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A single arm, open-label, multicenter phase II study of ^{177}Lu-DOTATATE radionuclide in adults with progressive or high-risk meningioma

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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PROTOCOL APPROVAL SIGNATURES

Protocol Title: **A single arm, open-label, multicenter phase II study of ^{177}Lu-DOTATATE radionuclide in adults with progressive or high-risk meningioma**

Protocol Number: s18-00719

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

_____
Signature

_____
Date

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List of Abbreviations

%IA	Percentage of Injected Activity
^{68}Ga	Gadolinium-68
^{68}Ga-DOTATATE	^{68}Ga-DOTA^{0}-Tyr^{3}-Octreotide
^{90}Y	Yttrium-90
^{111}In	Indium-111
^{175}Lu	Lutetium-175
^{176}Lu	Lutetium-176
^{177}Hf	Hafnium-177
^{177}Lu	Lutetium-177
^{177}Lu-DOTATATE	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotide
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
Bq	Becquerel (unit of radioactivity, 1 disintegration per second)
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CFR	Code of Federal Regulations
Cr	Creatinine
CrCl	Creatinine Clearance
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CRO	Contract Research Organization
CT	Computed-Tomography
CTO	Clinical Trials Office
Ci	Curie (unit of radioactivity; 1 Ci=37 GBq)
CXR	Chest X-ray
DOTA	4,7,10-Tetraazacyclododecane-N,N',N",N"'-tetraacetic acid
DLT	Dose Limiting Toxicity
drAEs	Drug-related adverse events
DHHS	Department of Health and Human Services
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescence in situ Hybridization
Ga	Gadolinium
GCPs	Good Clinical Practices
GEP-NET(s)	Gastro-Entero-Pancreatic Neuroendocrine Tumor(s)
h	Hours
HIPAA	Health Insurance Portability and Accountability Act
HGB	Hemoglobin
HR	Hazard Ratio
IA	Injected Activity
IB	Investigator's Brochure
IC_{50}	Concentration of 50% Inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry

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IRB	Institutional Review Board
KPS	Karnofsky Performance Status
LLN	Lower Limit of Normal
Lu	Lutetium
MBq	MegaBecquerel ($1x10^6$ Bq)
mCi	MilliCurie
MedDRA	Medical Dictionary for Regulatory Activities
MNM	Molecular nuclear medicine
MRI	Magnetic Resonance Imaging
N	Number (typically refers to participants)
NANO	Neurological Assessment in Neuro-Oncology
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
OS-12	Overall Survival at 12 months
PBMC	Peripheral blood mononuclear cells
PCC	Perlmutter Cancer Center
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFS-6	Progression Free Survival at 6 months
PHG-RM	Progressive or High Grade Residual Meningioma
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
QAU	Quality Assurance Unit
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RT	Radiation Treatment
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase (also known as AST)
SGPT	Serum Glutamic-Pyruvic Transaminase (also known as ALT)
SSTR 1-5	Somatostatin Receptor Subtype 1-5 (5 subtypes identified)
$T_{1/2}$	Half-Life of the Terminal Disposition Rate Constant
ULN	Upper Limit of Normal
US	United States
WB	Whole Blood
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
Y	Yttrium

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Protocol Summary/Synopsis

Title	A single arm, open-label, multicenter phase II trial of ^{177}Lu-DOTATATE radionuclide in adults with progressive or high-risk residual meningioma
Short Title	Phase II trial of ^{177}Lu-DOTATATE in adults with progressive or residual high-risk meningioma
Brief Summary	This single arm, open-label study will evaluate the efficacy of Lutathera (^{177}Lu-DOTATATE) administered intravenously every 8 weeks for a total of 4 doses in patients with progressive WHO I-III or residual high-risk ^{68}Ga-DOTATATE PET-MRI positive meningioma. ^{68}Ga-DOTATATE PET-MRI scans will be obtained prior to initiation of Lutathera treatment and 6 months after the initiation of Lutathera treatment. The latter will be performed within the 14 days prior to the last dose of Lutathera treatment.
Phase	Phase 2

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Objectives	**Primary Objective:** To determine the progression-free survival at 6 months (PFS-6) of Lutathera in patients with progressive WHO I-III or residual high-risk (WHO II/III) meningiomas that are positive on ^{68}Ga-DOTATATE PET-MRI. **Secondary Objectives:** 1) To evaluate the overall safety and tolerability of Lutathera in patients with meningioma. 2) To determine the Objective Response Rate (ORR), Overall Survival (OS) at 12 months (OS-12), median PFS, and median OS in patients receiving Lutathera for progressive or residual high-risk meningioma. **Exploratory Objectives:** • Exploratory cohort, n=10 (NYU site only). To evaluate the association of ^{177}Lu-DOTATATE dosimetry with: o pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET o change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET o Progression-free survival at 6 months (PFS-6) o Objective Response Rate (ORR) o Overall Survival at 12 months (OS-12) o median Progression Free Survival (mPFS) o median Overall Survival (mOS) • To evaluate the association of PFS-6 with: o Pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET o Change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET o SSTR2 expression by IHC o Meningioma molecular subtypes determined by DNA methylation array [22] o WHO grade o DNA mutations (e.g. NF2, SMO, PI3K/Akt pathway) • To evaluate the association of pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET with o SSTR2 expression by IHC o meningioma molecular subtypes determined by DNA methylation array [22] o WHO grade o DNA mutation (e.g. NF2, SMO, PI3K/Akt pathway)
Methodology	This is an open-label, single arm, multicenter, two-stage phase 2 clinical study.
Endpoints	**Primary Endpoint:** Progression-free survival at 6 months (PFS-6) **Secondary Endpoints:** • Safety/Tolerability • Objective Response Rate (ORR) • Overall Survival at 12 months (OS-12) • median Progression Free Survival (mPFS) • median Overall Survival (mOS)

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Study Duration	Approximately 30 months from start of patient enrollment to last subject completing all study procedures and completion of data analysis
Participant Duration	Approximately 12 months from time of first Lutathera treatment until time of last study visit.
Duration of IP administration	Duration of Lutathera (^{177}Lu-DOTATATE) treatment will be approximately 8 months. Lutathera will be administered intravenously once every 8 weeks (+/- one week) for up to a maximum of 4 doses.
Population	Up to 32 adult subjects with progressive WHO I-III or residual high-risk meningioma that have positive ^{68}Ga-DOTATATE PET-MRI will be enrolled **Eligibility Criteria:** <u>Inclusion Criteria</u> 1. Male or female subjects aged ≥ 18 years. 2. Karnofsky Performance Status ≥ 60. 3. Histologically confirmed diagnosis WHO grade I-III meningioma: a. For grade I meningioma, subjects must have: i. Progressive disease after at least surgical resection and radiotherapy, as defined as an increase in size of the measurable primary lesion (bidirectional area) on imaging by 25% or more between scans separated by no more than 12 months. or ii. Progressive residual tumor after maximal safe resection, be located at or near critical organs at-risk [24] and considered to be high-risk for radiation injury by the treating investigator. Prior external beam radiotherapy is not required for these subjects. b. For Grade II or III meningioma, subjects must have either: i. Progressive disease after at least surgical resection and radiotherapy, as defined as an increase in size of the measurable primary lesion (bi-directional area) on imaging by 25% or more between scans separated by no more than 12 months <u>or</u> ii. Residual measurable disease after surgery without requirement of progression. 4. Positive ^{68}Ga-DOTATATE uptake on PET-MRI. a. Positive uptake is defined as uptake higher than the background and SUV ratios adjusted to the liver and spleen uptake (adopted from Krenning score).[25]

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	b. ^{68}Ga-DOTATATE uptake in target lesions should be Krenning score ≥ 2. 5. Presence of measurable disease defined as at least one lesion measuring ≥10 mm in at least one dimension by contrast-enhanced MRI performed within 30 days prior to study registration. 6. Multifocal disease is allowed but is limited to ≤ 3 measurable intracranial mass lesions on the most recent post-contrast MRI. 7. Any neurological symptoms must be stable for at least 28 days prior to enrollment and patients should not require steroids to control neurological symptoms. 8. There is no limit on the number of prior surgeries, radiation therapy, radiosurgery treatments or systemically administered therapeutic agents. 9. For patients treated with external beam radiation, interstitial brachytherapy or radiosurgery, an interval ≥24 weeks must have elapsed from completion from these therapies to registration unless there is histopathologic confirmation of recurrent tumor or there is new enhancing tumor outside the radiation field (beyond the high dose region or the 80% isodose line). 10. An interval of ≥28 days (or 5 half-lives, whichever is shorter) from prior cytotoxic chemotherapy (6 weeks from nitrosoureas), biologic agent, investigational agent or any other systemic agent prescribed for the purpose of treating meningioma. 11. An interval of ≥28 days from craniotomy and ≥7 days from stereotactic biopsy. 12. Availability of a paraffin-embedded archival tumor block from most recent tumor resection sufficient to generate at minimum 8 unstained slides but preferably up to 25 unstained slides; or, if a paraffin tumor block is unavailable, at minimum 8 unstained slides but preferably up to 25 unstained slides. a. Pathology report indicating positive SSTR2 expression by immunohistochemistry in the most recent tumor specimen. 13. Patients must be willing and able to undergo regular MRI scans of the brain. 14. Patients must have recovered to CTCAE grade ≤1 or pretreatment baseline from clinically significant adverse events related to prior therapy (exclusions include alopecia, laboratory values listed per inclusion criteria, lymphopenia, sensory neuropathy ≤ grade 2, or other ≤ grade 2 not constituting a safety risk based on the investigator's judgment). 15. Adequate organ and bone marrow function as defined below (within 30 days of treatment initiation): a. White blood cell (WBC) ≥ 2,000/mm^3 b. Absolute neutrophil count (ANC) ≥ 1,000/mm^3

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c. Platelet count ≥ 75,000/mm^3
d. Hemoglobin ≥ 8 gm/dL
e. AST(SGOT)/ALT(SGPT) ≤ 3 x laboratory upper limit of normal (ULN)
f. Creatinine clearance (measured or calculated) ≥ 50 mL/min OR creatinine levels > 150 µMol/L (1.7 mg/dL)
g. Total serum bilirubin ≤ 3 X ULN (except participants with Gilbert's Syndrome, who can have a total bilirubin ≤ 5 X ULN)
h. Serum albumin level of more than 3.0 g/dL, unless the prothrombin time value was within the normal range

16. Women of childbearing potential (WOCBP) and men able to father a child must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in the study, she must inform her treating physician immediately.
17. Able to understand and willing to sign an IRB approved written informed consent document.

