CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208547Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 208547
Submission date: 7/1/15
Drug: ^{68}Ga dotatate
Sponsor: Advanced Accelerator Applications USA, Inc.
Indication: PET imaging of (b) (4) neuroendocrine tumors

Reviewing Division: Division of Medical Imaging Products

Background Comments:
The pharmacology/toxicology reviewer and team leader in the Division of Medical Imaging Products reviewed the nonclinical information for ^{68}Ga dotatate and found it adequate to support approval from a pharmacology/toxicology perspective for the indication listed above.

Carcinogenicity studies have not been conducted with ^{68}Ga dotatate. This is acceptable because the product is an imaging agent that is used acutely.

Developmental and reproductive toxicity studies have not been conducted with ^{68}Ga dotatate. Radiopharmaceuticals such as ^{68}Ga dotatate have the potential to cause fetal harm and the labeling will reflect that potential.

An appropriate established pharmacologic class for ^{68}Ga dotatate would be "radioactive diagnostic agent."

Conclusions:
I concur with the Division pharmacology/toxicology recommendation that this NDA can be approved. I have provided labeling comments separately.

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/s/

PAUL C BROWN
05/26/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208547
Supporting document/s:	001
Applicant's letter date:	July 1, 2015
CDER stamp date:	July 1, 2015
Product:	Kit for the preparation of ^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotate (aka ^{68}Ga-DOTATATE)
Indication:	001
Applicant:	Advanced Accelerator Applications USA, Inc. New York, NY
Review Division:	Medical Imaging
Reviewer:	Ronald Honchel, Ph.D.
Supervisor/Team Leader:	Adebayo Laniyonu, Ph.D.
Division Director:	Libero Marzella, M.D., Ph.D.
Project Manager:	Modupe Fagbami

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Over 80 percent of neuroendocrine tumors (NETs) express somatostatin receptor 2. The Indium-111 labeled somatostatin analogue OctreoScan is currently approved for the SPECT localization of tumors expressing somatostatin receptor. DOTATATE is a somatostatin analogue with a peptide structure similar to OctreoScan. PET/CT imaging of NETs with 68Ga-DOTATATE has many advantages over SPECT imaging with 111In-OctreoScan that include significantly improved imagining resolution, more accurate quantification of radiotracer uptake, lower radiation dose and shorter imaging time. The Sponsor is seeking the approval of their kit for the preparation of ^{68}Ga-DOTATATE as a radioactive diagnostic agent for (b) (4) NETs.

1.2 Brief Discussion of Nonclinical Findings

Many nonclinical studies were performed using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE. Since the only difference was the radiolabeled used, nonclinical data obtained using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE is applicable for evaluating 68Ga-DOTATATE. The IC50 of DOTATATE for somatostatin sst2 receptor was determined *in vitro* to be 0.98 nM using membranes prepared from CA20948 tumors. There were no drug-related effects on Irwin scores or body temperatures at doses up to 20 mg/kg ^{175}Lu-DOTATATE (~4800-fold safety factor based on the HED) in a rat neuro safety pharmacology study. ^{175}Lu-DOTATATE induced increased mean, systolic, and diastolic arterial blood pressures with associated bradycardia at all dose levels (40-800 µg/kg) in a dog cardiovascular safety pharmacology study. Blood pressure was never increased, and heart rate never decreased, by more than 22% and changes were not clearly dose related. There were no drug-related effects on body temperatures and EKG. ^{175}Lu-DOTATATE (100 µM) did not induce a significant reduction in hERG current in the hERG assay. ^{175}Lu-DOTATATE induced a respiratory stimulatory effect at the 20 mg/kg dose in a rat respiratory safety pharmacology study. A less pronounced effect and fewer respiratory parameters were affected at the 5 mg/kg dose level. There were no drug-related effects on respiratory parameters observed at the 1.25 mg/kg dose level (~300-fold safety factor based on the HED). In a pivotal toxicity study, rats were administered via intravenous injection 0 (vehicle), 1.25, 5.0, or 20 mg/kg ^{175}Lu-DOTATATE every 2 weeks for 42 days. An increased incidence in pancreatic acinar apoptosis was observed in the high dose treatment groups that had not completely reversed by the end of the recovery period. There were no other drug-related adverse effects observed in this study. The NOAEL was 5.0 mg/kg (~1200-fold safety factor based on the HED). In the other pivotal toxicity study, dogs were administered via intravenous injection 0 (vehicle), 80, 500, or 3200 µg/kg ^{175}Lu-DOTATATE once every 2 weeks for 43 days. There were no drug-related adverse effects observed in this study (~2600-fold safety factor based on the HED). ^{175}Lu-DOTATATE was not mutagenic in the Ames assay or the L5178Y TK$^{+/-}$ Mouse Lymphoma Cell assay.

1.3 Recommendations

1.3.1 Approvability

The drug is approvable from a nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Sponsor's Proposed Version:

8.1 Pregnancy

(b) (4)

Animal reproduction studies have not been conducted with (b) (4)

(b) (4)

Recommended Version:

8.1 Pregnancy

(b) (4) Animal reproduction studies have not been conducted with ^{68}Ga-DOTATATE. All radiopharmaceutical, including ^{68}Ga-DOTATATE, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the magnitude of the radiopharmaceutical dose. Assess pregnancy status before administering ^{68}Ga-DOTATATE to a female of child bearing potential. (b) (4) .

Sponsor's Proposed Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No (b) (4) animal studies on fertility, embryology, mutagenic potential, or carcinogenic potential have been conducted with ^{68}Ga-DOTATATE. However, genotoxicity studies conducted with a very similar molecule (mixture ^{175}Lu-DOTA (b) (4) (b) (4)) shows that these non-radioactive compounds do not induce mutation at the TK locus of L5178Y mouse lymphoma cells in vitro, nor reverse mutation in *Salmonella typhimurium*, or *Escherichia coli* (both in the absence or presence of S9 metabolic activation).

(b) (4)

(b) (4)

Recommended Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies have not been performed to evaluate the carcinogenic potential of ^{68}Ga-DOTATATE. A very similar molecule (mixture ^{175}Lu-DOTATATE/DOTATATE) was shown not to be mutagenic in the Ames assay and the L5178Y mouse lymphoma assay; however, any radiopharmaceutical including ^{68}Ga-DOTATATE has the potential to be mutagenic. The effect of ^{68}Ga-DOTATATE on fertility has not been evaluated.

