 0.199	5.352 ± 0.099	4.417 ± 0.125	4.163 ± 0.194	3.510 ± 0.273	3.468 ± 0.260
Adrenals	0.623 ± 0.049	0.580 ± 0.010	0.457 ± 0.030	0.411 ± 0.013	0.330 ± 0.019	0.277 ± 0.012
Thyroid	0.007 ± 0.002	0.005 ± 0.000	0.004 ± 0.000	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.001
Tumor	11.883 ± 0.944	11.213 ± 1.645	13.776 ± 0.720	8.373 ± 1.137	7.740 ± 0.993	5.847 ± 1.250
Total Urine				66.608 ± 0.445	66.608 ± 0.445	70.167 ± 1.384
Total Feces				6.225 ± 0.758	10.189 ± 0.143	12.156 ± 0.731
Total Excreted				72.833 ± 1.007	76.797 ± 0.433	82.323 ± 1.544
Total Recovered				92.713 ± 0.606	94.653 ± 0.930	98.153 ± 0.671

(Applicant Table reproduced from Study Number 20000701)

Following a single dose of ^{177}Lu-DOTA-Y^{3}-Octreotate, there was a dose dependent decrease in tumor volume in CA20948 tumor bearing rats. At the high dose of 5 mCi (185 MBq), some animals remained tumor free 8 months after treatment (Figure 1).

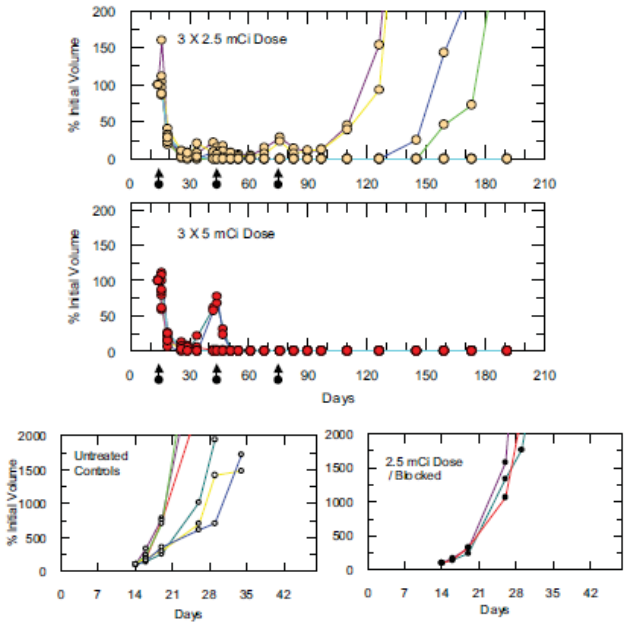
Figure 1: Radiotherapeutic effect of a single dose administration of [^{177}Lu]-DOTA-Y3-Octreotate to CA20948 tumor bearing Lewis rats (established tumors)



Tumor volumes at 24 hours post injection of radiolabeled material (1, 2.5 and 5 mCi per animal, n = 6 per group)
(Applicant Figure reproduced from Study Number 20000701)

Compared to single dose administration at the same dose level, an increased number of animals receiving 3 doses of ^{177}Lu-DOTA-Y^{3}-Octreotate had sustained tumor regression. Tumor growth in rats that received a 1 mg/kg blocking dose of cold peptide in addition to a single 2.5 mCi dose was, however, identical to the growth observed in untreated animals, showing that the radiotherapeutic effect was receptor mediated (Figure 2). Despite increases in tumor free survival compared to that seen at lower doses, treatment of animals with multiple doses of ^{177}Lu-DOTA-Y^{3}-Octreotate at the high dose of 5 mCi did result in long term toxicity, with most animals in this group developing renal disease and dying beginning 9 months post-treatment. Renal lesions (nodules and large neoplasms) were the only observed neoplasms (macroscopic inspection) in these animals, indicating that the kidney is the critical organ for toxicity. No attempt was made to reduce kidney uptake using protecting agents (free amino acids) in this study (Figure 3).

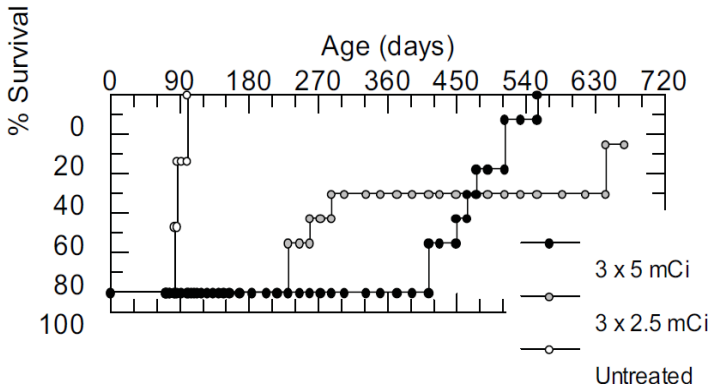
Figure 2: Effects of Multiple Dose Administration on Tumor Volume



(Applicant Figure reproduced from Study Number 20000701)

Radiotherapeutic effect of multiple dose administrations of [^{177}Lu]-DOTA-Y3-Octreotate to CA20948 tumor bearing Lewis rats. At 14 days post tumor implant, rats were injected with 2.5 or 5 mCi of radiolabeled peptide (n=8 per group) or received no treatment (controls, n=6). Additional doses were administered at 30 day intervals (3 doses total) to the 2.5 and 5 mCi treatment groups.

Figure 3: Survival of Rats Treated with [^{177}Lu]-DOTA-Y3-Octreotate (3 doses at 30-day interval)

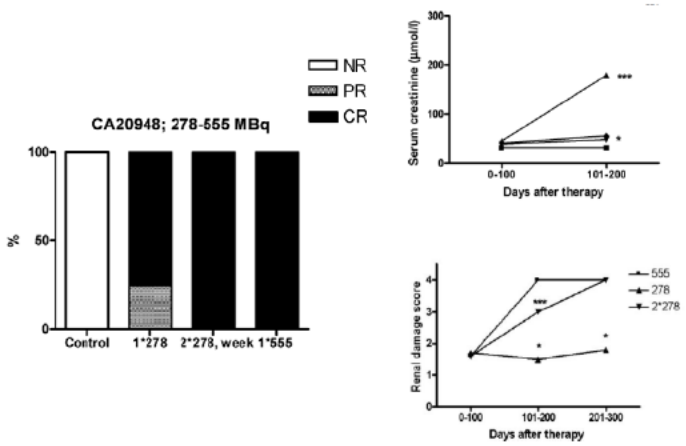


(Applicant Figure reproduced from Study Number 20000701)

Rollerman et al. (Eur J Nucl Med Mol Imaging 2007, 34:219-227) explored the effects of dose level, dose fractionation, and administration of the amino acid lysine on anti-tumor effects as well as the long-term renal and bone marrow effects of administration of ^{177}Lu-DOTA-Tyr^{3} Octreotate in rats. Male Lewis rats were implanted with CA20948 or AR42J pancreatic tumor cell lines. Octreotate treatment of CA20948-implanted animals with a single dose of 555 MBq

or with 1 or 2 once weekly doses of 278 MBq each resulted in prolonged anti-tumor activity. Twice weekly administration of 278 MBq resulted in a higher response rate than a single dose at this dose level. Renal damage was clear at the 555 MBq dose level based on increased creatinine levels compared to single or 2 weekly doses at 278 MBq as well as a renal damage score based on histopathological assessment of kidney tissue. Administration of 2 weekly doses of 278 MBq ^{177}Lu-DOTA-Tyr^{3} Octreotate did, however, result in histopathological findings of renal damage similar to those seen in animals treated with 555 MBq. This damage did progress more slowly at the 278 MBq dose compared to the 555 MBq dose without the same degree of rise in serum creatinine (Figure 4).

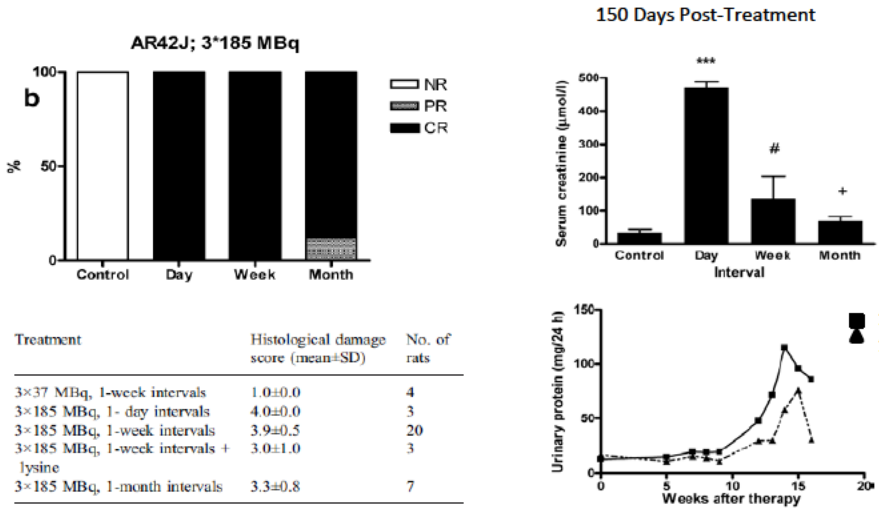
Figure 4: Anti-Tumor Activity and Renal Injury in CA20948-Implanted Rats



(Figure adapted from Rollerman et. al.)

To further investigate the effects of fractionation on long-term renal damage mediated by octreotate, the authors treated AR42J-implanted rats at an ^{177}Lu-DOTA-Tyr^{3} Octreotate dose level of 185 MBq given for a total of 3 doses on a daily, weekly, or monthly schedule. On the weekly schedule, the authors also examined the effects of amino acid administration on renal protection. Treatment on any of the three schedules resulted in similar anti-tumor activity, but increasing the dosing interval from daily to weekly or monthly did result in decreases in serum creatinine levels and urinary protein levels. The additional of amino acid treatment also decreased the levels of urinary protein and serum creatinine compared to radiation alone. Histopathologically, amino acid pretreatment effects were unclear.

Figure 5: Fractionation and Amino Acid Effects on Renal Damage



Treatment	Histological damage score (mean±SD)	No. of rats
3×37 MBq, 1-week intervals	1.0±0.0	4
3×185 MBq, 1- day intervals	4.0±0.0	3
3×185 MBq, 1-week intervals	3.9±0.5	20
3×185 MBq, 1-week intervals + lysine	3.0±1.0	3
3×185 MBq, 1-month intervals	3.3±0.8	7

(Figure adapted from Rollerman et. al.)