<u>Exclusion Criteria</u>

1. Patients with a clinical diagnosis of NF2 (either by NIH or Manchester criteria) or with a molecular diagnosis of NF2.
2. Patients with radiation-associated meningiomas.
3. Life Expectancy ≤ 6 months.
4. Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm. This includes treatment with Somatostatin LAR within 4 weeks prior to treatment, or any patient receiving treatment with short-acting Octreotide that cannot be interrupted for greater than 24 hours before treatment.
5. Peptide receptor radionuclide therapy at any time prior to registration.
6. Known hypersensitivity to somatostatin analogues or any component of the ^{68}Ga- DOTATATE or ^{177}Lu-DOTATATE formulations.
7. Known additional malignancy that is progressing or requires active treatment within 2 years of start of study drug. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and *in situ* cervical cancer that has undergone potentially curative therapy.
8. Current or planned participation in another study of an investigational agent or investigational device.
9. Active infection requiring intravenous therapy with antibiotics.
10. Uncontrolled intercurrent illness including, but not limited to, clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), congestive heart failure (≥ NYHA

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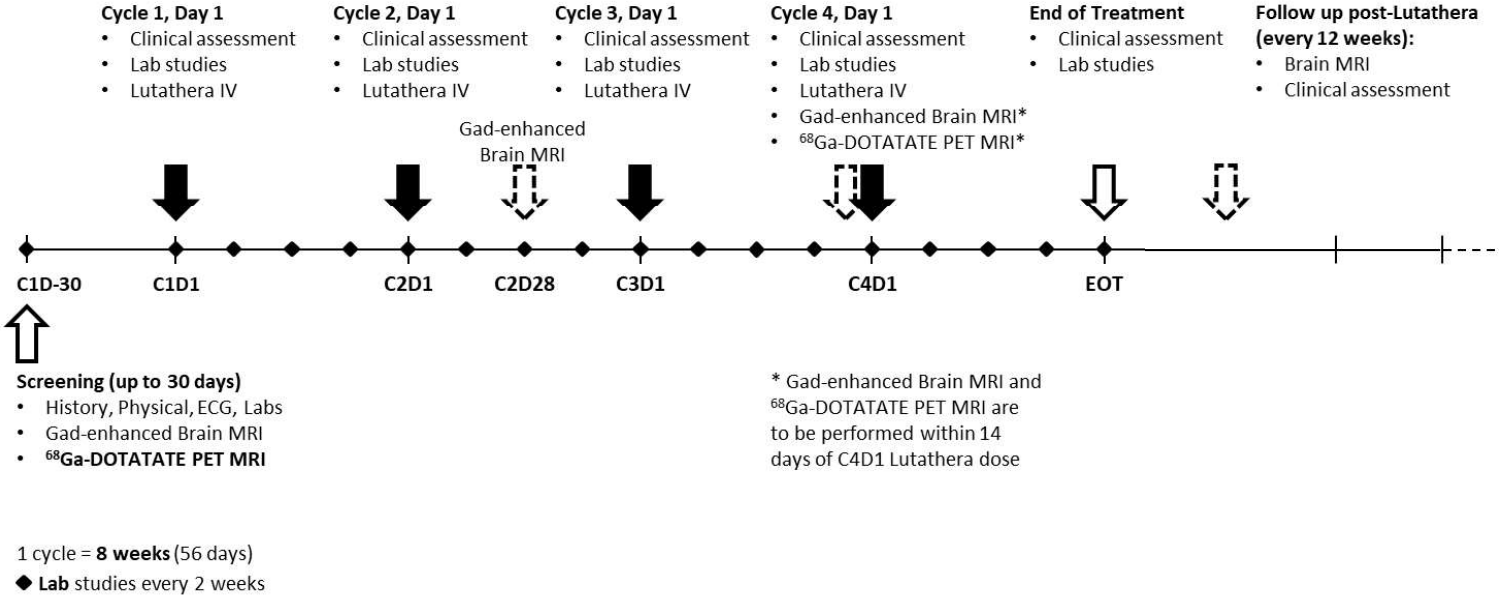
	class II), unstable angina pectoris, or serious cardiac arrhythmia requiring medication. 11. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). 12. Active Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test is positive). 13. Other severe acute or chronic medical or psychiatric conditions (within the past year) including recent or active suicidal ideation or behavior, or laboratory abnormalities that may increase the risk associated with study participation or treatment on study or may interfere with the interpretation of study results. 14. Pregnant and/or breastfeeding patients. Women of childbearing potential (WOCBP) must have a negative pregnancy test within 14 days of study entry.
Study Sites	Multicenter. Two study sites: 1) Perlmutter Cancer Center (PCC) at New York University Langone Health (NYULH), New York, NY (lead/coordinating) 2) Cleveland Clinic, Cleveland, OH
Number of participants	A minimum of 14 adult subjects (completion of stage I) and a maximum of 32 adult subjects (completion of stage II) will be enrolled across 2 sites.
Description of Study Agent/Procedure	Lutathera or ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotide is a radiopharmaceutical that consists of the somatostatin analog Octreotate linked to the metal chelator, DOTA. The compound has high affinity for somatostatin receptor, subtype 2 (SSTR2) which is nearly universally expressed in meningiomas. On day of treatment, infusion of a nephroprotective amino acid solution (e.g. Aminosyn II 15%) containing L-lysine and L-arginine will begin 30 minutes prior to administration of Lutathera. Lutathera at a dose of 7.4 GBq (200 mCi) will be administered intravenously over 30 minutes. After completion of Lutathera, infusion of the amino acid solution will continue for 3 hours (total infusion time = 4 hours).
Reference Therapy	The reference therapy for progressive WHO I-III is re-resection and/or radiotherapy. The reference therapy for residual high risk meningioma is radiation therapy.

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Key Procedures	• Lutathera administration 7.4 GBq (200 mCi) every 8 weeks (+/- 1 week) for 4 doses • Contrast-enhanced MRI for tumor assessment at time of enrollment and every 12 weeks • ^{68}Ga-DOTATATE MRI at time of enrollment and at 6 months, or earlier if subjects experience progressive disease prior to 6 months • Blood draws at enrollment and then every 2 weeks • Clinical assessments at enrollment and every 8 weeks • ^{177}Lu-DOTATATE dosimetry (NYU exploratory cohort only)
Statistical Analysis	Up to 32 patients will be enrolled and treated in this study. The primary endpoint is PFS-6. A Simon's two-stage clinical study design with a historical PFS-6 rate of 26% will be used. The null hypothesis that the true response rate (H_0) is 0.26 will be tested against a one-sided alternative response rate (H_1) of 0.47. In stage I of this study, 14 patients will be accrued. If there are 3 or fewer PFS-6 events among these 14 patients, the study will be stopped. Otherwise, 18 additional patients will be accrued for a total of 32 patients. The null hypothesis will be rejected if ≥13 achieve PFS-6 among the total of 32 patients. This design yields a type I error rate of 0.05 and a power of 80% when the true response rate is 0.47.

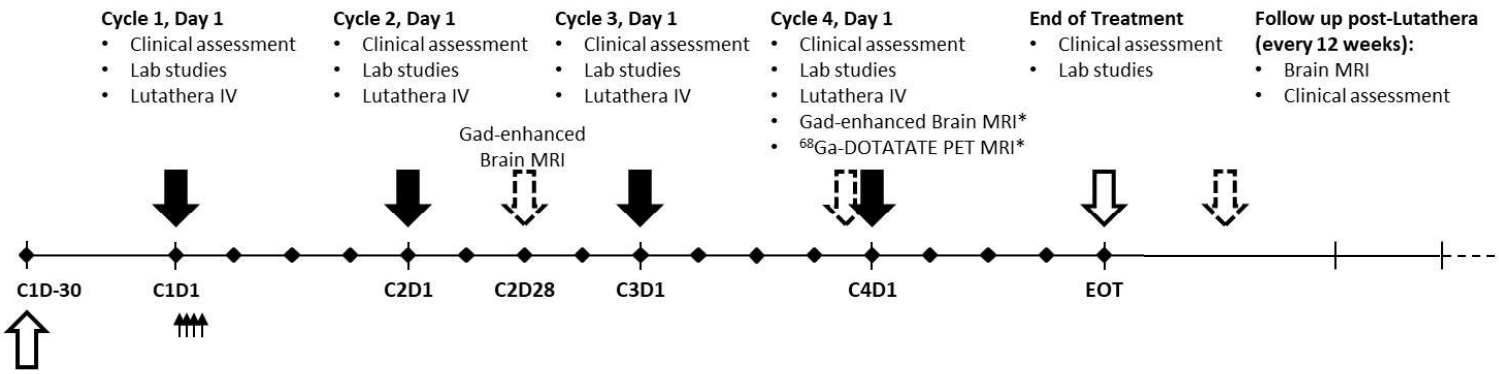
Schematic of Study Design

Figure 1. Study schema
A. General Study Cohort



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B. Exploratory Study Cohort (NYU only)



* Gad-enhanced Brain MRI and ^{68}Ga-DOTATATE PET MRI are to be performed within 14 days of C4D1 Lutathera dose

1 cycle = **8 weeks** (56 days)

◆ **Lab** studies every 2 weeks

↑ ^{177}Lu-DOTATATE Dosimetry evaluations

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1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

2.1.1 Intracranial Meningiomas

Meningiomas are the most common primary intracranial tumors with about 25,000 newly diagnosed cases/year in the US [1]. While WHO I meningiomas (~60% of all meningiomas) are benign and can be cured with surgical resection, atypical WHO II (35%) [2] and anaplastic WHO III (5%) [3] meningiomas represent aggressive tumors and commonly recur despite surgical resection and/or external beam radiotherapy (EBRT). The 5-year recurrence rate for WHO II and III meningiomas is 40% and 80-94%, respectively. In addition, EBRT is associated with a risk of early and delayed neurotoxicity, and certain intracranial structures are considered high risk ("organs at-risk") for radiation injury with EBRT, including the optic chiasm, optic nerves, brainstem, pituitary gland, hippocampus, eye/retina, internal carotid artery/circle of Willis, and cochlea [24]. Therefore, even WHO grade I meningiomas located at or near these critical organs at-risk are considered high risk if not completely resectable due to the risk of neurological complication or organ dysfunction due to radiation injury.

At time of recurrence from EBRT for any meningioma, there is no standard of care therapy and no chemotherapy has proven efficacy [4, 5]. The prognosis of patients with progressive meningioma is poor and the progression-free survival (PFS) at six months (PFS-6) for progressive WHO II/III is estimated at only 26% [5]. Therefore, more effective therapies for progressive and high-grade meningioma are a critical and unmet clinical need.

2.1.2 Rationale for ^{177}Lu-DOTATATE in Progressive or Residual High Risk Meningioma

Somatostatin receptors, and in particular somatostatin receptor 2 (SSTR2) are abundantly overexpressed in meningiomas. SSTR2 has been reported to be overexpressed in 79%-100% of grade II/III meningiomas [6-8]. Somatostatin has been demonstrated to inhibit meningioma cell growth *in vitro* [9]. Based on these data, SSTR2 represents a promising therapeutic target in meningioma and indeed, somatostatin analogues have induced partial responses in a subset of meningioma patients in small clinical trials and case series [10-12].

A phase III study demonstrated significantly improved PFS in patients with progressive metastatic malignant gastrointestinal neuroendocrine tumors when treated with the radiolabeled somatostatin analogue ^{177}Lu-DOTATATE (Lutathera) combined with long-acting octreotide (LAR) compared to LAR alone. This trial led to US FDA approval of Lutathera for somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors [13].

Therapeutic ^{90}Y or ^{177}Lu radiolabeled DOTATOC/DOTATATE, octreotide analogues targeting SSTR2, have shown promising activity in several small meningioma case series and prospective clinical studies [14, 15]. A recent phase II clinical trial evaluating ^{90}Y- or ^{177}Lu-DOTATOC reported 23 of 34 patients (68%) achieved stable disease, and disease stability was associated with longer overall survival [16]. A case series reported disease stabilization in 50% of patients treated with ^{177}Lu-DOTATATE/^{90}Y-DOTATOC, with PFS-6 of 57% for WHO II meningiomas [17]. In this study, both higher pre-treatment ^{68}Ga-radionuclide uptake and SSTR2 expression by immunohistochemistry (IHC) correlated with PFS-6 [17]. Additionally, ^{68}Ga-DOTATOC/ DOTATATE as a PET imaging tracer has potential for use as a predictive and pharmacodynamic biomarker for ^{177}Lu-DOTATATE in meningioma. Previous studies have shown that when utilized as tracers in PET/CT or PET/MR imaging, ^{68}Ga-DOTATOC/DOTATATE can accurately discriminate between progressive meningioma and tumor-free tissue [18, 19].