2 Drug Information

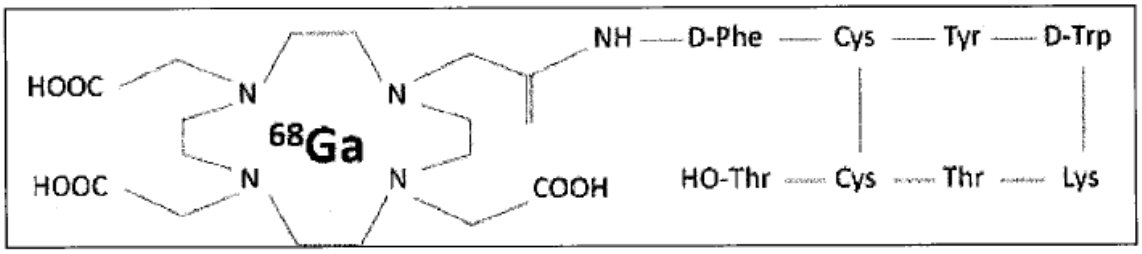
2.1 Drug

CAS Registry Number: 177943-89-4

Code Name: ^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotate (aka ^{68}Ga-DOTATATE)

Molecular Formula/Molecular Weight: 1435.6/$C_{65}H_{99}GaN_{14}O_{19}S_2$

Structure or Biochemical Description



Pharmacologic Class: Radioactive Diagnostic Agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77219 and PIND 122818 were cross-referenced.

2.3 Drug Formulation

Table 3. Composition of the final ^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotate for injection solution

	^{68}Ge/^{68}Ga generator elution conditions	
	Column 1: 5 ml of HCl 0.1 N (e.g. E&Z generator)	(b) (4)
Component	**Final composition**	
DOTA^{0}-Tyr^{3}-Octreotate (mass)	**40 µg**	(b) (4)
^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotate (radioactivity)	1110 MBq	
^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotate (mass)	(b) (4)	
Volume	(b) (4)	
Specific Activity (GBq/Total peptide)	(b) (4)	
Radioconcentration	(b) (4)	
Other Excipients	mg/vial	
1,10-phenanthroline	**0.005**	
Gentisic acid	**0.006**	
Mannitol	20	
Formic Acid	(b) (4)	
Sodium Hydroxide	(b) (4)	
Hydrochloric acid	(b) (4)	
Water for Injection	-	

2.4 Comments on Novel Excipients

There were no novel excipients identified at the time of this review.

2.5 Comments on Impurities/Degradants of Concern

There were no impurities or degradants of concern identified at the time of this review.

2.6 Proposed Clinical Population and Dosing Regimen

Diagnostic for (b) (4) neuroendocrine tumors (b) (4) NETs). The drug will be administered once via intravenous injection followed by PET/CT imaging. The mass dose to be administered is no more than 40 µg and the radiation dose is 0.054 mCi/kg.

2.7 Regulatory Background

Although not approved in the U.S., ^{68}Ga-DOTATATE has been administered to hundreds of patients in Europe. The Sponsor cross-referenced IND 77219. Many of the nonclinical studies evaluated under IND 77219 were performed using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE. Since the only difference is the radiolabel used, we previously agreed that nonclinical data obtained using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE is applicable for evaluating ^{68}Ga-DOTATATE.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Determination of binding affinity of somatostatin analogs using membranes prepared from CA20948 tumors.

Safety Pharmacology

^{175}Lu-DOTATATE: Behavioral Irwin test and effect on body temperature following single intravenous administration in the rat. Study # 20100186PGRP

^{175}Lu-DOTATATE: Evaluation of effects on blood pressure, heart rate, electrocardiogram and body temperature after single intravenous administration to conscious dogs. Study # 20100183PCCP

^{175}Lu-DOTATATE: Evaluation of effects on hERG current in stably transfected HEK-293 cells. Study # 20100184PEHPPB

^{175}Lu-DOTATATE: Evaluation of effects on respiration in the unrestrained conscious rat following single intravenous administration. Study # 20100185PCRP

Pharmacokinetics/ADME

Biodistribution of ^{177}Lu-DOTATATE in normal Sprague Dawley rats. Study # not stated.

Measurement of ^{175}Lu-DOTATATE unbound fraction in dog, rat, and human plasma. Study # not stated.

^{68}Ga-DOTATATE biodistribution in CD-1 healthy mice. Study # CEIP 039

^{68}Ga-DOTATOC biodistribution/imaging in rat pancreatic AR42J cancer model in mice. Study # CEIP 045

Toxicology

^{175}Lu-DOTATATE: 42-Day intravenous toxicity study in the rat by including recovery period and toxicokinetics. Study # 20100189TRP

^{175}Lu-DOTATATE: 42-Day intravenous toxicity study in the dog by including recovery period and toxicokinetics. Study # 20100182TCP

Genetic Toxicology

^{175}Lu-DOTATATE: Bacterial mutation assay. Study # 81900

^{175}Lu-DOTATATE: Mutation in L5178Y Mouse Lymphoma Cells. Study # 81910

3.2 Studies Not Reviewed

(b) (4)

3.3 Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

Determination of binding affinity of somatostatin analogs using membranes prepared from CA20948 tumors.

The IC50s for various somatostatin analogues was evaluated *in vitro* using membranes prepared from CA20948 tumors. Results are shown in the Sponsor's Table 1 below. DOTATATE exhibited the highest affinity of the ligand complexed derivatives. Cancer cell somatostatin receptor subtypes were not mentioned in the study report, but likely to be sst2.

TABLE 1

Compound	MP No.	IC50 (nM)	SE
Tyr3-octreotide	MP2249	0.48	0.03
OctreoScan (DTPA-octreotide)	MP1661	2.50	0.15
DTPA-tyr3-octreotate	MP2138	1.39	0.07
CMDTPA-tyr3-octreotate	MP2148	2.16	0.21
DOTA-tyr3-octreotate	MP2325	0.98	0.03

4.2 Secondary Pharmacology

Secondary pharmacology data was not submitted.

4.3 Safety Pharmacology

^{175}Lu-DOTATATE: Behavioral Irwin test and effect on body temperature following single intravenous administration in the rat. Study # 20100186PGRP

In this GLP study, male Wistar rats (n = 8/group) were scored by the Irwin assay and body temperatures collected. Rats were then administered via single intravenous injection 0 (vehicle), 1.25, 5.0, or 20 mg/kg ^{175}Lu-DOTATATE. A positive control group was administered 0.3 mg/kg clonidine. Irwin scores and body temperatures were recorded at 5, 30 min, 1, 2, and 4 hours after dosing. Clonidine produced the expected sedative, neurovegetative, myorelaxant, and hypothermic effects. There were no drug-related effects on Irwin scores or body temperatures observed in this study (~4800-fold safety factor based on the HED).