Safety Pharmacology

All safety pharmacology studies submitted were previously reviewed by Dr. Ronald Honchel under NDA 208547 for the use of ^{68}Ga-DOTATATE as a radioactive diagnostic agent for the management of gastro-entero-pancreatic neuroendocrine tumors (NETs).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Biodistribution of [Lu-177]-MP (DTPA-Tyr^{3}-Octreotate) in CA20948 tumor bearing Lewis rats. Study Report-19980721	^{177}Lu-DOTA-Tyr^{3}-Octreotate when injected intravenously to rats was mostly absorbed in pancreas, which is known to have high levels of somatostatin sub-type 2 receptors.
Distribution	
Effect of Blocking Dose on Biodistribution of [Lu-177]-MP2325 (DOTA-Tyr^{3}-Octreotate) in AR42J tumor bearing Lewis rats. Study Report 20000906	Uptake of Lu-177-MP2325 decreased in target tissues (tumor, pancreas, bone, stomach, small intestine, and adrenals) and increased in non-target tissues (kidneys) in the presence of blocking dose of Tyr^{3}-Octreotate.
Metabolism	
Comparative *in vitro* metabolism studies of	^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate was metabolized by Sprague-Dawley rat, Beagle dog and male human kidney homogenate but not metabolized

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>^{175}Lu-DOTA^{0}- Tyr^{3}-Octreotate with rat, dog and human kidney homogenate.
Study Report aaa05.

Assessment of the potential for ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate to inhibit human CYP450 enzymes in vitro (AAA/02)</td><td>by rat, dog or human hepatocytes.
Analysis of the 10 µM incubation samples detected the presence of five rat, eight dog, and seven human metabolites. No human specific metabolites were observed

^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate in pooled human liver microsomes can act as a mild direct inhibitor of CYP2C9 (32.9% at 10 µM). All IC_{50} values were greater than 10 µM.
^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not inhibit CYP1A2, 2B6, 2C8, 2C19, 2D6, 2E1 or 3A4 enzymes up to a concentration of at least 10 µM.</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Biodistribution of [Lu-177]-MP2325 (DOTA-Y3-Octreotate) in CA20948 tumor bearing Lewis rats.
Study Report 19990111</td><td>The urinary excretion was 65.0% at 24 hours. Fecal excretion was 8% at 24 hours (overall excretion rate of (Lu-177)-MP2138 was 73% at 24 hours). Overall recovery of the injected dose was 94% at 24 hours.</td></tr>
<tr><td>DDI</td><td></td></tr>
<tr><td>^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate: Assessment of the potential for P-gp mediated interactions using the Caco-2 cell line. (AAA/4)</td><td>^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate showed low to moderate passive permeability with no significant P gp involvement.
P-gp-mediated digoxin transport was only slightly reduced in the presence of ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate.
^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate did not show any P-gp specific interaction as a substrate or inhibitor.</td></tr>
<tr><td>TK data from general toxicology studies
42-day intravenous toxicity study in the rat by including recovery period and toxicokinetic
Study Number 20100180TRP.</td><td><u>Rat</u>
T1/2: Approximately 22 to 24 minutes
Accumulation: No accumulation in term of exposure and peak concentration
Dose proportionality: Increased in a dose proportional manner.
Toxicokinetic parameters Day 1 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>1250</td><td>5000</td><td>20000</td><td>1250</td><td>5000</td><td>20000</td></tr>
<tr><td>Cmax (ng/mL)</td><td>1581</td><td>7029</td><td>27238</td><td>1359</td><td>6931</td><td>28435</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>21.5</td><td>25.5</td><td>19.5</td><td>21.6</td><td>24.4</td><td>20.4</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>45110</td><td>175137</td><td>588732</td><td>40170</td><td>189919</td><td>670289</td></tr>
<tr><td>Cmax/Dose</td><td>1.26</td><td>1.41</td><td>1.36</td><td>1.09</td><td>1.39</td><td>1.42</td></tr>
<tr><td>AUC all/Dose</td><td>36.1</td><td>35.0</td><td>29.4</td><td>32.1</td><td>38.0</td><td>33.5</td></tr>
</table>
Toxicokinetic parameters Day 42 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>1250</td><td>5000</td><td>20000</td><td>1250</td><td>5000</td><td>20000</td></tr>
<tr><td>Cmax (ng/mL)</td><td>2149.2</td><td>6975.0</td><td>26257.9</td><td>1863.6</td><td>6299.2</td><td>26631.7</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>21.2</td><td>20.1</td><td>28.4</td><td>21.0</td><td>21.5</td><td>33.0</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>59576</td><td>184101</td><td>687521</td><td>47260</td><td>164712</td><td>719279</td></tr>
<tr><td>Cmax/Dose</td><td>1.72</td><td>1.40</td><td>1.31</td><td>1.49</td><td>1.26</td><td>1.33</td></tr>
<tr><td>AUC all/Dose</td><td>47.7</td><td>36.8</td><td>34.4</td><td>37.8</td><td>32.9</td><td>36.0</td></tr>
</table>
<u>Dog:</u></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>43-day intravenous toxicity study in the dog including recovery and toxicokinetic.
Study Number 20100182TCP</td><td>T1/2: Approximately 60 minutes
Accumulation: No accumulation
Dose proportionality: Yes
Toxicokinetic parameters Day 1 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>80</td><td>500</td><td>3200</td><td>80</td><td>500</td><td>3200</td></tr>
<tr><td>Cmax (ng/mL)</td><td>109±6</td><td>590±77</td><td>4245±169</td><td>100±7</td><td>681±66</td><td>4340±417</td></tr>
<tr><td>Tmax (min)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>T1/2 (min)</td><td>72±11</td><td>69±5</td><td>73±4</td><td>57±3</td><td>65±3</td><td>62±2</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>8027±549</td><td>32129±2094</td><td>253960±19697</td><td>6347±270</td><td>40981±3066</td><td>240018±14656</td></tr>
<tr><td>Cmax/Dose</td><td>1.4±0.1</td><td>1.2±0.2</td><td>1.3±0.1</td><td>1.3±0.1</td><td>1.4±0.1</td><td>1.4±0.1</td></tr>
<tr><td>AUC all/Dose</td><td>100±7</td><td>64±4</td><td>79±6</td><td>79±4</td><td>82±6</td><td>75±5</td></tr>
</table>
Toxicokinetic parameters Day 43 (Mean ± SD)
<table>
<tr><td>Sex</td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (µg/kg)</td><td>80</td><td>500</td><td>3200</td><td>80</td><td>500</td><td>3200</td></tr>
<tr><td>Cmax (ng/mL)</td><td>154±11</td><td>799±106</td><td>4309±313</td><td>142±8</td><td>649±96</td><td>4643±397</td></tr>
<tr><td>Tmax (min)</td><td>5±0</td><td>9±4</td><td>5±0</td><td>5±0</td><td>5±0</td><td>5±0</td></tr>
<tr><td>T1/2 (min)</td><td>38±6</td><td>57±5</td><td>59±3</td><td>49±2</td><td>54±4</td><td>64±5</td></tr>
<tr><td>AUC all (ng/ml*min)</td><td>6428±647</td><td>41714±4043</td><td>234594±7282</td><td>7817±607</td><td>35324±4243</td><td>228921±10396</td></tr>
<tr><td>Cmax/Dose</td><td>1.9±0.1</td><td>1.6±0.2</td><td>1.4±0.1</td><td>1.8±0.1</td><td>1.3±0.2</td><td>1.5±0.1</td></tr>
<tr><td>AUC all/Dose</td><td>80±8</td><td>84±8</td><td>73±2</td><td>98±7</td><td>71±8</td><td>72±3</td></tr>
</table></td></tr>
<tr><td>TK data from reproductive toxicology studies</td><td>Neither submitted nor required due to radioactive drug acting on rapidly dividing cells.</td></tr>
<tr><td>TK data from Carcinogenicity studies</td><td>None submitted</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

All general toxicology studies submitted were previously reviewed by Dr. Ronald Honchel under NDA 208547 for the use of ^{68}Ga-DOTATATE as a radioactive diagnostic agent for the management of gastro-entero-pancreatic neuroendocrine tumors (NETs).

5.5.2. Genetic Toxicology

Genetic toxicology studies for ^{175}Lutetium-DOTA ^{0}-Tyr^{3}-Octreotate were previously submitted and reviewed under NDA 208547 by Dr. Ronald Honchel. ^{175}Lutetium-DOTA ^{0}-Tyr^{3}-Octreotate was not mutagenic in these assays. As ^{177}Lu is a radioactive isotope the intended clinical product is genotoxic.

5.5.3. Carcinogenicity

None submitted or required

5.5.4. Reproductive and Developmental Toxicology

None submitted or required as ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radioactive product with an understood risk to development.

5.5.5. Other Toxicology Studies

None

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Primary Reviewer: M. Anwar Goheer Team Leader: Whitney Helms

Division Director: John Leighton

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant seeks approval of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the treatment of patients with [redacted] somatostatin receptor positive, neuroendocrine [redacted] tumors of the midgut [redacted]. The proposed dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is 7.4 GBq as a 30-min intravenous (IV) infusion once every 8 weeks for a total of 4 doses (29.6 GBq).

The application is materially incomplete in that the datasets provided in the NDA are inaccurate, incomplete, and inconsistent across databases. Thus, FDA cannot verify the information provided in the clinical study reports nor verify data proposed in the product labeling. FDA will issue a complete response letter to this NDA and list deficiencies for the Applicant to address. See the attachment for the clinical pharmacology specific deficiency list.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following is the Applicant-reported summary of clinical pharmacology data. The FDA is not able to review, verify or confirm these data due to the data deficiencies in the NDA submission.

The clinical pharmacology section of the NDA includes 2 single-dose pharmacokinetics (PK) studies of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, biodistribution of ^{177}Lu-DOTA^{0}-Tyr^{3}- Octreotate based on dosimetry scans from multiple images of the whole body, kidney, heart, liver and bone marrow and 1 QT/QTc prolongation study as well as 4 in vitro metabolic studies and 1 protein binding study.

Disposition

The following PK parameters represented as mean with standard deviation (SD) for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are based on noncompartmental analysis utilizing single dose PK data: C_{max} 9.3 ng/ml (4.1 ng/ml), volume of distribution 464 L (248 L), clearance 4.5 L/h (1.4 L/h) and AUC_{last} 34 ng.h/ml (13.7 ng.h/ml).

QT/QTc prolongation

A large change (i.e., >20 ms) in QTc interval was not detected in this ECG sub-study for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; however, mean changes above 10 ms were observed at 8 hours and 24 hours post-dosing. Placebo and ECG positive controls were not included in the sub-study. Increased heart rate (HR) was observed. The mean change from baseline in HR (ΔHR) peaked at 8 hours post infusion with ΔHR value of 18.7 bpm (90% CI: 12.4 to 25.0 bpm).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for the treatment of patients with (b) (4) somatostatin receptor positive, neuroendocrine (b) (4) tumors of the midgut (b) (4) is 7.4 GBq as a 30-min IV infusion once every 8 weeks for a total of 4 doses (29.6 GBq) with a co-infusion of a commercially available amino acid solution 30 minutes before and 3 hours after administration of each dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. Patients will also receive 30 mg Octreotide LAR as an intramuscular (IM) injection the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, and then every 4 weeks (b) (4).

Therapeutic Individualization

The applicant reported that age, sex, race, and hepatic function did not appear to have clinically meaningful effects on the PK profile of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. However, the PK profile of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with renal impairment has not been specifically studied. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is known to be substantially excreted by the kidney and the risk of adverse reactions to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate may be greater in patients with impaired renal function.