2.2 Lutathera

2.2.1 General Information

Lutathera (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, ^{177}Lu-DOTATATE), is a lutetium-177 (^{177}Lu) radiolabeled somatostatin analog peptide conjugated with the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

Lutathera has high affinity for somatostatin receptor, type 2 (SSTR2) and binds specifically to malignant cells that overexpress SSTR2. Lutetium-177 is a β-emitting radionuclide. The mean path length of the β-emission is about 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to effectively kill targeted tumor cells, with a limited effect on neighboring normal cells.

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Detailed background information on Lutathera® can be found in **Section 9.1**, the **Investigator's Brochure**, the **Lutathera® package** insert and the **Pharmacy Manual**.

2.2.2 Mechanism of Action

Lutathera (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) binds to somatostatin receptors (SSTRs) with the highest affinity to somatostatin receptor, type 2 (SSTR2), which is uniformly overexpressed in meningiomas. Upon binding to SSTR2-expressing cells, the compound is internalized. The β-emission from ^{177}Lu induces cellular damage by formation of free radicals in SSTR2-expressing cells. *In vitro* studies demonstrate that Lutathera efficiently kills targeted tumor cells with a limited effect on neighboring normal cells. The β-emitting radionuclide ^{177}Lu has a maximum tissue penetration range of 2.2 mm (mean penetration range of 0.67 mm).

The peptide oxodotreotide (DOTA) does not exert any clinically relevant pharmacodynamic effect at the concentration used (about 10 µg/mL in total for both, free and radiolabeled forms).

In vivo animal studies demonstrate that Lutathera has generally low uptake in non-receptor expressing tissues such as muscle and spleen, while it has a high specific uptake in pancreas (high SSTR expressing organ) and medium unspecific uptake in the kidney, which is the main excretion organ (very low SSTR expressing tissue). Moreover, concerning free lutetium-177 radiotoxicity, extensive studies on biodistribution showed low uptake in the bone, further reduced by adding chelating agent in the formulation for free lutetium.

Using rat SSTR-positive tumor models, it has been shown that Lutathera can result in complete ablation of implanted tumors. A high percentage (50%) of rats bearing SSTR positive tumors treated with Lutathera live a normal life span without tumor recurrence.

It has also been demonstrated that infusion of amino-acids (in particular lysine and arginine) can dramatically decrease the retention of radioactivity in kidneys and substantially reduce renal toxicity.

For complete details, see the Lutathera **Investigator's Brochure.**

2.2.3 Non-clinical metabolism

The metabolism of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and non-radioactive ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate was investigated in multiple *in vitro* and *in vivo* studies using tissues from rats, dogs, and humans as well as animal studies in rats and dogs. The key findings of these studies are summarized below. Please refer to the **Investigator's Brochure** for further details.

A biphasic decrease of radioactivity in blood was observed *in vivo* biodistribution studies in normal rats after i.v. administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate: the first phase with a half-life of about 15 min, a second one with t½ around 10.5 h, however, in the second phase, only a very small fraction of the injected dose was still present.

Studies in tumor models show a relatively high uptake in tumor and pancreas and notable kidney retention. Octreotate derivatives showed to have significantly higher uptake and retention in tumor tissue than corresponding octreotide derivatives, as well as lower kidney retention.

In vivo biodistribution / metabolism studies in tumor-bearing rats showed that the majority of radiolabeled Tyr3-Octreotate analogs are excreted mainly via the renal system, mostly as intact compound.

In vitro serum stability studies indicate that ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate remains intact in serum for at least 24 h. The findings indicate no transchelation of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate into serum proteins.

Plasma protein binding measurements performed on ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate indicated similar protein binding in rats and human (around 75%) at the concentrations reached in toxicology studies in rats and at the expected plasma levels in humans. In dogs, the plasma protein binding was found to be higher, around 94%.

In vitro metabolism studies conducted on the compound labelled with non-radioactive Lu-175 (^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate) indicate that ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate is not metabolized by rat, dog or human hepatocytes, while it is rapidly metabolized by rat, dog and human kidney homogenate. In the incubation samples five rat, eight dog and seven human

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metabolites were detected. No human specific metabolite was observed. These data confirm that the rat and the dog are suitable species for assessing the toxicological profile of ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

The potential of ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate to induce or inhibit human CYP450 enzymes was also assessed. The studies showed that the compound does not act as an inducer or inhibitor of human enzymes. A mild inhibition was observed on CYP2C9 (32.9% at 10 µM), at a concentration that is much higher than those that will be achieved in human and therefore it is considered not to have any biological significance.

Results of P-glycoprotein mediated interaction studies indicated that ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate does not show any P-glycoprotein specific interaction as a substrate or inhibitor.

2.2.4 Nonclinical Radiotoxicity and Toxicology

The toxicity of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and non-radioactive ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate was investigated *in vitro* and *in vivo.* The key findings of these studies are summarized below. Please refer to the **Investigator's Brochure** for further details.

Radiotoxicity
Results of the acute radiotoxicity studies (doses up to 4,550 MBq/kg) showed that blood chemistry and blood counts of RBCs and platelets were normal at all-time points. WBC counts showed a dose-dependent decrease at doses above 163 MBq/kg, but in all cases returned to normal after 1 month post-injection. Delayed toxicity evaluation showed that injection of high doses of the labelled peptide (555 MBq/rat, 2,220 MBq/kg) resulted in severe renal damage in rats, which was dose-dependent and became overt between 100 and 200 days after treatment. Fractionation of the dose (278 MBq/rat, or 1,110 MBq/kg, twice with one week interval, instead of 555 MBq/rat, or 2,220 MBq/kg once) significantly ameliorated kidney function. Lysine co-injection successfully prevented functional damage.

Toxicology of the non-radioactive compound ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate
An acute toxicity study conducted in female rats showed that the compound was well tolerated after single intravenous administration, without inducing any toxicity signs, up to the highest tested dose, 20,000 µg/kg (that is, around 700 fold the intended human dose scaled to rat based on body surface area).

In a repeat-dose toxicity study in Sprague Dawley rats ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate was administered intravenously four times (once every two weeks) at 1,250, 5,000 or 20,000 µg/kg. The compound induced no mortality and no major signs of toxicity. Some pancreatic acinar apoptosis was detected in male and female rats treated at the intermediate and highest dose. Therefore, the NOEL corresponds to 1,250 µg/kg, that is 40 times the human dose.

It should be noted that this safety margin estimated based on rat data is not expected to be affected by protein binding, as similar free fractions of the drug were measured in rat and human plasma at relevant concentrations (that is, concentration levels reached in the toxicology study in rats and those expected in humans respectively).

In a MTD study in dogs, ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate administered at ascending doses from 400 to 3,200 µg/kg (400, 800, 1,600 and 3,200 µg/kg) and as single doses of 6,400 and 10,000 µg/kg by the intravenous route induced no mortality and no evident drug-related signs of toxicity in male and female Beagle dogs, except for soft to liquid feces observed on the days following treatment at all doses, and spread red (at 400 – 3,200 µg/kg) or dark red (at 6,400 and 10,000 µg/kg) areas on the mucosa of the gastro-intestinal tract (jejunum, duodenum or rectum).

In the repeat-dose toxicity study in dogs ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate was administered intravenously four times during 43 days (once every two weeks) at 80, 500 or 3,200 µg/kg. The compound induced no mortality and no major signs of toxicity at any dose tested. The signs observed (salivation, vocalisation and soft to liquid feces, associated at the highest dose to slight increase in body temperature and a slight decrease of food consumption) were mild and reversible. Therefore, the NOAEL was concluded to be 3,200 µg/kg, that is 400 times the intended human dose.

Considering the difference between plasma protein binding in dog and human (free fraction in dog about 5 times lower than the free fraction in humans at concentration levels reached in the toxicology study in dogs and those expected in humans respectively), and reducing the ratio between NOAEL observed in dogs and the human dose by the same factor, the safety margin appears to be still very high (400/5 = 80).

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Genotoxicity studies showed that ^{175}Lu-DOTA^{0}-Tyr^{3}-Octreotate does not induce mutation at the TK locus of L5178Y mouse lymphoma cells *in vitro*, nor reverse mutation in *Salmonella typhimurium* or *Escherichia coli* in the absence or presence of S9 metabolic activation.

2.2.5 Clinical Pharmacology

2.2.5.1 Mechanism of Action

Lutathera (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, ^{177}Lu-DOTATATE) binds to somatostatin receptors (SSTRs) with the highest affinity to somatostatin receptors, type 2 (SSTR2) which is uniformly overexpressed in meningiomas. Upon binding to SSTR2-expressing cells, the compound is internalized. The β-emission from ^{177}Lu induces cellular damage by formation of free radicals in SSTR2-expressing cells. *In vitro* studies demonstrate that Lutathera efficiently kills targeted tumor cells with a limited effect on neighboring normal cells. The β-emitting radionuclide ^{177}Lu has a maximum tissue penetration range of 2.2 mm (mean penetration range of 0.67 mm).

2.2.5.2 Pharmacodynamics

^{177}Lu-DOTATATE exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology: The ability of Lutathera 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.

2.2.5.3 Pharmacokinetics and Product Metabolism

The pharmacokinetics (PK) of ^{177}Lu-DOTATATE have been characterized in patients with progressive, somatostatin receptor-positive neuroendocrine tumors. The mean blood exposure (AUC) of ^{177}Lu-DOTATATE at the recommended dose is 41 ng.h/mL [coefficient of variation (CV) 36 %]. The mean maximum blood concentration (Cmax) for ^{177}Lu-DOTATATE is 10 ng/mL (CV 50%), which generally occurred at the end of the Lutathera infusion.

Distribution
The mean volume of distribution for ^{177}Lu-DOTATATE is 460 L (CV 54%). Within 4 hours after administration, ^{177}Lu-DOTATATE distributes in kidneys, tumor lesions, liver, spleen, and, in some patients, pituitary gland and thyroid. The co-administration of amino acids reduced the median radiation dose to the kidneys by 47% (34% to 59%) and increased the mean beta-phase blood clearance of ^{177}Lu-DOTATATE by 36%. The non-radioactive form of lutetium dotatate (^{175}Lu-DOTATATE) is 43% bound to human plasma proteins.

Elimination
The mean clearance (CL) is 4.5 L/h (CV 31%) for ^{177}Lu-DOTATATE. 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.

Metabolism
^{177}Lu-DOTATATE does not undergo hepatic metabolism.

Excretion
^{177}Lu-DOTATATE is primarily eliminated renally with cumulative excretion of 44% within 5 hours, 58% within 24 hours, and 65% within 48 hours following Lutathera administration. Prolonged elimination of ^{177}Lu-DOTATATE in the urine is expected; however, based on the half-life of ^{177}Lu and terminal half-life of ^{177}Lu-DOTATATE, greater than 99% will be eliminated within 14 days after administration of Lutathera.