^{175}Lu-DOTATATE: Evaluation of effects on blood pressure, heart rate, electrocardiogram and body temperature after single intravenous administration to conscious dogs.

In part 1 of this GLP study, 8 telemeterized beagle dogs (4/sex) were administered via single bolus intravenous injection (2.5 mL/kg) 0 (vehicle), 80, 250, or 800 µg/kg ^{175}Lu-DOTATATE in a cross-over design with a minimum of 3 days between doses. Blood pressure, heart rate, body temperature, and EKG were recorded. ^{175}Lu-DOTATATE induced increased mean, systolic, and diastolic arterial blood pressures from 5 min through 6 hours after dosing with associated bradycardia. Blood pressure was never increased, and heart rate never decreased, by more than 22% and changes were not clearly dose related. There were no drug-related effects on body temperatures and EKG.

In part 2, the study was repeated with dogs administered via slow infusion (1.2 mL/min) intravenous injection of 0, 80, or 40 µg/kg ^{175}Lu-DOTATATE in a cross-over design with a minimum of 3 days between doses. ^{175}Lu-DOTATATE induced increased mean,

systolic, and diastolic arterial blood pressures for up to 6 hours after dosing at the 80 µg/kg dose level and for up to 4 hours after dosing at the 40 µg/kg dose level with associated bradycardia.

^{175}Lu-DOTATATE: Evaluation of effects on hERG current in stably transfected HEK-293 cells.

In this GLP study, HEK-293 cells stably transfected with hERG-1 cDNA were exposed to vehicle, then 100 µM ^{175}Lu-DOTATATE, and finally 100nM of positive control E-4031 and hERG current was monitored. ^{175}Lu-DOTATATE induced a maximum 19% decrease in hERG current compared to vehicle control values. E-4031 induced a further 91% inhibition of hERG current. Thus, ^{175}Lu-DOTATATE was considered negative for the hERG assay.

^{175}Lu-DOTATATE: Evaluation of effects on respiration in the unrestrained conscious rat following single intravenous administration.

In this GLP study, conscious male Wistar rats (n = 8/group) were administered via intravenous injection 0 (vehicle), 1.25, 5.0, or 20 mg/kg ^{175}Lu-DOTATATE. A positive control group was administered 0.3 mg/kg carbamlycholine chloride. Respiratory rate, peak inspiratory and peak expiratory flows, inspiration and expiration times, airway resistance index, tidal volume and minute volume were then evaluated using whole body plethysmography for 4 hours following dosing. Carbamylcholine chloride produced the expected bronchoconstrictor effect that included increases in peak inspiratory and peak expiratory flows, tidal volume, minute volume, and airway resistance index and a decrease in expiration time. ^{175}Lu-DOTATATE induced a respiratory stimulatory effect at the 20 mg/kg dose level that included increases in respiratory rate, peak inspiratory and peak expiratory flows, and minute volume, and decreases in inspiration time and expiration time. Less pronounced effects were observed at the 5 mg/kg dose level that included an increase in peak inspiratory flow and a decrease in inspiration time. There were no drug related effects observed at the 1.25 mg/kg dose level (~300-fold safety factor based on the HED).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Biodistribution of ^{177}Lu-DOTATATE in normal Sprague Dawley rats.

Sprague Dawley rats (n = 24) were administered via intravenous injection 250 µCi ^{177}Lu-DOTATATE and were euthanized at 5, 20, 15, 30, 60, 120, and 240 min after dosing. Blood, kidney, muscle and pancreas were removed and radioactivity levels were determined and the results shown in the Sponsor's Table 1 below. Blood and muscle clearance of radioactivity was rapid. Kidney radioactivity levels were relatively high compared to blood levels. Although kidney radioactivity levels decreased between 10 min and 30 min after dosing, kidney radioactivity levels remained constant from 30

min on. The high radioactivity levels observed in the kidney was expected due to renal clearance. Rat pancreas is known to have high levels of somatostatin-2 receptors and pancreas radioactivity remained relatively high throughout the study.

Table I
Biological Clearance of [177Lu]-DOTA-Tyr3-Octreotate in Sprague-Dawley Rats

Time	Blood	SE	SD	Kidney	SE	SD	Muscle	SE	SD	Pancreas	SE	SD
5	0.729	0.016	0.028	3.771	0.505	0.874	0.142	0.012	0.021	7.847	0.712	1.234
10	0.593	0.053	0.091	3.838	0.630	1.091	0.117	0.009	0.015	9.265	0.719	1.245
15	0.485	0.031	0.053	2.889	0.163	0.283	0.098	0.005	0.009	7.426	0.200	0.347
30	0.190	0.013	0.023	1.986	0.087	0.150	0.048	0.002	0.004	12.054	0.517	0.896
45	0.126	0.010	0.018	1.955	0.028	0.049	0.031	0.002	0.003	11.901	1.737	3.009
60	0.057	0.006	0.010	1.670	0.143	0.248	0.017	0.002	0.004	12.901	0.414	0.718
120	0.015	0.001	0.002	1.742	0.077	0.133	0.008	0.001	0.002	12.679	0.483	0.836
240	0.003	0.001	0.001	1.619	0.093	0.161	0.005	0.001	0.001	10.611	0.449	0.778

Measurement of ^{175}Lu-DOTATATE unbound fraction in dog, rat, and human plasma.

Rat, dog or human plasma (diluted 1:1 with PBS) was spiked with 1000 or 300 ng/mL ^{175}Lu-DOTATATE and dialysis was performed for 5 hr at 37ºC. Samples were then analyzed by LC-MS/MS. Results are summarized in the Sponsor's Table 2 below. The highest fraction of unbound drug was observed in rat plasma dialyzed with 1000 ng/mL ^{175}Lu-DOTATATE and human plasma dialyzed with 300 ng/mL ^{175}Lu-DOTATATE. Otherwise, the unbound fraction was fairly constant at ~5-10%.

Table 2. Lu-DOTATATE percent unbound fraction in Rat, Dog and Human plasma (Mean ± SD)

	% of Lu-DOTATATE unbound fraction		
Test Item Concentration	**Rat**	**Dog**	**Human**
300 ng/mL	9.8 ± 5.4	5.3 ± 1.6	25.0 ± 3.0
1000 ng/mL	26.8 ± 3.3	6.4 ± 0.6	9.4 ± 1.5

^{68}Ga-DOTATATE biodistribution in CD-1 healthy mice.