Outstanding Issues

The application is materially incomplete in that the datasets provided are inaccurate, incomplete, and inconsistent across databases. Thus, FDA cannot verify the information provided in the clinical study reports nor verify data used to support statements in the product labeling.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Drug product

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a Lutetium-177 labelled somatostatin peptide analog linked to the metal chelating moiety, DOTA. (b) (4)

(b) (4)

Bioanalytical methods

Plasma and urine concentrations for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate were determined by total radioactivity using auto-gamma counting in both the Erasmus and Netter-1 PK substudies. The development of the original bioanalytical method for determining ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate concentrations by auto-gamma counting is reported in Erasmus MC Dosimetry report. The

original method was not validated per draft FDA Guidance for Industry entitled "Bioanalytical Method Validation." The original method failed to show selectivity, accuracy, precision, and recovery as it did not include the following information: standards with known amount of analyte, determination of the upper and lower limits of quantitation, replicate measures, assessment of sample stability, and incurred sample reanalysis.

An additional HPLC method validation report is provided to support the identification of urine metabolites of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The HPLC method validation report is deficient due to the lack of internal standard while processing and analyzing the samples. This issue was communicated to the applicant during pre-NDA meeting on October 25, 2016. The Applicant acknowledged the concerns of the FDA and agreed to improve the HPLC method by including a cold reference standard of Lu-DOTA0-Tyr3-Octreoate and minimizing variability in the chromatographic retention of 177 Lu-DOTA0-Tyr3-Octreoate. The applicant stated that they will use the improved assay method to analyze the urine samples from the 8 remaining patients and asked the FDA if this data would be sufficient to fulfill the commitment made during the Type C meeting on August 27, 2015. In the NDA submission, the Applicant provided only a System Suitability Test (SST) on samples obtained for the last three patients (US11-025, US11-031 and US11-029). The SST only included cold reference sample before and after the run for each patient and did not include spiked internal standard as requested.

The methods for whole body and organ radiation dosimetry of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are reported in Dosimetry reports for both Erasmus and Netter-1 studies. Radiation dosimetry was used to determine the dose to critical organs (e.g., kidney and bone marrow). In addition, full body (planar) and 3D SPECT scans were performed on the day of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration.

ADME

The applicant reported that in vitro metabolic studies indicated that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was not metabolized by rat, dog or human hepatocytes (Study Report No. AAA-01), but it was metabolized by rat, dog and human kidney homogenate (Study Report No. AAA-05). This result is consistent with the metabolic fate of other peptides. In vitro drug interactions studies indicate that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate does not act as an inhibitor or an inducer of CYP450 enzymes (Study Report No. AAA-02 and No. AAA-03). Additional studies on P-gp interactions using a Caco-2 cell line indicate that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was not a substrate or inhibitor of P-gp (Study Report No. AAA-04). The unbound fraction (free fraction) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate as stated in Study Report No. BAN1116A27 was 25% at 300 ng/ml; and is 10% at 1000 ng/ml. The concentrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate used in the protein binding experiment in Study Report No. BAN1116A27 are not physiologically relevant as the reported average Cmax in patients was 9 ng/ml.

Pharmacokinetics

The PK parameters were determined by noncompartmental analysis with intensive PK samples collected in Netter-1 PK substudy, see table 1 below. The PK parameters were measured by total radioactivity in blood assuming this represents the parent compound only. Additional urine PK samples were also collected and the percentages of the activity of the injected parent drug recovered over specified period are listed in table 2 below.

Table 1. Pharmacokinetic parameters of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate from the Netter-1 study. The values are the means and (SD) of 19 patients ([a] patients = 18).

Parameter	Mean (SD)
C_{max} (ng/mL)	9.32 (4.07)[a]
$AUC_{t0\text{-}tlast}$ (ng.h/mL)	33.96 (13.73)
AUC (ng.h/mL)	41.36 (14.95)
Vz (L)	464 (248)
Systemic Cl (L/h)	4.53 (1.42)
Terminal $t_{1/2}$ (h)	71.7 (28.1)

Table 2. Urinary excretion of radioactivity from the Netter-1 study.

Approximate intervals (hours)	Cumulative activity decay corrected in urine as % of injected activity (SD)
0 - 2.0/2.5	24 (14)[a]
0 - 4/5	43 (19)[b]
0 - 16/23	58 (25)[b]
0 – 24/48	67 (27)[c]

Values are means (with standard deviation, SD) of [a]18, [b]19 and [c]14 patients.

Due to the identified study data deficiencies, FDA is not able to verify and confirm these PK results.

Per response to the midcycle communication, the Applicant indicated that in the Erasmus Phase I/II clinical trial, blood sampling times were not defined with the purpose of obtaining the classical PK parameters. Limited blood/urine data are therefore available and the PK analysis should be considered as an evaluation for general comparison/confirmation purposes versus the more structured PK analysis performed within the NETTER-1 Dosimetry, PK and ECG substudy. Summary data tables were not provided in the Applicant's response to the FDA Information Request (IR).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Evidence of effectiveness was intended to be obtained from the efficacy results of Erasmus and Netter-1 studies. Due to the study data deficiencies, the FDA is not able to review the evidence

of effectiveness from a clinical pharmacology perspective as described by the Applicant in the clinical study report.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The dosing regimen for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate was based on safety and dosimetry data from a single dose escalation part in the Erasmus Phase 1/2 study which resulted in a cumulative dose that remained below the defined radiation toxicity threshold to the kidney (23 Gy) and bone marrow (2 Gy).

Due to the study data deficiencies, the FDA is not able to determine the appropriateness of the proposed dosing regimen from a clinical pharmacology perspective.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alterative dosing regimen is proposed in the application. Per the Applicant, no correlations were found when comparing the following:

- Radiation dose absorbed to the bone marrow and neither acute or long term hematological toxicities.
- Long-term bone marrow toxicity normalized to dose (administered radioactivity) vs body weight or body surface area (BSA).
- Kidney dose and long-term kidney toxicity by creatinine clearance loss.
- Long-term radiation induced kidney toxicity normalized to dose (administered radioactivity) vs body weight or BSA.

Due to the study data deficiencies, the FDA is not able to determine if an altered dosing regimen or management strategy is required for patients with renal impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant reported that no significant inhibitory or induction effect on human CYP450 enzymes and P-gp specific interactions were seen suggesting that there is little potential for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to mediate clinically relevant drug-drug interactions. Concomitant infusion of amino acids 30 minutes before the start of infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and continuation at a constant rate for at least (b) (4) hours is required for renal protection.

These conclusions could not be verified, due to the study data deficiencies, the FDA is not able to determine the potential for drug-drug interactions or the contribution of amino acids in the disposition of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

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Primary Reviewer: Brian Furmanski Team Leader: Hong Zhao

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 7 lists the clinical trials included in this NDA submission.

The primary evidence to support the clinical safety and efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with SSTR positive midgut GEP-NETs is from Trial AAA-III-01, hereafter referred to as NETTER-1.

A sub-study of NETTER-1 was conducted in 20 patients who received ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at selected sites to evaluate dosimetry, PK and 24-hour holter cardiac monitoring. These patients were not randomized and the patients enrolled in the substudy were not considered in the primary or in the secondary analysis of the main study groups. A non-randomized cohort of patients receiving investigational treatments (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) was temporarily activated at all sites participating in the sub-study until a total of twenty (20) patients were enrolled. All patients included in the sub-study were treated as per the investigational treatment arm (4 infusions of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate +30 mg Octreotide LAR). During this period, the sites not participating in the sub-study continued to enroll patients using the randomization protocol of the main study. Please see the clinical pharmacology review for additional details regarding this study.

Data from Trial MEC 127.545/1993/84, hereafter referred to as the Erasmus Medical Center (EMC) study, was submitted with the intent to better characterize the safety and effectiveness of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with SSTR positive GEP-NETs. The EMC study entitled "Phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumors," was an investigator sponsored single-arm clinical study conducted at EMC in Rotterdam, The Netherlands, between January 2000 and March 2007. The study enrolled patients with various inoperable, SSTR positive tumors. The primary objective of the study was to assess the safety and activity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate given as 4 doses of 7.4 GBq at 6-13 week intervals. AAA performed a retrospective review of the data in 2012, and updated the analysis in 2015.

Table 6: Listing of Clinical Trials Relevant to this NDA

Trial	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Primary studies to support safety and efficacy						
NETTER-1 AAA-III-01 (Main Study)	International, open-label, randomized, stratified, phase III study	Investigational Arm: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 7.4 GBq every 8 weeks for four doses + Octreotide LAR 30 mg every 4 weeks Control Arm: Octreotide LAR 60 mg.	Primary: PFS Secondary: ORR per RECIST 1.1, OS, TTP, safety, HRQoL	N=229 Investigational arm=116 Control arm=113	Patients with metastatic or locally advanced, midgut carcinoid tumors with centrally confirmed progressive disease by RECIST	41 active sites 27 in Europe 14 in US
Secondary studies						
NETTER-1 AAA-III-01 (Sub-Study)	Single-arm, non-randomized cohort from NETTER-1 Main Study to evaluate dosimetry	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 7.4 GBq every 8 weeks for four doses + Octreotide LAR 30 mg every 4 weeks	To evaluate whole body and organ radiation dosimetry	N=20	Same as NETTER-1 main study	7 sites 5 in Europe 2 in US
EMC Study	Investigator-sponsored, open-label, single-arm study	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 29.6 GBq cumulative dose	Primary: ORR (CR, PR, MR) per modified SWOG criteria Secondary: Safety based on SAEs	N=1214 Dutch patients=810 Dutch patients with GEP-NET=558	Patients with various SSTR positive NETs	Single-center: Erasmus Medical Center in Netherlands

GBq: gigabecquerel, PFS: progression free survival, ORR: objective response rate, CR: complete response, PR: partial response, MR: minor response, SAE: serious adverse event

7.1.2. Review Strategy

The FDA statistical and clinical NDA review consisted of one primary statistical reviewer and one primary clinical reviewer for the safety and efficacy data.

The NDA submission contained one randomized trial, NETTER-1, entitled *"A multicentre, stratified, open, randomized, comparator-controlled, parallel group phase III study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours."*

The NDA submission also contained a single-center, investigator sponsored study entitled *"Phase I/II single arm study to evaluate the efficacy of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with somatostatin receptor positive tumors."*

The strategy for the clinical and statistical review was to focus on data from NETTER-1 and perform a detailed analysis including the CSR, CRFs, SAP, datasets, and SAS program. A review of data from EMC was planned to provide supportive data on safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate as well as a review of the data describing anti-tumor effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on the epidemiology and treatment of GEP-NETs.
- Review of the current literature on the use of PPRTs.
- Review of NETTER-1, including the CSR, protocol V1.0 to V4.1, protocol amendment for US version 1.0, and SAP V2 with track changes.
- Review and assessment of the Applicant analyses of the safety and efficacy of Lutathera as presented in the CSR.
- Review of datasets submitted to the NDA.
- Review of patient narratives of serious adverse events and deaths.
- Review of minutes of key meetings conducted during the development history of Lutathera.
- Requests for additional information from AAA and review of Applicant responses.
- Review of consultation reports from OSI and the Division of Medical Imaging Products (DMIP).
- Review and evaluation of proposed labeling.