Drug Interaction Studies
The non-radioactive ^{175}Lu-DOTATATE is not an inhibitor or inducer of cytochrome P450 (CYP) 1A2, 2B6, 2C9, 2C19 or 2D6 *in vitro*. It is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, or OCT1 *in vitro*.

Somatostatin and its analogs competitively bind to somatostatin receptors and may interfere with the efficacy of Lutathera. Therefore, long-acting somatostatin analogs must be discontinued at least 4 weeks and short-acting octreotide at least 24 hours prior to each Lutathera dose.

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2.2.6 Clinical Studies

2.2.6.1 Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The efficacy of Lutathera in patients with foregut, midgut, and hindgut gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was evaluated in the ERASMUS, a phase I/II study. In ERASMUS, Lutathera was initially provided as expanded access under a general peptide receptor radionuclide therapy protocol at a single site, the Erasmus Medical Center, Rotterdam, Netherlands. Patients were treated under ERASMUS between January 2000 and March 2007 and an independent verification of the source data of ERASMUS study and retrospective data analysis was conducted in 2008 to support the initiation of the NETTER-1 Phase III study (see below). Investigator Brochure, Lutathera Package Insert.

The Full Analysis Set (FAS) population of the phase I/II ERASMUS study consisted of 404 subjects with diagnosed GEP-NETs, who had an OctreoScan® tumor uptake score ≥ Grade 2 and at least one valid primary efficacy variable on active treatment. Lutathera 7.4 GBq (200 mCi) was administered every 6 to 13 weeks for up to 4 doses. The major efficacy outcome was investigator-assessed ORR. Fifty five percent (55%) of patients received a concomitant somatostatin analog. The median dose of Lutathera was 29.6 GBq (800 mCi).

The following results were observed:

- Objective tumor response (complete response (CR) + partial response (PR) + minor response (MR, defined as a tumor diameter decrease of 25% to 50%) in the overall GEP-NET FAS population was 59.4% (95% CI; 54.44-64.23%); in the subgroup of 157 Dutch carcinoid tumor patients for whom a longer follow-up was available, the objective tumor response was 61.2% (95% CI; 53.05 - 68.81%)
- Time to progression (TTP) from start of treatment in the overall GEP-NET FAS population was 1164 days (38 months) with a 95% CI of 994-1357 days (32.6-44.5months)
- Median PFS from start of treatment in the overall GEP-NET FAS population was 904 days (29 months) with a 95% CI of 812-994 days (26.6-32.6 months)
- Median OS from start of treatment in the overall GEP-NET FAS population was: 1496 days (49 months) with a 95% CI of 1375-1667 days (45.1-54.7 months).
- Baseline tumor assessments were obtained in 39% of patients. The investigator assessed ORR was 16% (95% CI 13, 20) in the 360 patients with GEP-NETs. The median duration of response (DoR) in the 58 responding patients was 35 months (95% CI: 17, 38).

A subset analysis was performed in 51 patients with progressive, well-differentiated advanced or metastatic SSTR-positive midgut carcinoid tumors. Radiological assessments were performed by an independent radiologist. The median PFS in these 51 subjects was 1375 days or 45 months (95% CI 678, 1732 days or 22, 57 months) according to RECISTv1.1 criteria.

The findings of the ERASMUS study suggest that there is a substantial anti-tumor effect in GEP-NET patients resulting from treatment with ^{177}Lu-DOTATATE. This resulted in a significant improvement in clinical end-point responses (TTP, PFS, and OS) for patients receiving ^{177}Lu-DOTATATE as compared to the responses reported in the literature for GEP-NET patients treated with the current best standard of care (Octreotide LAR).

2.2.6.2 Progressive, Well-differentiated Advanced or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors

The efficacy of Lutathera in patients with progressive, well-differentiated, locally advanced/inoperable or metastatic somatostatin receptor-positive midgut carcinoid tumors was established in NETTER-1 (NCT01578239), a randomized, multicenter, open-label, active-controlled trial.

The results of the planned interim analysis of NETTER-1 were recently published [13]. At that time of publication, 229 patients had been randomized (1:1) to receive either Lutathera 7.4 GBq (200 mCi) every 8 weeks for up to 4 administrations (maximum cumulative dose of 29.6 GBq) or high-dose long-acting octreotide (defined as 60 mg by intramuscular injection every 4 weeks). Patients in the Lutathera arm also received long-acting octreotide 30 mg as an intramuscular injection 4 to 24 hours after each Lutathera dose and every 4 weeks after completion of Lutathera treatment until disease progression or until week 76 of the study.

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The major efficacy outcome measure was progression free survival (PFS) as determined by a blinded independent radiology committee (IRC) per RECIST v1.1. Additional efficacy outcome measures were overall response rate (ORR) by IRC, duration of response, and overall survival (OS). Demographic and baseline disease characteristics were balanced between the treatment arms (for further details see Lutathera package insert).

The median PFS (95% CI) was 8.4 months (5.8, 9.1) in the long-acting octreotide only arm and not reached (not evaluable) in the Lutathera and long-acting Octreotide arm (HR 0.21; 95% CI 0.13, 0.33; p<0.001; **Figure 2**).

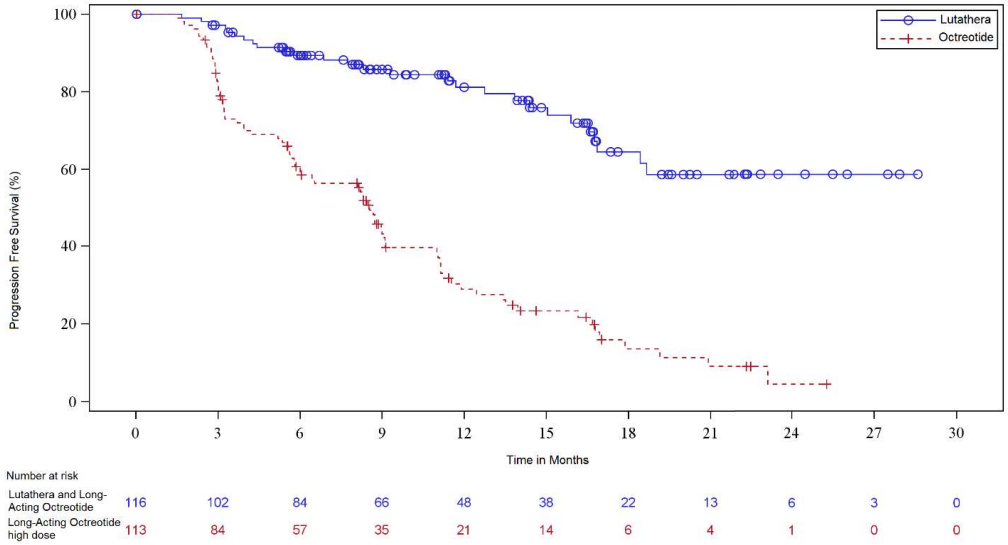


Figure 2. Progression-Free Survival in NETTER-1

The ORR (95% CI) was 3% (0.1%, 6%) in the long-acting octreotide only arm (complete response n=0, partial response n=3) and 18% (10%, 25%) in the Lutathera and long-acting Octreotide arm (complete response (p=0.015). NETTER-1 is still ongoing and at time of publication of the results of the interim analysis (January 2017) the data were not mature enough for an estimate of the median OS. Based on these published results, the FDA approved Lutathera for the treatment of progressive GEP-NETs in January 2018 (NDA# 208700).

2.2.6.3 Progressive Meningiomas

Several case series and small prospective clinical studies have evaluated the therapeutic utility of ^{90}Y or ^{177}Lu-labeled SSTR-targeting radionuclide therapy for patients with progressive intracranial meningioma [14-17, 20]. **Table 3** provides a summary of these studies.

Table 1. Selected case series using ^{90}Y or ^{177}Lu-labeled SSTR-targeting radionuclide therapy in patients with progressive intracranial meningioma

Study	Patients	Radionuclide	Outcome	Comments
Van Essen *et al.* 2006 [21]	n=5	^{177}Lu-DOTATATE 7.4 GBq/dose every 6-10 weeks	SD: 2/5 (40%) PD: 3/5 (60%)	Adverse events • Hematotoxicity • Nausea/vomiting • hair loss
Bartolomei *et al.* 2009 [14]	n=29	^{90}Y-DOTATOC 5-15 GBq /dose every 2-3 months for 2-6 therapy cycles	SD: 19/29 (66%) PD: 10/29 (34%) mOS=40 mo (all patients)	Adverse events • No acute toxicity (allergy, fever) • No neurological toxicity

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				• Gr. 1-2 GI toxicity (nausea, vomiting) in 9/29 (31%) • Reversible gr. 1 hematotoxicity in 18/29 (62%) • Gr. 1 nephrotoxicity in 1/29 (3%)
Minutoli *et al.* 2014 [20]	n=8	^{111}In-Pentetreotide 1.1-7.4 GBq/dose every 6-10 weeks In 1 patient combined with ^{90}Y-DOTATOC (1.1 GBq/dose) In 2 patients combined with ^{177}Lu-DOTATATE (1.8 GBq/dose)	PR: 2 patients SD: 5 patients PD: 1 patient	Adverse events • Mild transient bone marrow suppression (n=4) • No other acute toxicity, neurological or renal function impairment observed
Gerster-Gillieron *et al.* 2015 [15]	n=15	^{90}Y-DOTATOC 3.7 GBq/dose every 8 weeks x 2 doses	SD: 13/15 (87%) PD: 2/15 (13%) mPFS=24 mo	• SSTR2 positivity in tumor required for enrollment Adverse events • Gr 3/4 hematotoxicity in 5/15 (33%) • Gr 1 and transient neurological deterioration in 2/15 (13%) • Gr 2 nephrotoxicity in 1/15 (7%) • Gr 1 hepatotoxicity in 5/15 (33%)
Marincek *et al.* 2015 [16]	n=34	^{90}Y-DOTATOC 7.4 GBq/dose every 6 weeks for up to 4 doses or ^{177}Lu-DOTATOC 7.4 GBq/dose every 6 weeks for up to 4 doses	SD: 23/34 (68%) PD: 11/23 (34%)	• Prospective phase II study • Higher radionuclide uptake (score 3, higher than liver uptake) was predictive of longer survival Adverse events • Gr 1-3 hematotoxicity in 12/34 (68%) • Gr 4 nephrotoxicity in 1/34 (3%)
Seystahl *et al.* 2016 [17]	n=20	^{177}Lu-DOTATATE (n=15) or	SD: 10/20 (50%) PD: 10/20 (50%) mPFS=5.4 mo	• Higher ^{68}Ga-DOTATATE uptake associated with longer PFS

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		^{90}Y-DOTATOC (n=3) or ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC (n=1) Dose: 3.4-7.6 GBq/cycle for up to 4 cycles		• Higher SSTR2 expression (IHC) was associated with SD at 6 months Adverse events • Gr. 3/4 lymphopenia in 6/20 (30%)

A prospective phase II clinical trial [16] evaluated ^{90}Y-DOTATOC (1.5-18.3 GBq/dose) or ^{177}Lu-DOTATOC (7.4-22.2 GBq/dose) administered to 34 patients with progressive meningioma. Treatment was repeated every 6 weeks until tumor progression or permanent toxicity occurred. Patients received 1-4 treatment cycles. Pertinent outcome measures included OS, ORR and toxicity.