Mice (n = 4/timepoint) were administered via intravenous injection 0.3 mCi ^{68}Ga-DOTATATE and euthanized 30 min and 1, 2, and 4 hours after dosing. Blood and various organs were collected and radioactivity levels determine using a gamma-counter. Results are summarized in the Sponsor's Table 1 below. Significant radioactivity was only seen in renal organs and the urine. This was expected due to renal being the primary route of excretion.

Table 1. Biodistribution of ^{68}Ga DOTATATE in healthy mice expressed as %ID/gram of organ or tissue and comparison with ^{67}GaDOTATATE published by Foridevaux[3].

	%ID/g (mean + SD)				
	30min	1h	2h	4h	^{67}GaDOTATATE
Blood	1.425 ± 0.360	0.531 ± 0.189	0.144 ± 0.036	0.053 ± 0.007	0.07 ± 0.01
Urine	260.410 ± 132.761	98.903 ± 67.347	293.797 ± 152.904	17.729 ± 8.713	
Kidneys (x2)	8.085 ± 1.623	8.038 ± 1.534	6.230 ± 1.046	6.212 ± 1.566	4.25 ± 0.30
Adrenals (x2)	0.952 ± 0.065	0.851 ± 0.358	0.698 ± 0.314	0.398 ± 0.152	5.97 ± 0.68
Spleen	0.419 ± 0.086	0.282 ± 0.136	0.173 ± 0.058	0.137 ± 0.056	1.26 ± 0.14
Bladder	74.805 ± 52.224	7.777 ± 3.121	21.743 ± 7.822	2.246 ± 1.250	
Heart	1.582 ± 1.630	0.417 ± 0.155	0.255 ± 0.225	0.057 ± 0.007	0.18 ± 0.01
Lungs (x2)	1.395 ± 0.522	0.986 ± 0.597	0.610 ± 0.156	0.443 ± 0.365	0.70 ± 0.13
Thyroid	1.123 ± 0.807	0.552 ± 0.192	0.704 ± 0.540	0.017 ± 0.015	
Tail	2.009 ± 0.565	0.946 ± 0.066	0.405 ± 0.081	0.290 ± 0.112	
Pancreas	1.761 ± 0.543	1.793 ± 0.796	1.127 ± 0.225	0.882 ± 0.271	10.30 ± 0.99
Stomach	1.762 ± 1.006	1.462 ± 0.496	1.187 ± 0.316	1.024 ± 0.362	6.02 ± 0.55
Small bowel	0.612 ± 0.092	0.592 ± 0.329	0.294 ± 0.092	0.253 ± 0.069	1.51 ± 0.07
Large bowel	0.912 ± 0.302	0.889 ± 0.525	0.521 ± 0.139	0.466 ± 0.154	
Muscle	0.499 ± 0.165	0.217 ± 0.043	0.101 ± 0.015	0.048 ± 0.019	0.08 ± 0.03
Bone	1.098 ± 0.279	0.636 ± 0.148	0.458 ± 0.148	0.374 ± 0.076	1.16 ± 0.21
Liver	0.453 ± 0.133	0.384 ± 0.115	0.248 ±0.037	0.170 ± 0.046	1.80 ± 0.05
Head	0.791 ± 0.110	0.405 ± 0.104	0.172 ± 0.034	0.125 ± 0.021	
Carcass	0.892 ± 0.098	0.489 ± 0.133	0.196 ± 0.033	0.152 ± 0.034	

^{68}Ga-DOTATOC biodistribution/imaging in rat pancreatic AR42J cancer model in mice.

Female nude mice with implanted AR42J tumors were administered via intravenous injection 0.3 mCi ^{68}Ga-DOTATOC (note – DOTATATE was not used) followed by whole body micro-PET imaging. The study conclusions were that ^{68}Ga-DOTATOC showed a very good lesion diagnostic performance.

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

The single dose toxicity studies submitted by the Sponsor were performed using too few animals with too few toxicity parameters evaluated to provide useful interpretation of drug-induced toxicity.

6.2 Repeat-Dose Toxicity

Study title: ^{175}Lu-DOTATATE: 42-Day intravenous toxicity study in the rat by including recovery period and toxicokinetics.

Study no.:	21000180TRP
Study report location:	At the testing facility.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 23, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	^{175}Lu-DOTATATE, FDOTA0501, % purity not stated

Key Study Findings

Rats were administered via intravenous injection 0 (vehicle), 1.25, 5.0, or 20 mg/kg ^{175}Lu-DOTATATE every 2 weeks for 42 days on Days 1, 14, 28, and 42. An increased incidence in pancreatic acinar apoptosis was observed in high dose treatment groups that had not completely reversed by the end of the recovery period. There were no other drug-related adverse effects observed in this study. The NOAEL was 5.0 mg/kg (~1200-fold safety factor based on the HED).

Methods

Doses:	0 (vehicle), 1.25, 5.0, or 20 mg/kg
Frequency of dosing:	Every 2 weeks on Days 1, 14, 28, and 42
Route of administration:	Intravenous
Dose volume:	5 mL/kg
Formulation/Vehicle:	Solution/Saline solution + 4.6% (v/v) acetate buffer
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	10/sex/group main study; 5/sex/group recovery (high dose and vehicle control only)
Age:	7 weeks old at initiation of dosing
Weight:	Males 208 to 261 g; Females 163 to 215 g
Satellite groups:	6/sex/group for TK with blood samples collected predose, 5, 20, 60, 120, and 180 min post dose on Days 1 and 42.
Unique study design:	An Irwin assay was performed and body temperatures were recorded. This is not the same behavioral study reported in the above safety pharmacology section.
Deviation from study protocol:	There was only one minor deviation reported that did not affect the overall quality of the study.

Observations and Results

Mortality

There were no unscheduled deaths.

Clinical Signs

Animals were observed at least once a day for clinical signs. There were no drug-related clinical signs noted.

Body Weights

Animals were weighed weekly. As seen in the Sponsor's Table 2.3 below, a significant reduction of body weight gain was observed in treated males compared to controls during the second part of the treatment period that was considered possibly related to decreased feed consumption. The body weight gain in the high dose male group remained lower than the male vehicle control group during the recovery period.