Data Sources

The electronic submission including the study protocols, SAPs, CSRs, and datasets for this NDA submission is located in the following network paths:

- CSR, Protocol, SAP V2 and data in CDISC format: \\CDSESUB1\evsprod\NDA208700\003\

- Efficacy Programs review guide: \\CDSESUB1\evsprod\NDA208700\011\
- SAS programs for CSR Section 11 using Legacy raw and analysis data: \\CDSESUB1\evsprod\NDA208700\012\
- Revised ADSL data: \\CDSESUB1\evsprod\NDA208700\018\
- Legacy raw and analysis datasets with SAS programs for CSR generation: \\cdsesub1\evsprod\nda208700\0020\
- Revised SDTM and ADAM datasets with SAS programs for PFS, ORR, and OS subgroup analyses: \\cdsesub1\evsprod\nda208700\0021\
- Revised SDTM and ADAM datasets: \\cdsesub1\evsprod\nda208700\0022\
- Resubmit SAP V2 with track of change from V1: \\cdsesub1\evsprod\nda208700\002\
- Revised legacy datasets in SAS7dbat format: \\CDSESUB1\evsprod\NDA208700\0032\
- Revised legacy datasets in SAS7dbat format: \\CDSESUB1\evsprod\NDA208700\0033\

Data and Analysis Quality

During this NDA review, significant issues were uncovered regarding the quality and integrity of the submitted data. A brief timeline of events is provided below:

- June 17, 2016: Applicant orientation meeting held, including application "walk-through."

- June 9 – July 18, 2016: Multiple information requests (IRs) were sent to AAA from the clinical, statistical, clinical pharmacology and OSI review teams. The IRs were mainly related to missing and inconsistent data in the datasets, missing statistical programs required for FDA to verify data derivation from raw data to run analyses, and inadequate define files. Due to these deficiencies, FDA was not able to confirm the safety and efficacy data submitted in the CSR.

- June 30, 2016: During a teleconference, FDA informed AAA that the clinical and statistical review teams were not able to generate or confirm the tables and data provided in the NETTER-1 CSR based on the datasets submitted. In addition, AAA stated the data in the CSR were generated by the CRO based on legacy data and differed from the CDISC data that was submitted to FDA for review. AAA stated they were not able to convert the data to be CDISC compliant, and instead mapped the legacy raw and derived datasets into CDISC SDTM/ADaM for submission to FDA. It was not clear what programs AAA used to convert the raw data. FDA informed AAA that it is not acceptable that the data used to derive tables and information in the CSR differ from the data submitted to FDA.

- August 2, 2016: A post mid-cycle teleconference was held and AAA was informed that the clinical, statistical and clinical pharmacology review teams have determined the application is materially incomplete in that the datasets provided are inaccurate, incomplete, and inconsistent. Thus, FDA cannot verify the information provided in the

clinical study reports nor verify the results proposed in the product labeling. AAA was advised to do the following:

- Submit new datasets containing data that has been verified for accuracy within 30 days of this teleconference. The new datasets should be complete, verified for accuracy against the raw data from each trial as previously agreed in the pre-NDA meeting and subsequent communications, and be in such a format as to allow for use with software such as SAS and JMP. Additionally, a revised CSR to include any new results should be submitted to the NDA in both track change and clean versions.
- Consider withdrawal of the application and resubmit with accurate, complete, and reviewable datasets and revised CSRs as described above.

- August 11, 2016: During a teleconference, AAA agreed to submit the following to the NDA:
  - Due by October 10, 2016:
    - Clinical data: Data from submission (July 24, 2015, clinical cutoff date), with fully cleaned data.
    - Data format: Raw and analysis datasets as requested by FDA with consistent variable names and clear derivation definitions, legacy format data but ready for analysis in SAS and JMP.
    - Detailed Reviewers Guides including data dictionaries for all variables and derivation paths for all raw and derived variables.
  - Due by November 9, 2016:
    - Updated Tables/Figures/Listings.
    - Updated CSR, both red-lined and clean version, showing the impact of the updated/cleaned clinical data and matching the TFLs and datasets.
    - Notations of why any data changes occurred that impact the CSR.

- August 25, 2016: AAA submitted "test" datasets for FDA to review. FDA was not able to open the datasets in JMP and informed AAA that this appeared to be related to the file name used. AAA re-submitted "test" datasets in a revised format that was deemed acceptable.

- October 10, 2016: AAA submitted the datasets as agreed upon during the August 2, 2016, teleconference; however, FDA reviewers were not able to access the datasets and continued to have problems with the data format and missing data.

In summary , the quality of the original data submission and more than 10 data resubmissions were not adequate for FDA reviewers to review the application after more than 15 formal data quality-related information requests were sent to the applicant to request additional data, documentations, programs, and results, and face-to-face meeting, teleconference, and email communications with AAA. The reviewers observed key data related issues as detailed below:

- Under 21 CFR §§ 314.101(d) (1),(2), (4)-(9) and FDA MAPP 6025.4, the application does not contain accurate and complete English translation of data submission (e.g. the variable names were in Chinese character Adverseeventsm1 data under SN 22).

- The study data contained in the electronic submissions failed to be in a format that FDA can process, review, and archive (FDA Guidance for Industry Providing Regulatory Submissions in Electronic Format—Standardized Study Data). Currently, FDA can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the FDA's Data Standards Catalog.

  a. In general, FDA grants wavier for standardized study data that will enable an applicant to submit study data electronically using a version of a standard that was previously supported by FDA.

  b. FDA Data Standards Catalog states that FDA only accepts XPT, PDF, XML exchange format. The submitted database in SAS7bdata format was inadequate and is not ready for XPT transformation. The SAS7bdat data should follow the requirements as listed below to be able to transform to XPORT files:
     i. Dataset greater than 5 GB in size should be split in the smaller dataset no larger than 5 GB.
     ii. To reduce file size, the allotted length for each variable should be set to the maximum length of variable used across entire submission.
     iii. One data per transport file with the same name (e.g. ae.sas7bdat and ae.xpt).
     iv. Maximum length in characters for data and variable name is 8.
     v. Maximum length in characters for data and variable label is 40.
     i. Use American Standard Code for Information Interchange (ASCII) text codes. Furthermore, Ms. Joy Li from FDA's Computational Science Center point out that the encoding system used by AAA to generate the datasets (utf-8 Unicode) results in reading errors; therefore, utilize the default SAS coding system,wlatin1 (i.e. western world encoding).
     vi. Exclude punctuation, dashed, space, non-alphanumerical symbols, and special characters.
     vii. Exclude user-defined SAS format library. Instead, AAA may provide this information in the Controlled Terminologies.

  c. Each patient should be assigned to a single unique subject identifier (USUBJID) across the entire submission. Subject Identifier (SUBJID) should be different if screened more than once in a trial (e.g. SUBJID 002 in SITEID IT06 was moved to another site. Due to duplicate SUBJID 002 in multiple sites without reported USUBJID, FDA could not trace this patient's record).

- FDA has determined that the study data submitted could not provide sufficient information to understand the accuracy of the data (i.e., traceability of the AAA's analysis results back to the annotated CRF (aCRF). Traceability permits an understanding of the relationships between the analysis results (tables, listings and figures (TLFs) in the CSR, analysis datasets, tabulation datasets, and source data (See FDA's Study Data Technical Conformance Guide: Technical Specifications Document).
  a. In the original submission, the data used to generate the CSR and TLFs differ from the data submitted to FDA for review (as reported in the T-con on June 30, 2015).
  b. Under the most recent submission in SN 33 dated on October 13, 2016, the datasets submitted contain errors and are incomplete. The entire study data submission renders the application unreviewable, administratively incomplete, and inconsistent with regulatory requirements. AAA should ensure that the raw data used to generate these datasets have been audited for completeness, missing data points and errors, up to the time of database lock.

c. Detailed data related issues are identified and listed below for the most recent study data resubmission under SN33:

Study Data format: The entire study data was submitted in SAS7bdat format

Study Data:

i. Lack of unique subject identifier across entire submission.
ii. Provided four datasets (Labblood, eortc, laburinem2, and adverseeventm1) with greater than 5 GB in size.
iii. The lengths for data and variable name, data and variable label in the submitted sas7dbat files exceeded max length requirement to be ready for XPT transformation.
iv. Provided many system generated variables which were not used for analysis purpose.
v. Provided many data with user defined SAS format library, which caused difficulty to understand submitted study data.
vi. Provided 201 out of 229 randomized patient's scheme with many missing values in essential variables. It appears that the stratification factors were documented per CRF instead of IVRS database.
vii. Modified legacy raw dataset post clinical data cut-off. For example, the DM information was last modified on November 14, 2015. The most recent tumor evaluation was modified on September 23, 2016.
viii. Tumor assessments were provided in multiple datasets with many missing values in essential variables and lack of adequate documentations. FDA has difficulty understanding submitted tumor assessment related datasets.
ix. In the PFS primary analysis dataset, age, race, gender, stratification factors, and important disease characteristics variables were not included. Further data

manipulation is needed to conduct mandatory subgroup analyses by age, race, and gender.

x. Many mistakes were identified in the submitted data. For example, some lab tests are out of range. Furthermore, some lab test value did not have measurement unit to help FDA to understand the meaning of the value.

aCRF

xi. AAA failed to map variables on the aCRF to the corresponding variables in the datasets. (e.g. sex was reported as 916576 and 920197 but reported as Male and Female in aCRF for variable DM.DMSEX).

Define file:

ii. The define files associated with the datasets are generally inadequate and erroneous and do not allow reviewers to understand the variables and derivations in the datasets. For example, define files are missing metadata and there are inconsistencies between output variables and the assigned code.

iii. Did not have sufficient comments, adequate bookmarks, and hyperlinks to xpt file, aCRF, controlled terminologies, and computational method.

Controlled Terminologies:

- Provided inconsistent controlled terminology across datasets (e.g. yes vs. no value was coded as no vs. yes).
- Short of controlled terminology for essential variables (e.g. the treatment arm were coded as A vs. B in PFS.treat and 1 vs. 2 in PFS.treatx without control terminology for PFS.SAS7bdat).

SAS programs: Since the legacy raw and analysis datasets were used to generate CSR and tables, AAA did not provide all necessary SAS programs, SAS macro, SAS format library, and adequate documents in order to duplicate the analysis datasets derivation from raw dataset and analysis results in the CSR and USPI.

Reviewer's Guides: AAA did not provide Study data reviewer's guide and Analysis data reviewer's guide for legacy raw and analysis data respectively.

DSMB Meeting Minutes: AAA did not submit DSMB meeting minutes in the submission.

Subgroup Analyses: Safety and efficacy subgroup analyses were not investigated for gender, racial, geriatric subgroups, stratification factors and important disease characteristics.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

NETTER-1 (Protocol version 4.1, June 5, 2014)

Trial Design and Endpoints

Trial NETTER-1 is a randomized (1:1), open-label, multi-national (41 sites in 8 countries; 27 sites in Europe and 14 sites in the U.S.), and parallel-group Phase III trial comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus best supportive care (30 mg Octreotide LAR) to treatment with high dose (60 mg) Octreotide LAR in patients with inoperable, SSTR positive, histologically proven midgut carcinoid tumors, with progressive disease while on Octreotide LAR. The study was initiated with protocol version 1.0 dated November 14, 2011, the first patient was enrolled July 10, 2012, the first randomization date was September 6, 2012, and the study completion date was September 14, 2015.