The median follow-up period was 21.8 months. At that time 8 patients (24%) had died and 26 patients (77%) had survived. The mean survival was 27 years from time of diagnosis and 8.6 years from time of study enrollment. Twenty-three of 34 patients (68%) achieved stable disease (SD). Importantly, cox regression analysis showed that longer survival and following radionuclide therapy was associated with achieving stable disease compared to experiencing progressive disease (mean survival 9.6 vs 4.7 years, HR 0.017, 95% CI 0.001-0.35, p=0.01) and with high tumor uptake of the radiopeptide compared to low tumor uptake disease (HR 0.046, 95% CI 0.004-0.63, p=0.019). [16]

A retrospective observational study [17] evaluated efficacy and tolerability of treatment with ^{177}Lu-DOTATATE and/or ^{90}Y-DOTATOC given at 3.4-7.6 GBq/cycle every 6 weeks for up to 4 cycles in patients with progressive meningiomas. The median PFS in this study was 5.4 months and the median OS was not reached in this study. Forty-two percent of patients achieved PFS-6 and 79% achieved OS-12. Ten patients (50%) achieved stable disease and 10 patients (50%) experienced progressive disease. Higher tumor uptake of the diagnostic radionuclide ^{68}Ga-DOTATATE was associated with longer PFS (Spearman correlation r(SUV_{max})=0.37, p=0.0003 and r(SUV_{mean})=0.34, p=0.0024). In addition, higher (>grade 2) SSTR2 expression in the tumor tissue evaluated by immunohistochemistry correlated with stable disease six months after radionuclide therapy **[17]**.

2.2.7 Dose Rationale

^{177}Lu-DOTATATE (Lutathera) will be administered at a dose of 7.4 GBq (200 mCi) per dose every 8 (eight) weeks +/- 1 week for up to four doses or until disease progression, unacceptable toxicity, or withdrawal of consent.

Previous studies have used various dosing schedules of ^{177}Lu-labeled radionuclides. In the ERASMUS study, patients received ^{177}Lu-DOTATATE (Lutathera) at a dose of 7.4 GBq (200 mCi) every six to 13 weeks for up to four doses. In the NETTER-1 study, patients received ^{177}Lu-DOTATATE 7.4 GBq (200 mCi) per dose every eight weeks unless there was unacceptable toxicity, unequivocal disease progression, death of the patient or withdrawal of consent. The dose of ^{177}Lu in three studies evaluating ^{177}Lu-labeled peptides as monotherapy for progressive meningiomas ranged from 3.4-7.6 GBq/cycle administered every 6-10 weeks [16, 17, 21].

While there are no studies available which compared efficacy and toxicity of different dosing schedules, treatment appeared to be well tolerated in all of these studies. While hematopoietic toxicity was common in these studies and occurred in up to 68% of patients [14, 16, 21], this was typically mild and grade 3 or 4 hematopoietic toxicity was observed in about one third of patients only [15, 17].Other observed toxicities include GI toxicity (nausea/vomiting), nephrotoxicity and hepatotoxicity **(Table 3).**

2.3 Rationale for the Current Study

Meningiomas represent the most common primary intracranial tumors [1]. A subset of meningiomas are aggressive tumors that typically recur and/or progress despite treatment consisting of surgical resection and/or radiotherapy [2, 3], or are considered high risk due to residual tumor being located near critical intracranial organs at-risk for radiation injury [24]. Once any meningioma progresses, survival times are typically estimated in months and there are no effective medical therapies

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available [4, 5]. Somatostatin receptors and in particular somatostatin receptor 2 (SSTR2) are overexpressed in meningiomas and represents a promising treatment target [6-8].

^{177}Lu-DOTATATE (Lutathera) is a radionuclide-labeled octreotide analogue that preferentially targets SSTR2. Several case series and one prospective phase II clinical study demonstrated that treatment with ^{177}Lu-labeled radionuclides lead to promising treatment responses in patients with progressive intracranial meningiomas. Although clinical efficacy was not observed all patients in these prior studies, some data have indicated that higher pre-treatment ^{68}Ga-radionuclide uptake on PET imaging and confirmed SSTR2 expression by IHC correlated with longer progression-free survival [17].

We therefore hypothesize that treatment with ^{177}Lu-DOTATATE (Lutathera) will be effective for patients with SSTR2-expressing progressive WHO grade I-III or high-risk meningioma, as measured by PFS-6.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Based on detailed studies regarding the potential risks and adverse events observed in the NETTER-1 [13] and ERASMUS studies, the Lutathera package insert lists the following risks associated with Lutathera treatment:

Risk from Radiation Exposure
Lutathera contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. However, there is insufficient data available to quantify the exact risk for specific cancer subtypes and organs.

Radiation can be detected in the urine for up to 30 days following Lutathera administration. Patients, medical personnel and household contacts will therefore be advised in detail regarding specific measures to minimize radiation exposure during and after treatment with Lutathera consistent with institutional good radiation safety practices and patient management procedures.

Myelosuppression
In NETTER-1, myelosuppression occurred more frequently in patients receiving Lutathera with long-acting octreotide compared to patients receiving high-dose long-acting octreotide (all grades/grade 3 or 4): anemia (81%/0) versus (54%/1%); thrombocytopenia (53%/1%) versus (17%/0); and neutropenia (26%/3%) versus (11%/0). In NETTER-1, platelet nadir occurred at a median of 5.1 weeks following the first dose. Of the 59 patients who developed thrombocytopenia, 68% had platelet recovery to baseline or normal levels. The median time to platelet recovery was 2 months. Fifteen of the nineteen patients in whom platelet recovery was not documented had post-nadir platelet counts. Among these 15 patients, 5 improved to Grade 1, 9 to Grade 2, and 1 to Grade 3.

Blood cell counts will therefore be monitored and Lutathera will be withheld, dose-reduced, or permanently discontinued based on severity of adverse reaction.

Secondary Myelodysplastic Syndrome and Leukemia
In NETTER-1, with a median follow-up time of 24 months, myelodysplastic syndrome (MDS) was reported in 2.7% of patients receiving Lutathera with long-acting octreotide compared to no patients receiving high-dose long-acting octreotide. In ERASMUS, 15 patients (1.8%) developed MDS and 4 (0.5%) developed acute leukemia. The median time to the development of MDS was 28 months (9 to 41 months) for MDS and 55 months (32 to 155 months) for acute leukemia.

Renal Toxicity
In ERASMUS, 8 patients (<1%) developed renal failure 3 to 36 months following treatment with Lutathera. Two of these patients had underlying renal impairment or risk factors for renal failure (e.g., diabetes or hypertension) and required dialysis.

The recommended nephroprotective amino acid solution will therefore be administered before, during and after Lutathera to decrease reabsorption of ^{177}Lu-DOTATATE through the proximal tubules and decrease the radiation dose to the kidneys. The dose of the amino acid solution should not be increased if the dose of Lutathera is reduced. Patients will be advised to urinate frequently during and after administration of Lutathera.

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Serum creatinine and calculated creatinine clearance will be monitored and Lutathera will be withheld, dose-reduced, or permanently discontinued based on severity of reaction.

Patients with baseline renal impairment may be at greater risk of toxicity; more frequent assessments of renal function will be performed in patients with mild or moderate impairment. Lutathera has not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Hepatotoxicity
In ERASMUS, 2 patients (<1%) were reported to have hepatic tumor hemorrhage, edema, or necrosis, with one patient experiencing intrahepatic congestion and cholestasis. Patients with hepatic metastasis may be at increased risk of hepatotoxicity due to radiation exposure.

Serum transaminases, bilirubin and albumin levels will be and Lutathera will be withheld, dose-reduced, or permanently discontinued based on severity of reaction.

Neuroendocrine Hormonal Crisis
Neuroendocrine hormonal crises, manifesting with flushing, diarrhea, bronchospasm and hypotension, occurred in 1% of patients in ERASMUS and typically occurred during or within 24 hours following the initial Lutathera dose. Two (<1%) patients were reported to have hypercalcemia.

Given that this study will evaluate Lutathera with progressive and/or residual intracranial meningiomas and given that meningiomas are typically not secreting somatostatin, it is unclear if this type of adverse event also is to be expected in this study population.

Nevertheless, patients will be monitored for flushing, diarrhea, hypotension, bronchoconstriction or other signs and symptoms of tumor-related hormonal release. Intravenous somatostatin analogs, fluids, corticosteroids, and electrolytes will be administered as indicated.

Embryo-Fetal Toxicity
Based on its mechanism of action, Lutathera can cause fetal harm. There are no available data on the use of Lutathera in pregnant women. No animal studies using ^{177}Lu-DOTATATE have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including Lutathera, have the potential to cause fetal harm.

Pregnancy status will be verified in all females of reproductive potential prior to initiating Lutathera. Females and males of reproductive potential will be advised of the potential risk to a fetus. Females of reproductive potential will be advised to use effective contraception during treatment with Lutathera and for 7 months after the final dose. Males with female partners of reproductive potential will be advised to use effective contraception during treatment and for 4 months after the final dose.

Risk of Infertility
Lutathera may cause infertility in males and females. The recommended cumulative dose of 29.6 GBq of Lutathera results in a radiation absorbed dose to the testis and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

Females and males of reproductive potential will be advised of the potential risk of infertility prior to initiating Lutathera.

Table 2 and **Table 3** outline the incidence of adverse reactions and laboratory abnormalities observed in the NETTER-1 study [13]. The most common Grade 3-4 adverse reactions occurring with a greater frequency among patients receiving Lutathera with octreotide (treatment arm) compared to patients receiving high-dose octreotide (comparator arm) included lymphopenia (44%), increased GGT (20%), vomiting (7%), nausea and elevated AST (5% each), and increased ALT, hyperglycemia and hypokalemia (4% each).

Safety data are also available from 1214 patients enrolled in the ERASMUS study. A retrospective medical record review was conducted on a subset of 811 patients to document serious adverse reactions. Eighty-one (81%) percent of patients in the subset received a cumulative dose ≥ 22.2 GBq (≥ 600 mCi). With a median follow-up time of more than 4 years, the

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following rates of serious adverse reactions were reported: myelodysplastic syndrome (2%), acute leukemia (1%), renal failure (2%), hypotension (1%), cardiac failure (2%), myocardial infarction (1%), and neuroendocrine hormonal crisis (1%).

The adverse events observed in the clinical studies in patients receiving ^{177}Lu-labeled radionuclide therapy are outlined in **Table 3.** In general, hematopoietic, renal and hepatic toxicity also appear to be the most commonly observed adverse events.