Table 2.3 Effect on body weight - Male (mean table)

Treatment		D-1	D7	D13	D21	D27	D35	D41	D49	D56	D63
Vehicle	Mean	238	287	325	364	388	412	432	443	460	478
	SEM	4	4	5	6	7	7	8	20	20	24
	%	NA	+21	+37	+53	+63	+73	+82	+86	+93	+101
	N	15	15	15	15	15	15	15	5	5	5
Lu-DOTATATE	Mean	227	267	300	330	347	361	379	NA	NA	NA
1250 µg/kg	SEM	4	5	5	6	7	12	10	NA	NA	NA
	%	NA	+18	+32	+45	+53	+59	+67	NA	NA	NA
	N	10	10	10	10	10	10	10	0	0	0
	P	NS	NS	NS	**	**	**	**	NA	NA	NA
Lu-DOTATATE	Mean	229	278	315	349	371	386	404	NA	NA	NA
5000 µg/kg	SEM	3	3	4	5	6	7	7	NA	NA	NA
	%	NA	+21	+38	+52	+62	+69	+76	NA	NA	NA
	N	10	10	10	10	10	10	10	0	0	0
	P	NS	NS	NS	NS	NS	*	**	NA	NA	NA
Lu-DOTATATE	Mean	240	283	315	346	368	386	403	419	439	456
20000 µg/kg	SEM	4	4	4	6	7	8	8	15	17	19
	%	NA	+18	+31	+44	+53	+61	+68	+75	+83	+90
	N	15	15	15	15	15	15	15	5	5	5
	P	NS	NS	NS	NS	*	**	**	NS	NS	NS
	Threshold	22	22	22	22	22	22	22	69	69	69

Results expressed in g
D: days
Vehicle: 0.9% NaCl + acetate buffer
NS:P>0.05, *:P≤0.05, **:P≤0.01,
Analysis of variance for repeated measurements with Dunnett's test
%: variation expressed in percentage in relation to predose values
NA: not applicable
Threshold: smallest difference being statistically significant (P ≤ 0.05) calculated from Dunnett's test
Electronic authentication : created by Stéphanie Ragon on 14-FEV-2011 at 09:12:50.587
Study 20100180TRP

Feed Consumption

Feed and water consumption was recorded weekly for each cage. Feed consumption tended to be decreased in male treatment groups relative to vehicle control, but feed consumption was measured by cage, thus the n was too low/group to do statistical evaluation. There were no obvious drug-related effects on water consumption.

Ophthalmoscopy

Ophthalmic examination was performed before dosing, on Day 42, and at the end of the recovery period. There were no drug-related ophthalmic findings noted.

Hematology

Blood samples for hematology parameter analyzes including PT and aPTT were collected on Day 43. There were no apparent drug-related effects on hematology parameters.

Clinical Chemistry

Blood samples for clinical chemistry parameter analyzes were collected on Day 43. There were no toxicologically significant drug-related changes in clinical chemistry parameters.

Urinalysis

Urine was collected from rats placed in metabolic cages over an approximately 16 hr period. Drug-related changes in urinalysis parameters were observed in treatment groups and included: 1) lower creatinine level in males dosed at 1250, 5000 and 20000 µg/kg (-14%, -15% and -28%, respectively) and females dosed at 20000 µg/kg (-25%); 2) lower sodium level in males dosed at 1250 and 5000 µg/kg (-41% and -56%, respectively); and 3) higher excreted volume in males and females dosed at 20000 µg/kg (+27% and +28%, respectively). No changes in urinalysis parameters were recorded during the reversibility period. The above changes were not severe enough to be considered adverse. There were no drug-related changes in urinalysis parameters in recovery groups.

Gross Pathology

Main study animals were euthanized on Day 43 and recovery animals were euthanized on Day 127 and full necropsies were performed. There were no drug-related macroscopic findings.

Organ Weights

Organ weights were collected on the tissues/organs shown in the Sponsor's Table below. Lower absolute mean weights were observed for liver (12%-20% lower in treatment groups compared to control) and kidney (11% to 17% lower in treatment groups compared to control) in males. These decreases in organ weights were of questionable toxicological significance since the decreases were not dose related and there were no significant differences in relative liver and kidney weights. There were no other apparent drug-related changes in organ weights observed in this study.

	C	W	H		C	W	H		C	W	H
DIGESTIVE SYSTEM:											
Salivary glands (a)	X		X	Tongue	X		X	Oesophagus	X		X
Stomach (b)	X		X	Pancreas	X		X	Duodenum	X		X
Liver	X	X	X	Jejunum (with Peyer's patches)	X		X	Ileum	X		X
Caecum	X		X	Colon	X		X	Rectum	X		X
Other											
CARDIOVASCULAR SYSTEM:											
Aorta	X		X	Heart	X	X	X				
RESPIRATORY SYSTEM:											
Trachea	X		X	Lung	X		X	Pharynx/larynx	X		X
UROGENITAL SYSTEM:											
Urinary bladder	X		X	Kidneys	X	X	X	Ureters	X		X
Uterus	X	X	X	Testes	X	X	X	Ovaries	X	X	X
Vagina	X		X	Prostate	X		X	Oviducts	X		X
Epididymides	X	X	X	Seminal vesicles	X		X	Preputial gland			
Others:											
HAEMOLYMPHATIC SYSTEM:											
Bonne marrow (Sternum)	X		X	Mesenteric Lymph nodes	X		X	Sub-maxillary lymph node	X	X	X
Thymus	X	X	X	Spleen	X	X	X	Popliteal lymph node		X	
Others:											
ENDOCRINE SYSTEM:											
Adrenals	X	X	X	Thyroids/Parathyroids	X	X	X	Pituitary	X	X	X
NERVOUS SYSTEM:											
Brain (c)	X	X	X	Spinal cord (3 levels)(d)	X		X	Peripheral nerves (Sciatic)	X		X
MUSCULO SKELETAL SYSTEM:											
Skeletal muscle	X		X	Femur (with joint)	X		X	Sternum	X		X
INTEGUMENTARY SYSTEM:											
Skin/subcutis	X		X	Mammary glands	X		X				
EYES AND ADNEXA:											
Optic nerves	X		X	Eyes	X		X	Harderian glands	X		X
MISCELLANEOUS:											
Gross lesions	X		X	Body exsanguinated		X		Injection site	X		X

Checked (X) collected (column C), weighed (column W) and examined for histopathology (column H for control and top dose animals as well as low and mid dose animals wich died prematurely or were sacrified moribund).
(a): Mandibular, parotid, sublingual.
(b): Histopathological examination of glandular and keratinised.
(c): Histopathological examination of brain, cerebrum (2 levels), cerebellum, brain stem.
(d): Cervical, thoracic, lumbar.

Histopathology

Adequate Battery: Yes.

Peer Review: Not stated.