The key enrollment criteria were as follows:

- Metastatic or locally advanced, histologically proven midgut NETs,
- SSTR positive target lesions based on OctreoScan scintigraphy within 24 weeks prior to randomization while the patient was on a fixed dose of Octreotide LAR,
- Fixed dose of 20/30 mg Octreotide at 3-4 weeks intervals for at least 12 weeks prior to randomization, and
- Centrally confirmed progressive disease by RECIST Criteria.

Patients in the investigational arm received 4 doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 7.4 GBq at 8 week intervals (±1 week) or up to 16 weeks to allow for resolution of acute toxicities. For renal protection, an amino acid solution was started 30 minutes prior to start of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, and administered in parallel by IV infusion for a total of 4 hours. In addition, patients received 30 mg Octreotide LAR every 4 weeks ± 3 days for clinical symptom control until the PFS primary end-point, then until Week 72 from randomization after the PFS primary end-point, or early termination, unless the patient progressed or died.

Patients in the control arm received 60 mg octreotide intramuscular (IM) every 4 weeks ± 3 days until the final overall analysis of PFS, unless the patient progressed or died. After the final PFS analysis, all patients received study drug for a maximum of 72 weeks and then proceeded to the long-term follow-up assessment phase.

Unless clinically impossible, Octreotide LAR was not administered within 6 weeks of the next treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and short acting Octreotide subcutaneous (sc) was not allowed during the during the 24 hour period before the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date, unless the patient's clinical condition contraindicated treatment suspension (i.e. due to carcinoid syndrome symptoms). Treatment with 30 mg Octreotide LAR was resumed after the administration of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. The minimum interval before resuming Octreotide LAR (or short acting Octreotide sc) was 4 hours.

Disease assessment in both arms was performed every 12±1 weeks from time of randomization, and an IRC analyzed imaging and communicated final results to the investigator within 5 working days. Patients with progressive disease according to real-time central reading assessment per RECIST criteria discontinued therapy and proceeded to the long-term follow-up phase. The study schedule for both arms is summarized in the tables below (copied from protocol version 4.1):

Table 1: Visit Schedule: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Treatment Arm

Visit	Eligibility	Baseline	Study Treatment Phase																								Follow-Up Phase[7]
																									Further visits[6]		End of Study Treatment Phase Visit	
Week		Week -3	0	4	6	8	12	14	16	20	22	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	[1]Within 4±4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			↓			↓			↓			↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		
Informed Consent	x																											
OctreoScan®	< 24 weeks																											
Histology and Ki67[1]	x																											
Diagnosis and Extent of Cancer	x																											
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																											
Demographic Data	x																											
Relevant Medical History		x																										
Prior Therapy for Carcinoid Tumour	x	x																										
Confirmation of Eligibility and Randomization		▼																										
Diary Delivery (Symptoms and Rescue Med)	x		x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Cardiac Ejection Fraction		(x)[4]																										
ECG (at the end of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion)		x	x			x			x			x														x	
Physical Exam and Vital Signs		x			x		x	x			x				x			x			x			x	x	x	
Karnofsky Performance Status	x	x			x		x	x			x				x			x			x			x	x		
Quality of Life (EORTC GI.NET21; EORTC C30)		x					x					x			x			x			x			x	x		
Hematology[2]	x	x			x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	
Blood Chemistry[2]	x	x			x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	
Urinalysis[2]	x	x			x	x	x	x	x	x	x	x	x		x			x			x			x	x	x	x	
Pregnancy test[2]		x			x			x			x																	
Serum CgA[1]		x					x				x				x			x			x			x	x			
Cancer Related Symptoms[3]			x	x		x	x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant/Rescue Therapy																												
Antitumor-therapies after progression																												
Adverse Events[5]																												
Disease Assessment RECIST (CT, MRI)[1]	x						x					x			x			x			x			x		x	x	x
Survival Information																												

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Sections 4.2.1, 4.2.2 and 6.5.2 (footnote to Table 8) of the Protocol prior to administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

↓ TREATMENT: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; 4 administrations at 8±1-week intervals

↓ TREATMENT: 30 mg Sandostatin® LAR Depot injections to be administered the day after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion

Last Sandostatin® LAR Depot injection should have been administered at least 6 weeks before the next ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment date

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c. injections (to be stopped 24 h before each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate administration)

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the PFS Primary-End-Point occurs; then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained.

RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose.
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter at baseline for female of childbearing potential and during ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate therapy within 7 days prior to each treatment; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits
- During ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, laboratory tests will be performed within 2 weeks before and 4±1 weeks after each treatment. In addition, for the second, third and fourth ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatment, additional laboratory tests will be performed on the same day or within the day before each treatment. Laboratory assessments performed on the same day or within one day prior to administration of the second, third, and fourth doses of study drug must include at minimum:
  a. serum blood urea nitrogen and creatinine
  b. serum total bilirubin, aspartate aminotransferase and alanine aminotransferase
  c. hemoglobin, platelet count, total leukocyte count, and absolute neutrophil count.
- If a 40% increase over the baseline serum creatinine value occurs during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockcroft-Gault formula, patients must also have a measured creatinine clearance (or GFR) performed. Measured creatinine clearance should be through two 24-h urine collections. Total urinary protein should also be measured

[3]During the study, symptoms will be recorded in the e-CRF according to patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the 5years long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

a) Patients who have 76 weeks or more treatment/assessment stop treatment but continue 6-monthly assessments for overall 5-years from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient whichever occurs first (phone contacts or visits at Site). Laboratory assessments (haematology, biochemistry, urinalysis), further anti-tumour treatments, SAEs suspected in relationship to the study drug, tumour progression (local evaluation after the analysis of the PFS Primary End-Point) and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

- - - ► Information to be collected during the entire study

Table 2: Visit Schedule: Octreotide LAR Arm

Visit	Eligibility	Baseline	Study Treatment Phase																				Follow-Up Phase[7]
																					Further visits[6]		End of Study Treatment Phase Visit	
Week		Week -3	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	Monthly	Every 12 weeks	Within +4 weeks after the last study drug administration or early termination	Every 6 months
Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇		
Informed Consent	x																								
OctreoScan®	< 24 weeks																								
Histology and Ki67[1]	x																								
Diagnosis and Extent of Cancer	x																								
CT/MRI Scan Confirming Disease Progression[1]	< 4 weeks																								
Demographic Data	x																								
Relevant Medical History		x																							
Prior Therapy for Carcinoid Tumour	x	x																							
Confirmation of Eligibility and Randomization		▼																							
Diary Delivery (Symptoms and Rescue Med)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Cardiac Ejection Fraction		(x)[4]																							
ECG		x	x		x		x		x			x			x			x			x		x		
Physical Exam and Vital Signs		x				x			x			x			x			x			x		x		
Karnofsky Performance Status	x	x				x			x			x			x			x			x				
Quality of Life (EORTC GI-NET21; EORTC C30)		x				x			x			x			x			x			x				
Hematology[2]	x	x		x		x			x			x			x			x			x		x	x	
Blood Chemistry[2]	x	x		x		x			x			x			x			x			x		x	x	
Urinalysis[2]	x	x		x		x			x			x			x			x			x		x	x	
Pregnancy Test		x																							
Serum CgA[1]		x				x			x			x			x			x			x				
Cancer Related Symptoms[3]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant/Rescue Therapy			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	→	
Anti-tumour therapies after prgression																								→	
Adverse Events			⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	⬇	→	
Disease Assessment RECIST (CT, MRI)[1]	x					x			x			x			x			x			x		x	x	
Survival Information																								→	

Refer to §Section 6 for further details on Visits Assessments. Investigator must ensure that the laboratory parameters meet the retreatment criteria outlined in §Sections 4.2.1 and 4.2.2.

Investigator must maintain phone contact with the patient for the first week after the first treatment to verify the general status of the patient.

⬇TREATMENT: 60 mg 4-week interval Octreotide LAR Depot injections

IF REQUIRED, RESCUE TREATMENTS: Octreotide s.c injections

[1]Restaging is performed every 12±1 weeks since randomization. Centrally evaluated until the analysis of the PFS Primary End-Point (74 evaluable and centrally confirmed progressions or death events), then for the remaining randomized patients until Week 76 or at last visit due to early termination

Disease progression at inclusion to be confirmed centrally. For the purpose of determining disease progression the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions; 1) it is acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks); AND 2) it is acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan®, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan® has been obtained. RECIST Disease Assessment during the long-term follow-up will be performed locally.

[2]Tests included in the local laboratory assessments:

- Haematology: WBC with differential, Platelets, Hb, MCV and Haematocrit
- Blood chemistry: Serum Creatinine, (Creatinine Clearance - Cockcroft-Gault formula), Uric Acid, Albumin, Total Bilirubin, AP, AST/ASAT, ALT/ALAT, Gamma-GT, Sodium, Potassium, LDH, GlycoHb (haemoglobin A1C), fT4, Calcium and Glucose
- Urinalysis: RBC/hpf, WBC/hpf, Casts/lpf, Protein (dipstick test is accepted to assess protein), Pregnancy test if applicable (the latter only at baseline for female of childbearing potential; blood pregnancy test is accepted). 5-HIAA must be done on 24h urine collection: in case of logistic problems, the patient should be instructed to collect urine the day before the scheduled visit at Site. 5-HIAA exam is requested only at eligibility or baseline visit, at weeks 12, 24, 36, 48, 60, 72 or 76 (and following 3-monthly lab assessments until the analysis of the PFS Primary End-Point and at 6-months follow-up visits)

[3]During the study symptoms will be recorded in the e-CRF according patient diary notes

[4]Preferably via gated equilibrium radionuclide ventriculography (RVG), only in patients with history of congestive heart failure (patients with uncontrolled congestive heart failure (NYHA II, III, IV) aren't eligible according to exclusion criterion №-12)

[5]AEs/SAEs will be reported from signing the informed consent form onwards until the end of the treatment phase. During the long-term follow-up only SAEs related to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be reported to the Sponsor Safety Officer

[6]Any progressive patient ceases treatment/assessment and proceeds to the long-term follow-up assessment.
Any non-progressive patients continues treatment/assessments until the PFS Primary End-Point (i.e. 74 evaluable and centrally confirmed disease progressions or death events), then:

a) Patients who have 76-weeks or more treatment/assessment stop treatment but continue assessments for overall 5-year from the date of randomization of the last patient

b) Remaining randomized patients continue in the fixed 76-week treatment/assessment period unless progression occurs, then continue for overall 5-year from the date of randomization of the last randomized patient

[7]Patient must be contacted every 6 months until the moment 158 deaths have occurred, or 5 years from the date of randomization of the last randomized patient, whichever occurs first (phone contacts or visits at Site)

Laboratory assessments (haematology, biochemistry, urinalysis), tumour progression (local evaluation after the analysis of PFS Primary End-Point, further anti-tumour treatments and death will be reported. In case of phone contacts, medical reports/CT-MRI images must be provided by the patient to the Investigational Site.