Table 2. Adverse Reactions Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1

Adverse Reaction[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
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				
Fatigue	38	1	26	2
Peripheral edema	16	0	9	1
Pyrexia	8	0	3	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
Myalgia	5	0	0	0
Neck Pain	5	0	0	0
Nervous system disorders				
Headache	17	0	5	0
Dizziness	17	0	8	0
Dysgeusia	8	0	2	0
Psychiatric disorders				
Anxiety	12	1	5	0
Renal and urinary disorders				
Renal failure*	12	3	3	1
Radiation-related urinary tract toxicity**	8	0	3	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

[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays adverse reactions occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2% (grades 3-4)]
*Includes the terms: Glomerular filtration rate decreased, acute kidney injury, acute prerenal failure, azotemia, renal disorder, renal failure, renal impairment
**Includes the terms: Dysuria, micturition urgency, nocturia, pollakiuria, renal colic, renal pain, urinary tract pain and urinary incontinence

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Table 3. Laboratory Abnormalities Occurring in ≥ 5% (All Grades) of Patients Receiving LUTATHERA with Octreotide in NETTER-1

Laboratory Abnormality[1]	LUTATHERA and Long-Acting Octreotide (30 mg) (N = 111)		Long-Acting Octreotide (60 mg) (N = 112)	
	All grades %	Grade 3-4 %	All grades %	Grade 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				
Creatinine increased	85	1	73	0
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	29	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	54	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

*Values are worst grade observed after randomization
[1]National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Only displays laboratory abnormalities occurring at a higher incidence in LUTATHERA-treated patients [between arm difference of ≥5% (all grades) or ≥2%(grades 3-4)]

2.4.1.1 Other

Additional risks associated with participation in this study, include the risk of phlebotomy and breach of confidentiality. Risks associated with phlebotomy include weaknesses, redness, pain, bruising, bleeding, or infection at the needle site. Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

2.4.2 Known Potential Benefits

The potential benefits to subjects participating in this study are improved tumor control and improved survival. Currently there is no effective therapy for progressive WHO I-III and residual, high risk intracranial meningiomas once surgical and radiotherapeutic options have been exhausted. There is a lack of prospective clinical studies that prove improved survival in this setting.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective of this study is to determine the **Progression Free Survival at 6 months (PFS-6)** of Lutathera in patients with progressive WHO I-III and high-risk meningiomas that have positive ^{68}Ga-DOTATATE uptake on MR-PET.

3.2 Secondary Objectives

- To evaluate the overall **safety and tolerability** of Lutathera in patients with meningioma.

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- To determine the following efficacy variables in patients receiving Lutathera for progressive or residual high-grade meningioma.

    - Objective Response Rate (ORR)
    - Overall Survival at 12 months (OS-12)
    - median Progression Free Survival (mPFS)
    - median Overall Survival (mOS)

3.3 Exploratory Objectives

For further details regarding background and rationale for the Exploratory Objectives, please see **Section 4.2.3 Exploratory Endpoints** and **Attachment 5.**

- Exploratory cohort, n=10 (NYU site only). To evaluate the association of ^{177}Lu-DOTATATE dosimetry with:
    - pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - Progression-free survival at 6 months (PFS-6)
    - Objective Response Rate (ORR)
    - Overall Survival at 12 months (OS-12)
    - median Progression Free Survival (mPFS)
    - median Overall Survival (mOS)

- To evaluate the association of PFS-6 with:
    - pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - SSTR2 expression by IHC
    - meningioma molecular subtypes determined by DNA methylation array [22]
    - WHO grade
    - DNA mutations (e.g. NF2, SMO, PI3K/Akt pathway)

- To evaluate the association of pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET with
    - SSTR2 expression by IHC
    - meningioma molecular subtypes determined by DNA methylation array [22]
    - WHO grade
    - DNA mutation (e.g. NF2, SMO, PI3K/Akt pathway)

4 Study Design and Endpoints

4.1 Description of Study Design

This is a single arm, open-label, multicenter, two-stage, phase 2 clinical study to evaluate the efficacy of Lutathera (^{177}Lu-DOTATATE) in patients with progressive WHO I-III or high-risk meningioma that have positive ^{68}Ga-DOTATATE uptake on MR-PET.

4.2 Study Endpoints

Please refer to **Section 10.3, Description of Statistical Methods** for description of the Statistical Analysis Plans for the Study Endpoints outlined below.

4.2.1 Primary Study Endpoint

Progression Free Survival at 6 months (PFS-6) is defined as the proportion of subjects who achieve a complete response (CR), partial response (PR), or stable disease (SD) at 6 months from start of Lutathera treatment. Radiographic treatment response will be assessed by measuring the bidirectional tumor diameters on contrast-enhanced MRI in patients who received at least one dose of Lutathera compared to baseline measurements at time of study enrollment.

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4.2.2 Secondary Study Endpoints

- **Safety and adverse events:** Safety will be assessed by reported/elicited adverse events, laboratory assessments including hematology and chemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.

- **Objective Response Rate (ORR)** is defined as the best response [Complete Response (CR) + Partial Response (PR) + stable disease (SD)] recorded from the start of the study until the end of study in patients who received at least one dose of Lutathera.

- **Overall Survival at 12 months (OS-12)** is defined as the proportion of subjects who are alive at 12 months from start of Lutathera treatment. Survival data will be captured by clinical follow-up every 8 weeks during treatment with Lutathera and by follow-up phone calls every 12 weeks for up to 2 years after completion of treatment with Lutathera.

- **Progression Free Survival (PFS)** is defined as the number of days from the treatment start date to the date of documented disease progression or death due to any cause.

- **Overall Survival (OS)** is defined as the number of days from the treatment start date to the date of death due to any cause.

4.2.3 Exploratory Endpoints

For further details regarding background and rationale for the Exploratory Endpoints, please see **Attachment 5.**

- Exploratory cohort, n=10 (NYU site only). We aim to better understand to what extent and over what time period the radioactive dose from ^{177}Lu-DOTATATE is present and distributed within the target lesions compared to the rest of the body. We aim to explore the ^{177}Lu-DOTATATE dosimetry with:
    - pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET
    - Progression-free survival at 6 months (PFS-6)
    - Objective Response Rate (ORR)
    - Overall Survival at 12 months (OS-12)
    - median Progression Free Survival (mPFS)
    - median Overall Survival (mOS)

- **^{68}Ga-DOTATATE PET MR Imaging**: In addition to testing whether ^{68}Ga-DOTATATE PET MR uptake at baseline predicts response to Lutathera, we will explore the degree of ^{68}Ga-DOTATATE uptake on PET MRI at baseline to assess whether there is correlation to PFS-6, and also whether ^{68}Ga-DOTATATE uptake on PET MRI at 6 months post-treatment serves as a pharmacodynamic biomarker for Lutathera in meningioma. We hypothesize that the degree of ^{68}Ga-DOTATATE uptake on PET MRI will correlate with response to treatment. To test this, we will perform 3D list mode ^{68}Ga-DOTATATE PET imaging combined with T1 DCE / T2* DSE perfusion MR imaging on all patients in the trial at baseline prior to initiation of Lutathera treatment and 6 months after the initiation of Lutathera treatment prior to the last dose of Lutathera treatment (C4D1). Upon the completion of the study, each subject's PET MR imaging will be post-processed with texture-based analysis as a part of the Artificial Intelligence initiative at NYU. We aim to detect statistical and structural features that would allow us recognize patterns of treatment response and failure at early time points.

  We aim to explore the
    - Degree of pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET with:
        - PFS-6
        - SSTR2 expression by IHC;
        - meningioma molecular subtypes determined by DNA methylation array [22];
        - WHO grade;
        - and DNA mutations (NF2, SMO, PI3K/Akt pathway, etc).
    - Association of change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET compared to baseline with:

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  - PFS-6
  - SSTR2 expression by IHC
  - meningioma molecular subtypes determined by DNA methylation array [22];

- **SSTR2 Immunohistochemistry:** We hypothesize that degree of SSTR2 expression will correlate with outcome (PFS-6), baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

- **Genome-wide DNA methylation profiling**: A recent comprehensive analysis of ~500 meningiomas demonstrated that a DNA methylation-based meningioma classification has significantly greater power for predicting tumor recurrence and prognosis compared to the histopathologic grade based on WHO classification, thus identifying aggressive tumors with greater accuracy [22]. We hypothesize that response will correlate with DNA methylation-based meningioma subtypes. To test this, we will perform DNA methylation-based meningioma classification on all patients enrolled in the study and correlate DNA methylation-based subtype with outcome (PFS-6), SSTR2 expression, and baseline ^{68}Ga-DOTATATE uptake by PET MRI.

- **Whole exome next-generation sequencing:** We will perform whole-exome next-generation sequencing on all archival tumor specimens (NYU genomics core) to evaluate associations between recurrent mutations recently identified in meningiomas (e.g. NF2, SMO, PI3K/Akt pathway, etc) and outcome (PFS-6), SSTR2 expression, baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female subjects aged ≥ 18 years.
2. Karnofsky Performance Status ≥ 60.
3. Histologically confirmed diagnosis of WHO grade I-III meningioma:
    a. For grade I meningioma, subjects must have:
        i. Progressive disease after at least surgical resection and radiotherapy, as defined as an increase in size of the measurable primary lesion (bidirectional area) on imaging by 25% or more between scans separated by no more than 12 months.

        or

        ii. Progressive residual tumor after maximal safe resection, be located at or near critical organs at-risk [24] and considered to be high-risk for radiation injury by the treating investigator. Prior external beam radiation therapy is not required for these subjects.

    b. For Grade II or III meningioma, subjects must have either:
        i. Progressive disease after at surgical resection and radiotherapy, as defined as an increase in size of the measurable primary lesion (bi-directional area) on imaging by 25% or more between scans separated by no more than 12 months

        or

        ii. Residual measurable disease after surgery without requirement of progression.

4. Positive ^{68}Ga-DOTATATE uptake on PET-MRI.
    a. Positive uptake is defined as uptake higher than the background and SUV ratios adjusted to the liver and spleen uptake (adopted from Krenning score).[25]

    b. ^{68}Ga-DOTATATE uptake in target lesions should be Krenning score ≥ 2.

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5. Presence of measurable disease defined as at least one lesion measuring ≥10 mm in at least one dimension by contrast-enhanced MRI performed within 30 days prior to study registration.

6. Multifocal disease is allowed but is limited to ≤ 3 measurable intracranial mass lesions on most recent postcontrast MRI.

7. Any neurological symptoms must be stable for at least 28 days prior to enrollment and patients should not require steroids to control neurological symptoms.

8. There is no limit on the number of prior surgeries, radiation therapy, radiosurgery treatments or systemically administered therapeutic agents.

9. For patients treated with external beam radiation, interstitial brachytherapy or radiosurgery, an interval ≥24 weeks must have elapsed from completion from these therapies to registration unless there is histopathologic confirmation of recurrent tumor or there is new enhancing tumor outside the radiation field (beyond the high dose region or the 80% isodose line).

10. An interval of ≥28 days (or 5 half-lives, whichever is shorter) from prior cytotoxic chemotherapy (6 weeks from nitrosoureas), biologic agent, investigational agent or any other systemic agent prescribed for the purpose of treating meningioma.

11. An interval of ≥28 days from craniotomy and ≥7 days from stereotactic biopsy.

12. Availability of a paraffin-embedded archival tumor block from most recent tumor resection sufficient to generate at least 8 unstained slides but preferably up to 25 unstained slides; or, if a paraffin tumor block is unavailable, at least 8 unstained slides but preferably up to 25 unstained slides.

    a. Report of positive SSTR2 expression by immunohistochemistry in the most recent tumor specimen.

13. Patients must be willing and able to undergo regular MRI scans of the brain.

14. Patients must have recovered to CTCAE grade ≤1 or pretreatment baseline from clinically significant adverse events related to prior therapy (exclusions include alopecia, laboratory values listed per inclusion criteria, lymphopenia, sensory neuropathy ≤ grade 2, or other ≤ grade 2 not constituting a safety risk based on the investigator's judgment).