Histological Findings

An increased incidence in pancreatic acinar apoptosis was observed in the high dose treatment groups. Minimum to moderate pancreatic acinar apoptosis was reported in 16 of 20 high dose animals at the end of treatment period compared to minimal apoptosis being observed in 2 of 20 vehicle control animals. Minimum to moderate pancreatic acinar apoptosis was reported in 3 of 10 high dose animals at the end of the recovery period compared to 0 of 10 control animals.

Special Evaluation

There were no clear drug-related effects on behavioral parameters or body temperatures.

Toxicokinetics

TK results are summarized in the Sponsor's Tables 4 & 5 below. Systemic exposure (AUC) increased in a dose-related manner. There were no gender-related effects on exposure. The AUCs observed on Day 42 were similar to those observed on Day 1.

Table 4: Toxicokinetic parameters Day 1

		Male			Female		
		Group 2	Group 3	Group 4	Group 2	Group 3	Group 4
Dose	*ug/kg*	1250	5000	20000	1250	5000	20000
C_{max}	*ng/mL*	1580.8	7028.6	27237.7	1359.3	6931.2	28434.8
t_{max}	*min*	5	5	5	5	5	5
λ_z	*1/min*	0.032211	0.027200	0.035562	0.032111	0.028433	0.034028
$T_{half\ life}$	*min*	21.5	25.5	19.5	21.6	24.4	20.4
AUC_{all}	*ng/mL*min*	45109.6	175137.1	588731.7	40170.0	189918.9	670288.5
C_{max}/Dose	*(ng/mL)/(ug/kg)*	1.26	1.41	1.36	1.09	1.39	1.42
AUC_{all}/Dose	*(ng/mL*min)/(ug/kg)*	36.1	35.0	29.4	32.1	38.0	33.5

Table 5: Toxicokinetic parameters Day 42

		Male			Female		
		Group 2	Group 3	Group 4	Group 2	Group 3	Group 4
Dose	*ug/kg*	1250	5000	20000	1250	5000	20000
C_{max}	*ng/mL*	2149.2	6975.0	26257.9	1863.6	6299.2	26631.7
t_{max}	*min*	5	5	5	5	5	5
λ_z	*1/min*	0.032742	0.034561	0.024405	0.033068	0.032301	0.021024
$T_{half\ life}$	*min*	21.2	20.1	28.4	21.0	21.5	33.0
AUC_{all}	*ng/mL*min*	59575.7	184100.1	687521.1	47260.2	164711.6	719279.4
C_{max}/Dose	*(ng/mL)/(ug/kg)*	1.72	1.40	1.31	1.49	1.26	1.33
AUC_{all}/Dose	*(ng/mL*min)/(ug/kg)*	47.7	36.8	34.4	37.8	32.9	36.0

Dosing Solution Analysis

Dosing formulations were analyzes via RP-HPLC with UV detection. The actual doses administered were within 10% of the nominal dose.

Study title: ^{175}Lu-DOTATATE: 42-Day intravenous toxicity study in the dog by including recovery period and toxicokinetics.

Study no.: 20100182TCP
Study report location: At the testing facility.
Conducting laboratory and location: (b) (4)
Date of study initiation:
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: ^{175}Lu-DOTATATE, Batch # FDOTA0501, % purity not stated.

Key Study Findings

Dogs were administered via intravenous injection 0 (vehicle), 80, 500, or 3200 µg/kg ^{175}Lu-DOTATATE once every 2 weeks (Days 1, 15, 29, and 43) for 43 days. There were no drug-related adverse effects observed in this study (~2600-fold safety factor based on the HED).

Methods

Doses:	0 (vehicle), 80, 500, or 3200 µg/kg
Frequency of dosing:	Single injections on Days 1, 15, 29, and 43
Route of administration:	Intravenous
Dose volume:	2.5 mL/kg
Formulation/Vehicle:	Solution/ Saline plus 1.4% (v/v) acetate buffer
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4/sex/group main study; 2/sex/group (high dose and vehicle control only) for recovery groups
Age:	6-7 months old
Weight:	Males 7.0 to 11.2 kg; Females 6.1-9.2 kg
Satellite groups:	None.
Unique study design:	Systolic blood pressure was measured prior to dosing and Days 43, 71, 99, and 127.
Deviation from study protocol:	There were only 2 minor deviations that did not affect the overall quality of the study.

Observations and Results

Mortality

A low dose female was found moribund and died on Day 5. The probable cause of death was determined to be pulmonary disease unrelated to drug administration. There were no other unscheduled deaths observed in this study.

Clinical Signs

Animals were observed once daily for clinical signs. Increased salivation, vocalization, or soft to liquid feces were observed during drug administration that was more marked in the highest dose group. These findings were transient and reversible and not severe enough to be considered adverse.

Body Weights

Animals were weighed weekly. There were no drug-related effects on body weights observed in this study.

Feed Consumption

Feed consumption was recorded daily. Feed consumption was slightly lower in the high dose groups that continued during the recovery period.

Ophthalmoscopy

Ophthalmic examinations were performed prior to dosing, on Day 43, and on Day 127. A mid-dose male showed inflammation of conjunctivae with sign of pain to light on Day

23. This finding was not considered drug-related due to only observed in 1 animals and lack of dose response. There were no other ophthalmic findings observed in this study.

ECG

ECGs were performed prior to dosing and Days 43, 71, 99, and 127. There were no drug-related effects on ECG parameters noted in this study.

Hematology

Blood samples for hematology parameter analyzes including PT and aPTT were collected prior to dosing and on Days 44, 72, 100, and 128. There were no significant drug-related effects on hematology parameters observed in this study.

Clinical Chemistry

Blood samples for clinical chemistry parameter analyzes were collected prior to dosing and on Days 44, 72, 100, and 128. There were no significant drug-related effects on clinical chemistry parameters observed in this study.

Urinalysis

Animals were placed in metabolism cages and urine collected for a 16 hr period prior to the end of the treatment period and on Days 72, 100, and 128. Drug-related changes in urinalysis parameters are shown below. Urinary parameters returned to baseline during the recovery period.

- a higher urinary volume excreted (+68%, +38% and +81% at 80, 500 and 3200 μg/kg, respectively), when compared to predose values
- a lower urinary osmolality (-35%, -33% and -51% at 80, 500 and 3200 μg/kg, respectively) and urinary creatinine level (-29%, -18% and -51%, respectively)
- a lower potassium concentration (-24% and -43% at 500 and 3200 μg/kg, respectively)

Gross Pathology

Main Study animals were euthanized on Day 44 and Recovery animals on Day 128 and full necropsies were performed. There were no drug-related macroscopic findings noted.