-----→ Information to be collected during entire the study

According to permuted block randomization scheme, patients were randomized and stratified by 1) somatostatin receptor scintigraphy tumor uptake score centrally assessed (Grade 2, 3 and 4, the highest score measured among all the target lesions will be used for stratification purpose); and 2) length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤ 6 and > 6 months).

FDA's review of efficacy is limited to analyses of primary endpoint PFS per IRC assessment and key secondary measures: ORR, OS, and duration of response (DoR) for NETTER-1. The clinical data cutoff dates for the pre-planned PFS analysis was July 24, 2015.

Eligibility Criteria

Inclusion Criteria

1. Presence of metastasized or locally advanced, inoperable (curative intent) at randomization time, histologically proven, midgut carcinoid tumor (to be centrally confirmed).
2. Ki67 index ≤ 20% (to be centrally confirmed).
3. On Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for ≥ 12 weeks prior to randomization.
4. Age ≥18 years.
5. Progressive disease based on RECIST Criteria, Version 1.1 while receiving an uninterrupted fixed dose of Octreotide LAR (20-30 mg/3-4 weeks). Disease progression must be centrally confirmed. In order to make the assessment, two CT (or MRI) scans are required; the oldest scan must not be older than 3 years from the date of randomization and the most recent scan must not be older than 4 weeks from the date of randomization. Both scans must be obtained while the patient is receiving the same fixed dose of Octreotide LAR (20-30 mg/3-4 weeks) with the following exceptions:
    a. Acceptable if the oldest scan is obtained within 12 weeks of the patient receiving a fixed dose regimen of Octreotide LAR (20-30 mg/3-4 weeks);
    b. Acceptable for either scan to be obtained before or during the time a patient receiving a fixed dose of Octreotide LAR has switched to an equivalent dose of short acting Octreotide for up to 6 weeks in order to obtain an OctreoScan, provided the patient returns to the Octreotide LAR fixed dose after the OctreoScan has been obtained.
6. Confirmed presence of somatostatin receptors on all target lesions documented by CT/MRI scans, based on positive OctreoScan imaging within 24 weeks prior to randomization in the study (to be centrally confirmed). The OctreoScan should be one that was performed while the patient was on a fixed dose of Sandostatin LAR. If a patient has had an OctreoScan performed while Octreotide LAR treatment-naïve, the patient must have a repeat OctreoScan performed after 3 months of Octreotide LAR treatments before entering the clinical study to prove that the index lesions or new lesions still meet the criteria for inclusion.

7. The tumor uptake observed in each target lesion using OctreoScan should be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed).
8. Karnofsky Performance Score (KPS) ≥60.
9. Presence of at least 1 measurable site of disease.

Exclusion Criteria

1. Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min calculated by the Cockroft Gault method.
2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x109/L (2000/mm3); platelets <75x109/L (75x103/mm3).
3. Total bilirubin >3 x ULN.
4. Serum albumin <3.0 g/dL unless prothrombin time is within the normal range.
5. Pregnancy or lactation.
6. For female patients of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel).
7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomization in the study.
8. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomization in the study.
9. Any surgery, radioembolization, chemoembolization, chemotherapy and radiofrequency ablation within 12 weeks prior to randomization in the study.
10. Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior to randomization in the study.
11. Known brain metastases, unless these metastases have been treated and stabilized for at least 24 weeks, prior to randomization in the study. Patients with a history of brain metastases must have a head CT with contrast to document stable disease prior to enrollment in the study.
12. Uncontrolled congestive heart failure (NYHA II, III, IV).
13. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN.
14. Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, unless the tumor uptake observed on target and non-target but measurable lesions by OctreoScan imaging during continued Octreotide LAR treatment is at least as high as normal liver uptake observed by planar imaging.
15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study.
16. Prior external beam radiation therapy to more than 25% of the bone marrow.

17. Current spontaneous urinary incontinence.
18. Other known co-existing malignancies except non-melanoma skin cancer and carcinoma in situ of the uterine cervix, unless definitively treated and proven no evidence of recurrence for 5 years.
19. Patients who have not provided a signed informed consent form to participate in the study, obtained prior to the start of any protocol related activities.
20. Patient with known incompatibility to CT Scans with I.V. contrast due to allergic reaction or renal insufficiency. If such patients can be imaged without the use of CT contrast material (i.e., can tolerate MRI scans), such patients would not be excluded.
21. Patients who have participated in any therapeutic clinical study/received any investigational agent within the last 30 days are excluded from participation in this trial.

Sample Size Considerations

The primary endpoint was PFS as assessed by IRC according to RECIST 1.1 and was centrally confirmed. Assuming that the median PFS was 14 months in the control arm and 30 months in the experimental arm, a total of 74 centrally confirmed PFS events per IRC assessment were needed to detect a hazard ratio of 0.47 with 90% power at a 2-sided alpha level of 5%.

The trial was also designed to test OS. Assuming that the median OS was 32 months in the control arm and 50 months in the experimental arm, a total of 158 death events were needed to detect a hazard ratio of 0.64 with 80% power at a 1-sided alpha level of 2.5%. An interim analysis was planned at the final PFS analysis. Per SAP V1, the OBF boundary method was used with respective alpha allocation of 0.0085% for the OS interim analysis. Based on a lack of number of projected OS events at the interim analysis, the meaning of 0.0085% is unclear.

Major secondary endpoints include OS and ORR. A hierarchical procedure was proposed to adjust for multiplicity in testing the secondary endpoints in the order of ORR and OS.

Analysis sets

The primary efficacy analysis population was the ITT population, which included all randomized patients who received any amount of study drug. Patients would be categorized by the treatment arm to which they were assigned at randomization, regardless of the actual treatment received. The ITT population was named as Full Analysis Set in the SAP and protocol.

The PPS included all randomized patients, who had no major protocol violations.

The SAF included all randomized patients who received any amount of study drug. Analysis of safety data would be performed according to the actual treatment a patient has received.

The ITT was used for all analyses of efficacy, demographics and baseline characteristics. The PPS was used for the sensitivity efficacy analyses. The safety set was used for all safety analyses.

Efficacy Measures

PFS was defined as the time from the date of randomization to the earliest date of IRC confirmed tumor progression or death from any cause.

The ORR was defined as the proportion of all randomized patients with the best overall response of partial response (PR) or complete response (CR).

OS was defined as the time from randomization to death from any cause, or to the last contact at the date of data cut-off, during the entire study period (treatment phase and follow-up phase).

Efficacy Analysis Methods

PFS

The analysis for PFS would be performed using an un-stratified log-rank test. The median PFS with corresponding two-sided 95% CIs and survival curves were to be estimated using the Kaplan-Meier (KM) method.

Tumor response was assessed every 12+/- 1 weeks per IRC assessment using RECIST v.1.1 until disease progression. Tumor response for patients who have not progressed after the data cut-off for the primary analysis would be assessed every 12 weeks until week 76 unless disease progression or death.

In general, SAP followed the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Per amended actual censoring rules for primary PFS analysis, under SN21 (see Table 7), AAA did not follow SAP pre-specified censoring rules. In the future NDA submission, AAA should provide the following information as listed below in the primary PFS analysis:

- AAA used a 210-day gap as the threshold to calculate the flag of two continuous missing tumor assessments. FDA recommends that AAA use 175 [(12*2+1)*7] days instead. Using a 210-day threshold, only four patients were reported to be censored due to 2 continuous missing assessments. Due to the data deficiencies, FDA could not identify the actual number of patients who were censored in the range of 175-210 days.
- A sensitivity analysis with the observation censored on the date of last adequate tumor assessment for patients:
    - Who are alive, on study, and progression-free at the time of the analysis;
    - Who are given/change anti-cancer therapy other than the study treatment prior to observing progression, and

  - Who discontinue (due to personal preference or toxicity), withdraw, or are lost to follow-up.
- AAA should use consistent algorithm to calculate time to event duration. Conventionally, FDA calculates time to event date as (event date –randomization date + 1).

FDA could not evaluate the derivation of PFS data. Hence, FDA is uncertain about the definition for centrally confirmed PFS per IRC assessment. Per RECIST 1.1, disease progression does not need to be confirmed.

Table 7 Actual Censoring Rule for Priamry PFS Analysis

Condition	Date of event/censoring	Event/Censored
For the primary analysis of PFS, any tumor assessments with >210 days gap, and any tumor assessments post subsequent cancer therapies are excluded first, before the following conditions are checked:		
• CONDITION 1: If first tumor assessment is more than 210 days or death date is more than 210 days from randomization	Date of Randomization	Censored
• CONDITION 2: If there is a Progressive Disease Date	Date of 1st Progressive Disease	Event
• CONDITION 3a: If there is a death date within 210 days from randomization or last non-PD date •	Death Date	Event
• CONDITION 3b: Otherwise if the death is more than 210 days from last non-PD date	Date of last adequate disease assessment	Censored
• CONDITION 3c: Otherwise if the death is more than 210 days from randomization date	Date of Randomization	Censored
• CONDITION 4: If there is no progression	Date of last adequate disease assessment	Censored
• CONDITION 5: If none of the above conditions apply but there is a randomization date	Date of Randomization	Censored
• CONDITION 6: If none of the above conditions apply and there is no randomization date	Not applicable – the subject is not included in the FAS	

Source: Response to FDA IR under SN21 Page 3

Step down adjusted Cox's proportional hazards model was planned in the SAP. In the CSR, AAA also reported below PFS sensitivity analyses:

- Per INV assessment in the ITT and PPS.
- Per IRC assessment in the PPS.
- Assigning the event time to the next scheduled image time.
- Ignoring early censoring because of new anti-cancer treatments started before progressive disease or death.
- Ignoring early censoring because of more than 2 missing consecutive visits.
- Ignoring both early censoring because of more than 2 missing consecutive visits and early censoring because of new anti-cancer treatments started before progressive disease or death.

ORR

The analysis for ORR would be treatment arms compared using the Fisher exact test.

OS

The OS analysis method is identical to that for PFS analysis. Sensitivity analyses were included in the SAP to evaluate potential impact of:

- subsequent anti-tumor treatments after progression,
- the presence and number of distant metastases,
- the extent of tumor burden / tumor mass (centrally assessed), and
- treatment compliance.

Above pre-planned OS sensitivity analyses were not included in the CSR. To evaluate the effect of crossover from control arm to experimental arm on OS, AAA could conduct OS sensitivity analyses using the rank preserving structural failure time (RPSFT) model (Robins and Tsiatis, 1991).

Protocol Amendments

The following provides a summary of the major amendments made to the U.S. protocol.

- July 6, 2012:
  - Definition of PFS, TTP and OS were modified to be based on time from the date of randomization rather than the date of first treatment.
  - Clarified and added safety assessments for blood chemistry and urine tests for both arms.
  - Added details of the DSMB responsibilities.
  - Added details on the sub-study conduct and data analysis.
  - Modified appendices for recommended precautions for patients treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, randomization procedures and determination of administered radioactivity.