15. Adequate organ and bone marrow function as defined below (within 30 days of treatment initiation):
    - White blood cell (WBC) ≥ 2,000/mm^3
    - Absolute neutrophil count (ANC) ≥ 1,000/mm^3
    - Platelet count ≥ 75,000/mm^3
    - Hemoglobin ≥ 8 gm/dL
    - AST(SGOT)/ALT(SGPT) ≤ 3 x laboratory upper limit of normal (ULN)
    - Creatinine clearance (measured or calculated) ≥ 50 mL/min OR creatinine levels > 150 µMol/L (1.7 mg/dL)
    - Total serum bilirubin ≤ 3 X ULN (except participants with Gilbert's Syndrome, who can have a total bilirubin ≤ 5 X ULN)
    - Serum albumin level of more than 3.0 g/dL, unless the prothrombin time value was within the normal range

16. Women of childbearing potential (WOCB) and men able to father a child must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in the study, she must inform her treating physician immediately.

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17. Able to understand and willing to sign an IRB approved written informed consent document.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with a clinical diagnosis of NF2 (either by NIH or Manchester criteria) or with a molecular diagnosis of NF2.

2. Patients with radiation-associated meningiomas.

3. Life Expectancy ≤ 6 months.

4. Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm. This includes treatment with Somatostatin LAR within 4 weeks prior to enrollment, or any patient receiving treatment with short-acting Octreotide that cannot be interrupted for greater than 24 hours before treatment.

5. Peptide receptor radionuclide therapy at any time prior to registration.

6. Known hypersensitivity to somatostatin analogues or any component of the ^{68}Ga- DOTATATE or ^{177}Lu-DOTATATE formulations.

7. Known additional malignancy that is progressing or requires active treatment within 2 years of start of study drug. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and *in situ* cervical cancer that has undergone potentially curative therapy.

8. Current or planned participation in another study of an investigational agent or investigational device.

9. Active infection requiring intravenous therapy with antibiotics.

10. Uncontrolled intercurrent illness including, but not limited to, clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), congestive heart failure (≥ NYHA class II), unstable angina pectoris, or serious cardiac arrhythmia requiring medication.

11. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

12. Active Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test is positive).

13. Other severe acute or chronic medical or psychiatric conditions (within the past year) including recent or active suicidal ideation or behavior, or laboratory abnormalities that may increase the risk associated with study participation or treatment on study or may interfere with the interpretation of study results.

14. Pregnant and/or breastfeeding patients. Women of childbearing potential (WOCBP) must have a negative pregnancy test within 14 days of study entry.

5.3 Vulnerable Subjects

Any patient who lacks capacity to provide informed consent will be excluded. The participating investigator will assess the subject's capacity to provide informed consent to ensure subjects who lack capacity to provide informed consent are not enrolled. The assessment will include open-ended questions (i.e., not yes or no questions) regarding the purpose and involvement of the research. The investigator evaluating patient capacity will be an M.D. with experience in evaluating patient capacity. Students and employees who are also patients will be invited to participate in the study. Students' and employees' decision of whether or not to participate will not affect their academic status, grades, or employment. If they

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agree to participate, this information will not be linked to any type of academic or employee record. Their supervisors will not be informed of whether or not they have chosen to participate in this study.

5.4 Subject Recruitment and Screening

All efforts will be made to actively recruit and retain women and members of minority groups and their subpopulations in this study, with the objective of accruing a study population that resembles the age, gender, ethnic and racial composition of the adult U.S. population as closely as possible. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of these populations. If any differences are observed in the outcomes of these populations, these results will be reported.

Patients will be recruited for the study from investigator or sub-investigator clinical practices. Screening requirements and diagnostic testing necessary to meet all inclusion (**Section 5.1**) and exclusion criteria (**Section 5.2**) are listed in detail in **Section 7.1**. Identification of prospective subjects will be conducted by reviewing the medical records of patients in the investigator or sub-investigator's clinical practice and the investigator and sub-investigators will use all efforts to limit its use of protected health information. For study requirements to maintain subject confidentiality and management of study information according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), refer to **Section 13.4** and **Section 14.1.**

Informed consent will take place in the investigator or sub-investigator's clinical practice per institutional guidelines when a patient is deemed potentially eligible for participation by the study investigator or sub-investigator. See **Section 13.3** for complete details of the informed consent process. Patients will be asked to give medical information about themselves specific to the inclusion and exclusion criteria outlined in the protocol. Only study investigators will have access to this information. Information collected will include Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth), Parameters for eligibility, Parameters for exclusion, and Parameters for stratifications.

5.4.1 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject’s medical chart.

5.4.2 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Overall Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial’s six-month Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC’s semi-annual reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide remote interim monitoring visits beginning within the first 6-8 weeks of first subject enrollment and every 6-8 weeks thereafter.

5.5 Registration Procedures

5.5.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient’s standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office (CTO). The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each criterion has been met

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Registration will occur within 48 business hours of research coordinators' receipt of all the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be distributed to the study team upon registration.

Pretreatment evaluation will therefore be dictated by standard clinical practice. Eligible patients will be entered into the study by the study coordinator.

All patients will be required to sign a written informed consent prior to being registered on this study. Any patient not registered to the study before treatment begins will be considered ineligible and registration will be denied. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

5.5.2 Patient Registration at Other Participating Institutions

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULH policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

Enrollment at additional sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYULH Perlmutter Cancer Center Clinical Trials Office. Once, all required documents are provided to NYULH PCC Clinical Trials Office an activation notification will be sent to the PI and research coordinator at that site.

Central registration for this study will take place at NYULH PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYULH PCC Quality Assurance Unit and forward a copy of the signed consent to NYULH PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYULH via email (PCC-QAU@nyulangone.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 business hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC Clinical Trials Office will return a signed eligibility confirmation worksheet with the subject's unique study number. The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within 5 days; issues that would cause treatment delays should be discussed with the overall PI, Alexandra Miller, MD, PhD. Subjects must not start any protocol procedures prior to registration. Pretreatment evaluation will therefore be dictated by standard clinical practice. Except in very unusual circumstances, each participating institution will order the study agent directly from the supplier.

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Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYULH PCC Clinical Trials Office and to their IRB as per site institutional policy. See **Section 8.4** for detailed instructions on reporting requirements.

5.6 Duration of Study Participation

The duration of the study subject's participation will be approximately 12 months and individual time periods are estimated to be as follows:

- Screening: up to 30 days
- Duration of Lutathera (^{177}Lu-DOTATATE) treatment: 32 weeks
- Duration until End of Treatment visit: 56 (±7 days) days

After participation in this study, subjects will be contacted periodically until death to obtain survival data.

5.7 Total Number of Participants and Sites

A Simon 2-stage design will be used for this study. Recruitment for stage I will end when 14 participants are enrolled across four participating study sites. If the study proceeds to stage II, an additional 18 participants will be enrolled for a total of 32 participants across four participating study sites.

5.8 Participant Withdrawal or Termination

5.8.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for subject withdrawal from the study may include but are not limited to:

- Subject withdrawal of consent
- Disease progression
- Intolerable toxicity
- Initiation of a different anti-meningioma therapy,
- Any medical condition that the investigator or sponsor determines may jeopardize the subject's safety if he or she continues in the study or continues treatment with the study drug.
- Failure of the subject to adhere to protocol requirements (e.g., not complying with protocol required visits, assessments, and dosing instructions)
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Study termination by the sponsor

Every effort should be made to obtain information on patients who withdraw from the study, including the reason for taking a participant off study. The date the participant was removed, must be documented. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

5.8.2 Handling of Participant Withdrawals or Termination

For End of Study procedures and required assessments see **Section 7 Study Schedule and Procedures**, and **Schedule of Events** (**Attachment 1**). After the end of Study, each subject will be followed for 30 days for adverse event and serious adverse event reporting. Assessments may continue for ongoing reportable adverse events. Participants removed from protocol treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

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Subjects who discontinue for any reason will have post-study follow-up for survival. After coming off study, each subject will be contacted every 3 months by telephone or medical record review to assess survival status until they meet criteria for removal from study as detailed below.

- Withdrawal of permission to record at least survival data
- Lost to follow-up
- Death

If a subject withdraws permission to record at least survival data after coming off treatment, this must be documented along with the date the subject withdraws permission. Subjects will be considered lost to follow up if no medical records are available to be reviewed and two phone calls each to the subject and then the subject's next-of-kin (if the subject does not respond) are not returned over two consecutive 3 month periods.

5.9 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators at each participating site, the funding agency (Advanced Accelerator Applications), the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Lutathera)

6.1 Lutathera (^{177}Lu-DOTATATE)

Lutathera (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, ^{177}Lu-DOTATATE), is a lutetium-177 (^{177}Lu) radiolabeled somatostatin analog peptide conjugated with the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

^{177}Lu-DOTATATE has a high affinity for somatostatin receptor, type 2 (SSTR2). It specifically binds to and effectively kills malignant cells that overexpress SSTR2.

6.1.1 Acquisition of Lutathera

Lutathera clinical supply will be provided by Advanced Accelerator Applications USA, Inc.

Ordering Lutathera: All orders for Clinical Research Lutathera Infusions must be made using an Order Form provided by Advanced Accelerator Applications USA, Inc. and must be faxed or e-mailed to the address below. To ensure availability, orders should be placed at least 2 weeks prior to calibration date.

E-Mail: orders-US@adacap.com
Fax: 973-272-1112

6.1.2 Lutathera Formulation, Appearance, Packaging, and Labeling

Formulation and Appearance

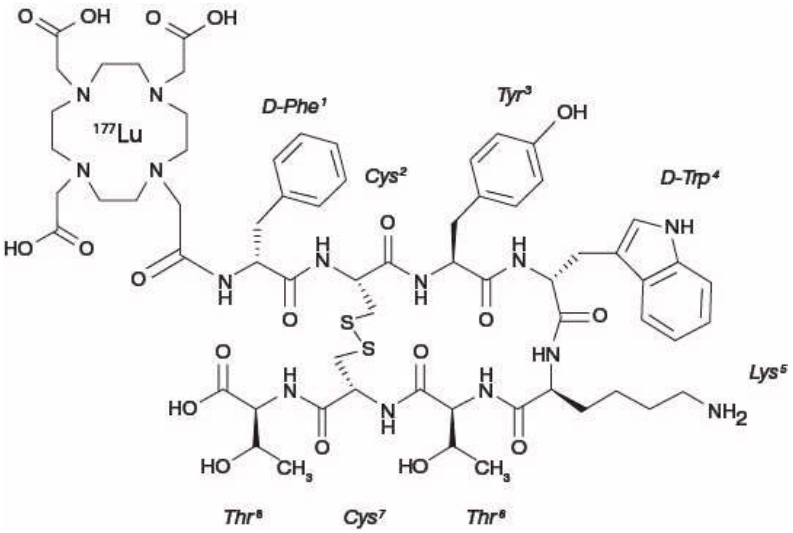
Lutathera is presented as a sterile, preservative-free and clear, colorless to slightly yellow solution for intravenous use supplied in a colorless Type I glass 30 mL single-dose vial. Each vial contains 370 MBq/mL (10 mCi/ml) of ^{177}Lu-DOTATATE. The total amount of radioactivity per single-use vial is 7.4 GBq (200 mCi) ± 10% calibrated to the date and

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time of injection. The solution volume in the vial is adjusted from 20.5 mL to 25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity.

^{177}Lu-DOTATATE is described as ^{177}Lu-N-[(4,7,10-Tricarboxymethyl-1,4,7,10-tetraazacyclododec-1-yl) acetyl]-Dphenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic (2-7) disulfide. The molecular weight is 1609.6 Daltons. The structural formula is described in **Figure 3**.