Organ Weights

Organ weights were collected on the tissues/organs shown in the Sponsor's Table below. There were no drug-related changes in organ weights observed in this study.

	C	W	H		C	W	H		C	W	H
DIGESTIVE SYSTEM:											
Salivary glands (a)	X		X	Tongue	X		X	Oesophagus	X		X
Stomach (b)	X		X	Pancreas	X		X	Duodenum	X		X
Liver	X	X	X	Jejunum (with Peyer's patches)	X		X	Ileum	X		X
Caecum	X		X	Colon	X		X	Rectum	X		X
Gall bladder	X	X	X								
CARDIOVASCULAR SYSTEM:											
Aorta	X		X	Heart	X	X	X				
RESPIRATORY SYSTEM:											
Trachea	X		X	Lung	X		X	Pharynx/larynx	X		X
UROGENITAL SYSTEM:											
Urinary bladder	X		X	Kidneys	X	X	X	Ureters	X		X
Uterus	X	X	X	Testes	X	X	X	Ovaries	X	X	X
Vagina	X		X	Prostate	X		X	Oviducts	X		X
Epididymides	X	X	X								
Others:											
HAEMOLYMPHATIC SYSTEM:											
Bonne marrow (Sternum)	X		X	Mesenteric Lymph nodes	X		X	Sub-maxillary lymph node	X		X
Thymus	X	X	X	Spleen	X	X	X	Popliteal lymph node		X	
Bone marrow smears (f)	X		X								
Others:											
ENDOCRINE SYSTEM:											
Adrenals	X	X	X	Thyroids/Parathyroids	X	X	X	Pituitary	X	X	X
NERVOUS SYSTEM:											
Brain (c)	X	X	X	Spinal cord (3 levels)(d)	X		X	Peripheral nerves (Sciatic)	X		X
MUSCULO SKELETAL SYSTEM:											
Skeletal muscle	X		X	Femur (with joint) (e)	X		X	Sternum	X		X
INTEGUMENTARY SYSTEM:											
Skin/subcutis	X		X	Mammary glands	X		X				
EYES AND ADNEXA:											
Optic nerves	X		X	Eyes	X		X				
MISCELLANEOUS:											
Gross lesions	X		X	Body exsanguinated		X		Injection site			X

Checked (X) collected (column C), weighed (column W) and examined for histopathology (column H for control and top dose animals as well as low and mid dose animals which died prematurely or were sacrified moribund).
(a): Mandibular, parotid, sublingual.
(b): Histopathological examination of fundus and pylori.
(c): Histopathological examination of brain, cerebrum (2 levels), cerebellum, brain stem.
(d): Cervical, thoracic, lumbar.
(e):Histopathological examination of femoral epiphysis.
(f): should be prepared from each animal, not examined in first instance. It only need to be examined microscopically if effects on the hematopoietic system are noted.

Histopathology

Adequate Battery: Yes

Peer Review: Not stated.

Histological Findings

There was a slight treatment-related increase in the degree of pancreatic apoptosis observed in mid and high dose main study animals. Since this finding was also observed in 1 of 4 control males and 3 of control 4 females it was not considered to be adverse. There were no other drug-related macroscopic findings observed in this study.

Special Evaluation

The methodology was not stated, but the results section stated that body temperatures in treated animals were significantly increased for the groups and timepoints shown below compared to predose values. Body temperatures in the treated recovery group were similar to those recorded for the vehicle control recovery group.

- in animals dosed at 80 μg/kg only on D1 (+0.4˚C)
- in animals dosed at 500 μg/kg on D1, D8, D22 and D43 (+0.5˚C, +0.4˚C, +0.9˚C and +0.8˚C, respectively)
- in animals dosed at 3200 μg/kg on D1, D8, D15 and D29 (+0.6˚C, +0.4˚C, +0.7˚C and +1.0˚C, respectively)

There were no drug-related effects on systolic blood pressure noted in this study.

Toxicokinetics

Blood samples for TK analyzes were collected predose and 5, 20, 60, 120, and 180 min after dosing on Day 1 and Day 43. Mean TK results are summarized in the Sponsor's Tables 4 & 5 below. Systemic exposure (AUC) increased in a dose-related manner. There were no gender-related effects on exposure. The AUCs observed on Day 43 were similar to those observed on Day 1.

Table 4: Toxicokinetic parameters Day 1 (Mean ± SD)

		MALE			FEMALE		
Dose	ug/kg	80	500	3200	80	500	3200
C_{max}	ng/mL	109.4 ± 6.0	590.3 ± 76.9	4245.1 ± 169.1	99.7 ± 6.8	681.1 ± 65.4	4340.3 ± 416.6
T_{max}	min	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0
λ_z	1/min	102.6 ± 14.4	102.7 ± 8.4	96.5 ± 5.7	122.2 ± 6.9	107.0 ± 5.4	112.1 ± 4.1
$t_{½}$	min	72.0 ± 10.7	68.8 ± 5.1	72.6 ± 4.2	57.3 ± 3.2	65.3 ± 3.4	62.1 ± 2.4
AUC_{all}	ng/mL*min	8026.5 ± 549.4	32129.1 ± 2094.0	253960.0 ± 19696.9	6346.9 ± 269.5	40981.3 ± 3065.9	240018.1 ± 14656.1
C_{max}/Dose	(ng/mL)/(ug/kg)	1.37 ± 0.08	1.18 ± 0.15	1.33 ± 0.05	1.25 ± 0.09	1.36 ± 0.13	1.36 ± 0.13
AUC_{all}/Dose	(ng/mL*min)/(ug/kg)	100 ± 7	64 ± 4	79 ± 6	79 ± 4	82 ± 6	75 ± 5

Table 5: Toxicokinetic parameters Day 43 (Mean ± SD)

		MALE			FEMALE		
Dose	ug/kg	80	500	3200	80	500	3200
Cmax	ng/mL	153.8 ± 10.5	798.7 ± 105.9	4308.6 ± 313.0	142.0 ± 7.6	648.9 ± 95.5	4642.9 ± 396.2
Tmax	min	5 ± 0	9 ± 4	5 ± 0	5 ± 0	5 ± 0	5 ± 0
λ_z	1/min	195.0 ± 26.8	123.4 ± 10.1	118.2 ± 6.2	1141.5 ± 5.7	130.3 ± 7.8	111.1 ± 9.8
t½	min	37.9 ± 5.8	57.4 ± 5.2	59.1 ± 3.0	49.2 ± 2.0	53.8 ± 3.5	63.7 ± 4.9
AUCall	ng/mL*min	6428.1 ± 647.7	41714.3 ± 4043.3	234593.4 ± 7281.8	7817.2 ± 607.6	35323.9 ± 4243.4	228920.7 ± 10396.2
Cmax/Dose	(ng/mL)/(ug/kg)	1.92 ± 0.13	1.60 ± 0.21	1.35 ± 0.10	1.77 ± 0.10	1.30 ± 0.19	1.45 ± 0.12
AUCall/Dose	(ng/mL*min)/(ug/kg)	80 ± 8	84 ± 8	73 ± 2	98 ± 7	71 ± 8	72 ± 3

Dosing Solution Analysis

Dosing formulations were analyzes via RP-HPLC with UV detection. The actual doses administered were within 10% of the nominal dose.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: ^{175}Lu-DOTATATE: Bacterial mutation assay.