- July 24, 2013:
  - Biased coin randomization scheme replaced by stratified permuted block scheme with a balanced ratio (1:1) between the treatment arms, and stratification for specific center enrolment was deleted.
  - The method to control the family-wise type I error rate for OS and ORR was included as well as a detailed description of the statistical analysis for OS.
  - The end of study definition was modified and the description of the primary analysis adapted accordingly.
  - Patient replacement for the primary analysis was excluded and the primary

analysis using log-rank test was specified.
  - Clarifications related to study procedures (e.g. CT/MRI timelines, Octreoscan), the study population characteristics, and the allowed time-windows for the Octreotide LAR injections.
  - Clarified discontinuation criteria for individual patients.
  - Further options for additional allowed amino acid solutions, details on the drug administration procedures in the control arm, details about the administration procedures of rescue medication, and details about the handling of study medication were added.
  - Further details on SAE and AESI reporting were included.

- September 23, 2013:
  - Added details on the dosimetry sub-study procedures related to the performance of optional dosimetry.
  - Increased the number of sites participating in the sub-study was increased.

- March 25, 2014:
  - Adjusted sample size and increased follow-up period from 3 to 5 years to detect a statistically significant and clinically relevant difference in OS.
  - Specified that the primary analysis to be conducted after 74 PFS events.
  - Added secondary endpoints: Duration of Response (DoR) and Time to Second Progression (PFS2) as exploratory objectives.
  - Specified that the End of Study (EOS) is when 158 deaths have occurred, or 5 years have elapsed since the date of randomization of the last randomized patient, whichever occurs first.
  - Added specifications regarding the use of an unstratified log-rank test in the primary analysis of PFS.
  - Added details on Dose Modifying Toxicity criteria and procedures.
  - Modified the substudy exclusion criteria regarding subsequent treatments.
  - Added additional criteria for discontinuation related to screening failures, study termination, and study withdrawal.
  - Added description of handling discrepancies in the evaluation of the progressive status between investigator and central assessor.
  - Clarified procedures for dropouts, replacements and deliberate treatment interruption criteria.
  - Added recommendations regarding the amino acids solution infusion and regarding the use of antiemetics.
  - For patients on the sub-study, additional information and clarifications included ECG assessments, physical examination and vital signs data collection procedures, timing of the exams in relation to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate treatments, dosimetry, PK and cardiac assessments.

- June 5, 2014:

- Specified recruitment, randomization, and data analyses details for the sub-study.

7.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated in the NDA CSR for NETTER-1 that the study was conducted in accordance with:

1. The principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and subsequent amendments,
2. The International Conference on Harmonisation, Good Clinical Practice (ICH GCP guidelines E6, 1996),
3. The FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50, 54, 56, 312, and
4. The Data Protection Act 1998, the 18th World Medical Assembly, Helsinki 1964 and later revisions.

The Applicant also states that in compliance with local laws, the investigational centers initiated the study procedures after approval has been obtained from the Radioprotection Agencies, Competent Authorities and the Ethical Committee.

Financial Disclosure

The Applicant submitted PDFs of Statement of Financial Interests for Investigators (NDA Module 1.3.4) to the NDA on March 31, 2016. There was no summary of the financial interests or arrangements provided, and each form was reviewed for disclosures. A request for missing documentation and clarifying information was sent to the Applicant on June 9, 2016. The Applicant submitted responses to the information request on June 16, 2016 and July 1, 2016. The Applicant did not identify any sub-investigators or principal investigators who participated and completed their respective "Statement on Financial Interests" form as having a financial arrangement as defined in 21 CFR 54.2(a), a proprietary interest in the product or significant equity interest in the covered studies as defined in 21 CFR 54.2(b) or as the recipient of significant payments as defined in 21 CFR 54.2(f).

Patient Disposition

According to the CSR for NETTER-1, at the cut-off date for the primary endpoint analysis (July 24, 2015) 341 patients had been screened at 41 centers, with a total of 229 patients randomized across 27 European sites and 14 U.S. sites. Eighty-seven (87) patients who were screen failures and an additional twenty-five (25 patients) who consented to the sub-study were excluded from the Full Analysis Set (FAS). FDA reviewers were not able to confirm patient disposition as described by the Applicant in the CSR, due to the data deficiencies described above.

Protocol Violations/Deviations

Due to the data deficiencies, FDA reviewers were not able to evaluate the protocol violations/deviations as described in the CSR. FDA's analysis results are not included in this section.

Demographic Characteristics

Due to study data deficiencies, FDA reviewers were not able to confirm the demographic results as described in the CSR. FDA's analysis results are not included in this section.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Due to study data deficiencies, FDA reviewers were not able to confirm the important concomitant drugs results as described in the CSR. FDA's analysis results are not included in this section. Note that results for important disease characteristics (e.g. disease stage) and stratification factors per IVRS database and/or aCRF were not included in the CSR.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Due to study data deficiencies, FDA reviewers were not able to confirm related results as reported in the CSR. FDA's analysis results are not included in this section.

Efficacy Results – Primary Endpoint

Per CSR, the experimental arm demonstrated an improvement in PFS compared with control arm based on 74 IRC confirmed PFS events in the ITT population. The un-stratified log-rank test P value was reported to be less than 0.0001. The median PFS was not reached for the experimental arm and 8.4 months (95% CI: 5.8, 9.1) for the control arm. The corresponding un-stratified HR was reported as 0.21 (95% CI: 0.13, 0.33) in the experimental arm compared to the control arm. The estimated HRs for sensitivity analyses using different censoring methods (see Efficacy Analysis Methods for PFS for details) range from 0.12 to 0.57.

Due to study data deficiencies, FDA reviewers were not able to verify these results as reported in the CSR. FDA's analysis results are not included in this section.

Efficacy Results – ORR

Per CSR, the ORRs were 18% (95% CI: 10.4%, 25.3%) and 3% (95% CI: 0%, 6.3%) in the experimental arm and control arm respectively. The Fisher exact test p value was 0.0008. Note that CSR reported ORR results were on a subpopulation of ITT which included patients with non-missing central response.

Due to study data deficiencies, FDA reviewers were not able to verify results as reported in the CSR. FDA's analysis results are not included in this section. FDA recommends that ORR analysis include confirmed ORR per IRC assessment at least 4 weeks apart on the ITT population.

Efficacy Results – OS

Per CSR, the experimental arm did not demonstrate an improvement in OS compared with control arm based on 40 OS events (experimental arm: 14, control arm: 26) on the ITT population, which were immature at the clinical data cut-off. The un-stratified log-rank test P value of 0.0043 was greater than pre-planned two sided significance level of 0.0085% at OS interim analysis. The median OS was not reached for both arms. The corresponding un-stratified HR was 0.40 (95% CI: 0.21, 0.77) in the experimental arm compared to the control arm.

Due to study data deficiencies, FDA reviewers were not able to verify these results as reported in the CSR. FDA's analysis results are not included in this section.

Additional Analyses Conducted on the Individual Trial

AAA amended efficacy results for PFS and OS across subgroups defined by gender, race, age (>= 65 vs. <65), and geographic region (US vs. non-US) under SN21.

Due to study data deficiencies, FDA reviewers were not able to verify results as reported in the CSR. FDA's analysis results are not included in this section. AAA should include subgroup efficacy analyses by important baseline disease characteristics and stratification factors.

7.3. Review of Safety

FDA intended to focus the clinical review of the safety of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in patients with GEP-NETs on the evaluation of the data from the NETTER-1 and EMC studies. Due to the data and dataset deficiencies described, FDA was not able to conduct a review of the safety data, or confirm the safety findings as described by the Applicant in the CSR; therefore, FDA analysis of safety is not included in this section.

7.3.1. Safety Review Approach

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the safety findings as reported by the Applicant; therefore, FDA analysis of safety is not included in this section.

Overall Exposure

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm exposure data as reported by the Applicant; therefore, FDA analysis of exposure is not included in this section.

Relevant characteristics of the safety population:

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the relevant characteristics of the safety population as reported by the Applicant; therefore, FDA analysis of the characteristics of the safety population is not included in this section.

Adequacy of the safety database:

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the adequacy of the safety database; therefore, FDA analysis of the adequacy of the safety database is not included in this section.

7.3.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Please refer to Section 7.2.1 under "Data and Analysis Quality."

Categorization of Adverse Events

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the categorization of adverse events as reported by the Applicant; therefore, FDA analysis of the categorization of adverse events is not included in this section.

Routine Clinical Tests

According to the NETTER-1 protocol, laboratory assessments included the following: hematology, blood chemistry and urinalysis. Assessments were performed at screening and throughout the study as follows:

- ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate arm:
  - Within 2 weeks before and 4±1 weeks after each dose.
  - 2nd, 3rd, 4th dose required additional laboratory assessment performed within one day of study drug administration.
  - Every 12±1 weeks thereafter.

- 60 mg Octreotide LAR arm: 4 weeks after the first treatment and every 12±1 weeks thereafter.

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the results of routine clinical tests performed as reported by the Applicant; therefore, FDA analysis of clinical tests is not included in this section.

7.3.3. Safety Results

Deaths

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the information for patient deaths as reported by the Applicant; therefore, FDA analysis of deaths is not included in this section.

Serious Adverse Events

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm serious adverse events as reported by the Applicant; therefore, FDA analysis of serious adverse events is not included in this section.

Dropouts and/or Discontinuations Due to Adverse Effects

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the patient dropouts or discontinuations due to adverse effects as reported by the Applicant; therefore, FDA analysis of patient dropouts and discontinuation due to adverse effects is not included in this section.

Significant Adverse Events

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the significant adverse events as reported by the Applicant; therefore, FDA analysis of significant adverse events is not included in this section.

Treatment Emergent Adverse Events and Adverse Reactions

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm treatment emergent adverse events and adverse reactions as reported by the Applicant; therefore, FDA analysis of treatment emergent adverse events and adverse reactions is not included in this section.

Laboratory Findings

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm the laboratory findings as reported by the Applicant; therefore, FDA analysis of laboratory findings is not included in this section.

Vital Signs

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm vital signs as reported by the Applicant; therefore, FDA analysis of vital signs is not included in this section.

Electrocardiograms (ECGs)

The NETTER-1 study protocol specified that ECGs were performed at baseline, immediately after each ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion or before each Octreotide LAR injection, and at the end of study.

QT

Due to the data and dataset deficiencies described, FDA was not able to evaluate the review of QT assessment as reported by the Applicant; therefore, FDA analysis of QT assessment is not included in this section.

Immunogenicity

Immunogenicity was not evaluated in the NETTER-1 study.

7.3.4. Analysis of Submission-Specific Safety Issues

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm information for specific safety issues such as renal toxicity and bone marrow toxicity; therefore, FDA analysis of submission-specific safety issues is not included in this section.

7.3.5. Safety Analyses by Demographic Subgroups

Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm safety findings by demographic subgroups; therefore, FDA safety analysis by demographic subgroups is not included in this section.

7.3.6. Specific Safety Studies/Clinical Trials

The NETTER-1 sub-study was conducted to evaluate whole body and organ radiation dosimetry of patients receiving ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and the significance of reaching dosimetry limits to critical organs, specifically the kidney BED of 38 Gy and the red marrow absorbed dose of 3.7 Gy. Due to the data and dataset deficiencies described, FDA was not able to review, verify or confirm reported dosimetry findings.

7.3.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies have been performed to assess the potential of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for carcinogenicity.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in pediatric patients has not been

established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Due to the deficiencies of the data and datasets described above, FDA was not able to assess whether there were cases of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate overdose.

7.3.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Expectations on Safety in the Postmarket Setting

At this time, a recommendation cannot be made regarding postmarking requirements for safety related concerns with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

7.3.9. Integrated Assessment of Safety

Due to the data and dataset deficiencies described, FDA was not able to conduct an integrated assessment of safety based on data from all studies submitted to the NDA; therefore, FDA's integrated assessment of safety is not included in this section.

SUMMARY AND CONCLUSIONS

7.4. Statistical Issues

FDA has determined that datasets contained in the electronic submissions failed to be in a format that FDA can process, review, and archive. Furthermore, FDA has determined that the study data could not provide sufficient information to understand the provenance of the data.

7.5. Conclusions and Recommendations

With numerous data errors, missing essential information, and inadequate documentation, the clinical and statistical review teams could not process and review the submitted study data. Thus, we do not recommend approval for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at this moment.

X X

Primary Statistical Reviewer: Huanyu Chen Statistical Team Leader: Kun He

X X

Primary Clinical Reviewer: Joohee Sul Clinical Team Leader: Suzanne Demko

8 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this NDA. The Division plans to obtain the advice of two oncologists with experience in diagnosing and treating patients with NETs, and a patient advocate with an interest in NETS.

9 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with this NDA. This NDA is exempt from the requirement to assess the safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.

10 Labeling Recommendations

10.1. Prescribing Information

FDA comments on format and compliance with PLR, PLLR and applicable labeling guidance were communicated in the Filing Communication letter issued on June 23, 2016.

10.2. Patient Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

At this time, FDA is not able to comment on whether there are safety issues that warrant consideration of a REMS.

11.2. Conditions of Use to Address Safety Issue(s)

At this time, FDA is not able to comment on the conditions of use to address safety issues.

11.3. Recommendations on REMS

At this time, FDA is not able to comment on whether a risk evaluation and mitigation strategy is recommended.

12 Postmarketing Requirements and Commitments

At this time, FDA is not able to comment on recommendations for any postmarketing requirements or postmarketing commitments.

13 Appendices

13.1. References

1. Yao, J. C., M. Hassan, A. Phan, C. Dagohoy, C. Leary, J. E. Mares, E. K. Abdalla, J. B. Fleming, J. N. Vauthey, A. Rashid and D. B. Evans (2008). "One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States." J Clin Oncol 26(18): 3063-3072.
2. Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. Lyon: IARC Press; 2010
3. Rindi, G., G. Kloppel, H. Alhman, M. Caplin, A. Couvelard, W. W. de Herder, B. Erikssson, A. Falchetti, M. Falconi, P. Komminoth, M. Korner, J. M. Lopes, A. M. McNicol, O. Nilsson, A. Perren, A. Scarpa, J. Y. Scoazec, B. Wiedenmann, p. all other Frascati Consensus Conference and S. European Neuroendocrine Tumor (2006). "TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system." Virchows Arch 449(4): 395-401.
4. Rindi, G., G. Kloppel, A. Couvelard, P. Komminoth, M. Korner, J. M. Lopes, A. M. McNicol, O. Nilsson, A. Perren, A. Scarpa, J. Y. Scoazec and B. Wiedenmann (2007). "TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system."
5. Storsberg J, Gardner N, Kvols L. Survival and prognostic factor analysis in patients with metastatic pancreatic endocrine carcinomas. Pancreas. 2009; 38:255-8.
6. Ter-Minassian M, Chan JA, Hooshmand SM, et al. Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. Endocrine-related cancer 2013;20:187-96.
7. Hobday, T. J., J. Rubin, K. Holen, J. Picus, R. Donehower, R. Marschke, W. Maples, R. Lloyd, M. Mahoney, and C. Erlichman. "MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study." In ASCO Annual Meeting Proceedings, vol. 25, no. 18_suppl, p. 4504. 2007.
8. Phan, A. T., J. C. Yao, D. R. Fogelman, K. R. Hess, C. S. Ng, S. A. Bullock, P. Malinowski, E. Regan, and M. Kulke. "A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC)." In ASCO Annual Meeting Proceedings, vol. 28, no. 15_suppl, p. 4001. 2010.
9. Robins JM, Tsiatis AA Correcting For Non-Compliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Commun. Statist.-Theory Meth. 1991;20(8):2609-2631.
10. FDA Mapp 6025.4 available at http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm370948.htm

11. FDA *Data Standards Catalog* available at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
12. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.
13. FDA Guidance for Industry: *Providing Regulatory Submissions In Electronic Format — Standardized Study Data* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334
14. FDA Guidance for Industry: *Study Data Technical Conformance Guide: Technical Specifications Document*, available at http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
15. FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf
16. Reubi JC, JC Schär, B Waser, S Wenger, A Heppeler, JS Schmitt, and HR Mäcke, 2000, Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use, Eur J Nucl Med, 27(3):273-82.
17. Rollerman EJ, EP Krenning, BF Bernard, M de Visser, M Bijster, TJ Visser, M Vermeij, J Lindemans, and M deJong, 2007. Long-term toxicity of [177Lu-DOTAO, Tyr3] octreotate in rats, Eur J Nucl Med Mol Imag, 34(2):219-27.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): NETTER-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 357		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

14 Division Director (DHOT)

X

John Leighton

15 Division Director (OCP)

X

Nam Atiqur Rahman

16 Division Director (OB)

X

Rajeshwari Sridhara

17 Division Director (Clinical)

I concur with the review teams' recommendation to issue a complete response letter for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (per 21 CFR 314.110). FDA clinical, statistical, and clinical pharmacology reviewers were unable to confirm or assess the clinical effects of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate because the datasets were not sufficiently executable for review and because certain datasets contained missing variables, data (e.g., unique subject ID numbers, tumor measurements, laboratory values, exposure data) or inconsistencies. Certain data elements also did not correspond to values in the CRFs or contained apparent errors (e.g., laboratory test values); therefore, the datasets cannot be considered accurate and complete as described in 21 CFR 11.10(b). As such, the complete response letter will be sent based on the reason described in 21 CFR 314.125(b)(4): *There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling*.

Furthermore, I concur with the review teams' recommendation to issue a complete response letter for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate based on objectionable conditions observed during inspections of manufacturing facilities in Italy and the Netherlands. The complete response action is based on the reason described in 21 CFR 314.125(b)(1): *The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.*

21 CFR 314.110 states that if FDA determines, after an application is filed or an abbreviated application is received, that the data submitted are inadequate to support approval, the Agency might issue a complete response letter without first conducting required inspections and/or reviewing proposed product labeling. FDA review staff did not complete review of product labeling because the data could not be confirmed; however, FDA completed required inspections necessary to take action on this application.

If the Applicant's results are confirmed following resubmission, I believe that this application is potentially approvable if FDA reviewers concur that a statistically significant and clinically meaningful effect on progression free survival has been demonstrated and this effect is supported by an overall favorable risk-benefit determination.

AAA publically stated (http://www.adacap.com/wp-content/uploads/2016/11/2016-11-28-PR-AAA-3Q16-Financials-ENG-FINAL.pdf) that they are planning to extend the expanded access program in the United States in order to facilitate access to ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate prior to resolving the deficiencies in the complete response letter. This will include opening new centers in the U.S. In the interim, to facilitate AAA's ability to take corrective actions in regards

to the datasets, FDA issued a multidisciplinary Discipline Review Letter (clinical, statistical, and clinical pharmacology) on November 21, 2016, prior to taking action on the application.

X

Steven Lemery

18 Office Director (or designated signatory authority): Richard Pazdur

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/s/

SUSAN B TRUITT
12/15/2016

M A GOHEER
12/15/2016

JOHN K LEIGHTON on behalf of WHITNEY S HELMS
12/15/2016

BRIAN D FURMANSKI
12/15/2016

HONG ZHAO
12/15/2016
I concur.

JOOHEE SUL
12/15/2016

HUANYU CHEN
12/15/2016

KUN HE
12/15/2016

SUZANNE G DEMKO
12/16/2016

JOHN K LEIGHTON
12/16/2016

NAM ATIQUR RAHMAN
12/16/2016

RAJESHWARI SRIDHARA

12/16/2016

STEVEN J LEMERY
12/16/2016

RICHARD PAZDUR
12/19/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translation Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES- MEMO

NDA:	208,700
Drug Name:	LUTATHERA ® (177Lu-DOTA0-Tyr3-Octreotate)
Indication:	Somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors including foregut, midgut and hindgut, neuroendocrine tumors
Applicant:	Advanced Accelerator Applications USA, Inc.
Receipt Date:	March 31, 2016
PDUFA Goal Date:	December 28, 2016
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Primary Reviewers:	Huanyu (Jade) Chen, Ph.D.
Concurring Reviewers:	Kun He, Ph.D., Statistical Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Biologic Oncology Products 2
Clinical Team:	Joohee Sul, M.D., M.D., Clinical Reviewer
	Suzanne Demko, PA-C, Clinical Review Team Leader
	Patricia Keegan, M.D., Division Director
Project Manager:	Susan Truitt, R.N., M.S.

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, this NDA is not recommended to support approval at this moment.

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/s/

HUANYU CHEN
11/18/2016

KUN HE
11/18/2016

RAJESHWARI SRIDHARA
11/22/2016

Office of Clinical Pharmacology Memo

NDA	208700
Link to EDR	\\CDSESUB1\evsprod\NDA208700
Submission Date	March 31, 2016; April 18, 2016; April 28, 2016; October 18, 2016; October 19, 2016
Submission Type	NME (Priority)
Brand Name	LUTATHERA
Generic Name	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
Dosage Form and Strength	7.4 GBq every 8 weeks for four doses
Route of Administration	Intravenous infusion over 30 minutes
Proposed Indication	Treatment of adult patients with (b) (4) somatostatin receptor positive, neuroendocrine (b) (4) tumors of the midgut (b) (4)
Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Associated INDs	077219
OCP Review Team	Brian D. Furmanski, Ph.D., Hong Zhao Ph.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. The application is materially incomplete in that the datasets provided in the NDA are inaccurate, incomplete, and inconsistent across databases. Thus, FDA cannot verify the information provided in the clinical study reports nor verify data proposed in the product labeling. The decision is made to issue a Complete Response Letter listing the identified deficiencies for the applicant to address.

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/s/

BRIAN D FURMANSKI
11/21/2016

HONG ZHAO
11/21/2016
I concur.

NAM ATIQUR RAHMAN
11/21/2016
I agree with Team's recommendation.

MEMORANDUM

Date: November 14, 2016
From: M. Anwar Goheer, PhD
Pharmacology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
Through: Whitney S. Helms, Ph.D.
Supervisory Toxicologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA #208700
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (LUTATHERA)
Re: Approvability of Pharmacology and Toxicology

Advanced Accelerator Applications USA submitted NDA 208700 for 177Lu-DOTA-Tyr-Octreotate (Lutathera) for the treatment of patients with (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut and hindgut (neuroendocrine tumors (b) (4)). Lutathera is a radiolabeled somatostatin analogue. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

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/s/

M A GOHEER
11/14/2016

WHITNEY S HELMS
11/14/2016

JOHN K LEIGHTON
11/14/2016