Study no.:	81900
Study report location:	Conducting Laboratory.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 22, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	^{175}Lu-DOTATATE, Batch # LT101124A, % purity not stated

Key Study Findings

^{175}Lu-DOTATATE was not mutagenic in the Ames assay.

Methods

Strains:	*S. typhimurium* TA1535, TA1537, TA98 and TA 100 and *E.coli* strain WP2 *uvr*A
Concentrations in definitive study:	902, 285, 90.2, 28.5, and 9.02 µg/plate for the toxicity test. 902, 451, 226, 113, and 56.4 µg/plate for Main assay I and II.
Basis of concentration selection:	MFD
Negative control:	Vehicle
Positive control:	See the Sponsor's Table below
Formulation/Vehicle:	Solution/acetate buffer pH 4.7
Incubation & sampling time:	For the toxicity study and Main Study I, tester strain bacteria, test item, and S9 mix or phosphate buffer were added to molten overlay agar, vortexed and then poured on the minimal media agar plate. For Main Study II, bacterial suspension, tester strain bacteria, test item, and S9 mix or phosphate buffer were vortexed together and incubated for 30 min at 37ºC. This mixture was then added to molten overlay agar, vortexed and then poured on the minimal media agar plate. All plates were incubated for 72 hr at 37ºC. Afterwards, the number of revertant colonies were counted for each plate.

Tester strain	*Absence of S9*	*Presence of S9*
TA1535	sodium azide 1 µg/plate	2-aminoanthracene 1 µg/plate
TA100	sodium azide 1 µg/plate	2-aminoanthracene 1 µg/plate (2 µg/plate)
TA1537	9-amino-acridine 50 µg/plate	2-aminoanthracene 1 µg/plate
TA98	2-nitrofluorene 2 µg/plate	2-aminoanthracene 1 µg/plate (2 µg/plate)
WP2 *uvr*A	methylmethanesulphonate 500 µg/plate	2-aminoanthracene 10 µg/plate (20 µg/plate)

Study Validity

Triplicate plates were used for each concentration in each study. No toxicity was observed in the absence or presence of S9 metabolism. No precipitation was observed in any study at any concentration. Mean plate counts for vehicle and positive control plates were within historical range values. These results indicate a valid study.

Results

^{175}Lu-DOTATATE did not induce 2-fold increases in the number of revertant colonies at any dose level in the presence or absence of S9 mix in either Main Study.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: ^{175}Lu-DOTATATE: Mutation in L5178Y Mouse Lymphoma Cells.

Study no.:	81910
Study report location:	Conducting Laboratory
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 22, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	^{175}Lu-DOTATATE, Batch # LT101124A, % purity not stated

Key Study Findings

Methods

Cell line:	L5178Y $TK^{+/-}$ Mouse Lymphoma Cells
Concentrations in definitive study:	395, 198, 98.8, 49.4, and 24.7 µg/mL without S9 mix and 395, 316, 253, 202 and 162 µg/mL with S9 mix.
Basis of concentration selection:	MFD and no relevant toxicity or precipitation in a preliminary toxicity study at concentrations up to 395 µg/mL.
Negative control:	Vehicle
Positive control:	Methylmethanesulphonate (10 µg/mL) without S9 mix and Benzo-a-pyrene (2.0 µg/mL) with S9 mix.
Formulation/Vehicle:	Solution/Acetate buffer
Incubation & sampling time:	Cells and test article with and without S9 mix were incubated for 3 and 24 hr at 37ºC. Cells were washed in PBS, resuspended in fresh media and incubated at 37ºC in 5% CO_2 for 2 days to allow for the expression of the mutant phenotype.

Study Validity

Duplicate cultures were prepared for each concentration. Relative total growth (RTG) was calculated and the mutation frequency was determined. Vehicle control values were within historical range. Positive controls induced marked increases in mutant frequencies. The results indicate a valid study.

Results

^{175}Lu-DOTATATE did not induce an increase in the number of mutant colonies at any dose level in the presence or absence of S9 mix in either Main Study.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

The only nonclinical genetic toxicology data submitted was for the Ames assay and the L5178Y $TK^{+/-}$ Mouse Lymphoma Cell assay.

8 Carcinogenicity

Carcinogenicity data was not submitted.

9 Reproductive and Developmental Toxicology

Reproductive and Developmental Toxicology data was not submitted.

10 Special Toxicology Studies

Special Toxicology study reports were not submitted.

11 Integrated Summary and Safety Evaluation

The Sponsor cross-referenced IND 77219. Many of the nonclinical studies evaluated under IND 77219 were performed using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE. Since the only difference is the radiolabel used, nonclinical data obtained using ^{177}Lu-DOTATATE or ^{175}Lu-DOTATATE is applicable for evaluating ^{68}Ga-DOTATATE. Many of the nonclinical study reports included in the submission were related to the oncology therapeutic indication or were not needed for microdosing and/or labeling. Such studies were not reviewed. The submission included 3 single-dose toxicity studies; however, these acute toxicity studies were not properly designed for evaluating drug-induced toxicity (too few animals used and/or too few parameters evaluated) with 2 of the studies clearly designed for dose-range finding. The repeat-dose toxicity studies were properly designed and were reviewed. There were no nonclinical concerns at the time of this review with the inactive ingredients, impurity, solvents, or degradants identified in the final drug product. Overall, the nonclinical data support that the NDA should be approved from a nonclinical perspective.

12 Appendix/Attachments

None.

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

/s/

RONALD HONCHEL
12/04/2015

ADEBAYO A LANIYONU
12/04/2015

I agree with Dr. Honchel recommendation for the approval of this NDA application from a discipline perspective. Dr. Honchel comments and recommendations on labeling are noted. Labeling language consistent with the Pregnancy and Lactation Labeling Final Rule is being made at the review team level.