Figure 3. Structural Formula of ^{177}Lu-DOTATATE



In addition to ^{177}Lu-DOTATATE, each single-dose vial contains acetic acid (0.48 mg/mL), sodium acetate (0.66 mg/mL), gentisic acid (0.63 mg/mL), sodium hydroxide (0.65 mg/mL), ascorbic acid (2.8 mg/mL), diethylene triamine pentaacetic acid (0.05 mg/mL), sodium chloride (6.85 mg/mL), and Water for Injection (ad 1 mL). The pH range of the solution is 4.5 to 6.

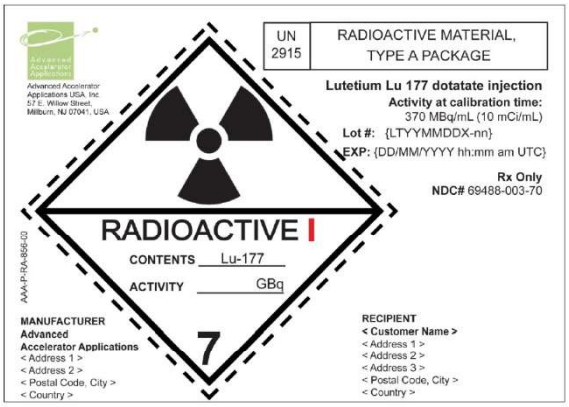
Lutathera is manufactured by Advanced Accelerator Applications, a Novartis company. The product used in this study has essentially the same composition as the product used in the NETTER-1 study [13] and in the Phase I/II clinical trial performed at the Erasmus MC. It is produced in cGMP industrial manufacturing facilities.

Packaging and Labeling
Lutathera is provided in Type I glass vials closed with a bromobutyl rubber stopper and sealed with an aluminum Flip Off® crimp seal closure. The product vial is packaged in a lead shielded container placed in a plastic sealed container (**NDC# 69488-003-01**). The product is shipped in a Type A package (**NDC# 69488-003-70**).

The information given on the package label is illustrated in **Figure 4**.

Figure 4. Lutathera sample package label

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6.1.3 Physical and radiopharmaceutical properties of Lutathera

Lutathera is a ready-to-use radiopharmaceutical drug compound. ^{177}Lu-DOTATATE is a β-emitting radionuclide. The mean path length of the β-emission is about 2.2 mm (mean penetration range of 0.67 mm), which is sufficient to effectively kill targeted tumor cells, with a limited effect on neighboring normal cells.

^{177}Lu decays to stable hafnium-177 (^{177}Hf) with a half-life of 6.647 days, by emitting β-radiation with a maximum energy of 0.498 MeV (78.6%) and photonic radiation (γ) of 0.208 MeV (11%) and 0.113 MeV (6.4%). The average beta energy is approximately 0.13 MeV.

Table 4 gives details regarding the radiations of ^{177}Lu and **Table 5** gives details regarding the radioactive decay times of ^{177}Lu.

Table 4. ^{177}Lu Main radiations (per Lutathera® package insert)

Radiation	Energy (keV)	Iβ%	Iγ%
β^-	β	176.5	12.2
β	β	248.1	0.05
β^-	β	384.9	9.1
β^-	β	497.8	78.6
γ	71.6		0.15
γ	112.9		6.40
γ	136.7		0.05
γ	208.4		11.0
γ	249.7		0.21
γ	321.3		0.22

Table 5. Physical Decay of ^{177}Lu (per Lutathera® package insert)

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	48 (2 days)	0.812
1	0.996	72 (3 days)	0.731
2	0.991	168 (7 days)	0.482
5	0.979	336 (14 days)	0.232
10	0.958	720 (30 days)	0.044
24 (1 day)	0.901	1080 (45 days)	0.009

6.1.4 Lutathera Storage and Stability

Storage

The Lutathera drug product is stored by the Nuclear Medicine specialists (physician and technologist) in appropriate premises.

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Lutathera must be stored at a temperature below +25 °C (77 °F) but not lower than +3 °C (37.4 °F) in its original package for radioprotection purposes, according to national regulations concerning radioactive products.

Lutathera drug must not be frozen. Storage of radiopharmaceuticals must be in accordance with national regulation on radioactive materials. It must be kept out of the sight and reach of children at all times.

Stability and Shelf Life

The shelf life of Lutathera is 72 hours from the date and time of calibration. Vial radioactivity must be verified before infusion. Lutathera should be discarded appropriately at 72 hours.

6.1.5 Handling and Safety Precautions

Lutathera is a **r**adiopharmaceutical compound and should be received, used and administered only by authorized users in the designated clinical setting. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organization. Recommendation in the Safety Data Sheet (SDS) should be followed. The SDS will be provided separately to the study sites.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, sweating etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. For instruction on preparation of the medicinal product before administration, see **Section 6.2**, **t**he **Lutathera Investigator Brochure**, the **Lutathera Package Insert** and the **Pharmacy Manual**.

Safety Precautions

Waterproof gloves and effective radiation shielding should always be used when handling Lutathera.

Pregnancy status of women of reproductive potential should be performed prior to each Lutathera dose.

In the event of vial leak, breakage or damaged product receipt

If at any time in the preparation of the Lutathera drug product the integrity of the container and vial is compromised it should not be used and the Radiation Safety office should be notified immediately.

Minimizing radiation exposure

Always use the principles of distance, time and shielding (reducing the manipulation of the vial and using the material already supplied by the manufacturer) to reduce radiation exposure. Patients should be isolated during treatment in a room with private bathroom, if possible. Each study member involved in treatment and imaging, during and within 7 days after the treatment should wear radiation safety badge and if necessary the ring.

Administration procedures should be carried out in a way to minimize risk of contamination and irradiation of the operators. Adequate shielding is mandatory. It is mandatory to wear protective high quality (latex/nitrile) gloves when handling the medicinal product to avoid direct contact with the radiopharmaceutical (vial/syringe). Any unused medicinal product or waste material should be disposed according to local requirements.

This preparation is likely to result in a relatively high radiation dose to most patients. The administration of 7,400 MBq may result in significant environmental hazard. This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered, hence the patients should be provided with the radiation safety measures to be followed after the treatment by the radiation safety officer. Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations.

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6.1.6 Lutathera Product Preparation Procedures prior to Administration

Before use, packaging must be inspected for damage, and a survey meter should be used to determine if any radioactive contamination is present.

The vial must not be opened. If the integrity of the vial is compromised, the product should not be used.
Administration procedures should be carried out in a way to minimize risk of contamination from the medicinal product and accidental irradiation of the operators. It is necessary to wear waterproof gloves and suitable effective protection when handling Lutathera.

Flow valves should be manipulated aseptically when connecting them to the infusion system.
Any unused medicinal product or waste material should be disposed of in accordance with local and federal laws.

The solution should be inspected visually prior to use, and only clear colorless to yellowish solutions free of visible particles should be used. The visual inspection of the solution should be performed under a shielded screen for radioprotection purposes.

Lutathera is not to be used before receipt of the batch release certificate.

The amount of radioactivity in the radiopharmaceutical vial must be measured with an appropriate and calibrated device prior to infusion in order to confirm that the actual amount of radioactivity to be administered is equal to the planned amount at the infusion time. See **Attachment 6**.

Please refer to the pharmacy manual for complete details.

6.1.7 Lutathera Treatment Regimen

The treatment regimen consists of 4 administrations of 7.4 GBq (200 mCi) +/-10% at the date and time of infusion. The recommended interval between two infusions is 8 weeks (± 1 week), which could be extended up to 16 weeks in case of dose modifying toxicity.

6.1.8 Patient preparation

Patient should be encouraged to drink a sufficient amount of water necessary to urinate every hour on the day of infusion and the day after. Patient should be encouraged to defecate every day and to use laxative if needed.

The doctor will explain to the patient the general recommendations and precautions that should be followed to limit radiation exposure to third parties.

For renal protection purpose, it is mandatory to start a 4-hour co-infusion of an amino acid solution 30 minutes prior to start Lutathera infusion.

To avoid treatment-related nausea and vomiting, it is recommended to inject an intravenous bolus of an antiemetic drug 30 minutes before the start of Lutathera infusion.

6.1.9 Concomitant amino acids (renal protection)

Concomitant infusion of amino acids is required for renal protection. This amino acid infusion must start 30 minutes before the start of Lutathera infusion and must be continued at a constant rate for at least 4 hours. During the administration of amino acids and the following hours, the patient should be encouraged to urinate as frequently as possible.

Since the amino acids solution renal protection relies upon the reduction of Lutathera renal residence time, it is not recommended to decrease the amino acids solution posology when administering a reduced dose of Lutathera.

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The amino acid solution could be prepared as a compounded product, in compliance with the good practices and according to the composition specified in the following table.

Table 6. Composition of the standard amino acid solution

Compound	Amount
Lysine HCl	25 g
Arginine HCl	25 g
Appropriate sterile solvent (e.g. water for injection)	1 L

Alternatively, some commercially available amino acid solutions can be used if compliant with the following specifications:

Table 7. Specifications for commercial amino acid solutions

Item	Specification
Lysine content	Between 18 and 24 g
Arginine content	Between 18 and 24 g
Volume	1.5 L to 2.2 L
Osmolarity	< 1050 mOsmol

Considering the high quantity of amino acids and the significant volumes that commercially available solutions may require to meet the above specifications, the compounded solution is considered the product of choice, especially in patients whose amino acids and/or water supply must be limited (e.g. patient at risk of liver failure, heart failure, or renal failure).

6.1.10 Method of Administration

Lutathera is a ready to use single dose vial.

Lutathera must be administered by slow intravenous infusion, over a 20 to 30-minute time span (see **Attachment 7** for administration method examples).

Lutathera must not be injected as a bolus.

Different infusion methods can be used. Healthcare professionals will choose the most appropriate infusion method according to their experience, patient's characteristics and relevant radioprotection measures.

The following table summarizes the required procedure.

Table 8. Lutathera administration procedure

Product to inject	Start time (h)	Infusion rate* (mL/h)	Duration
Antiemetic**	0	bolus	-
Amino acids solution, either extemporaneously compounded (1 L) or commercially available (1.5 L to 2.2 L)	0	250 - 550	4 hours
Lutathera	0.5	50	≈ 30 minutes

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* Infusion rates may be reduced at the discretion of the physician.
** Physicians are advised to use antiemetics which are commonly prescribed in their institutions for treatment of nausea induced by chemotherapeutic drugs. Among such antiemetics, the use of Aprepitant (Emend®) as a prophylactic treatment prior to the start of the infusion with the amino acids solution should be considered. Haloperidol (Haldol®) could also be considered as an adjunct treatment (either i.v. or oral) in case the advised antiemetic regimens are not successful and patients continue to vomit. Lorazepam (Ativan®) could also be considered as an adjunct treatment.

There is some evidence that corticosteroids can induce down-regulation of somatostatin receptors, therefore their use should be avoided in the setting of 177Lu-DOTA0-Tyr3-Octreotate administration. Nevertheless, in the case where the treatments previously provided for nausea and vomiting are insufficient, corticosteroids can be used, as long as it is not given before initiating or within one hour after the end of 177Lu-DOTA0-Tyr3-Octreotate infusion.

After the administration is completed, the infusion line and Lutathera vial must be immediately flushed with at least 25 mL of sodium chloride 9 mg/mL solution for injection, unless the infusion method used already requires NaCl to flow through the vial and the line.

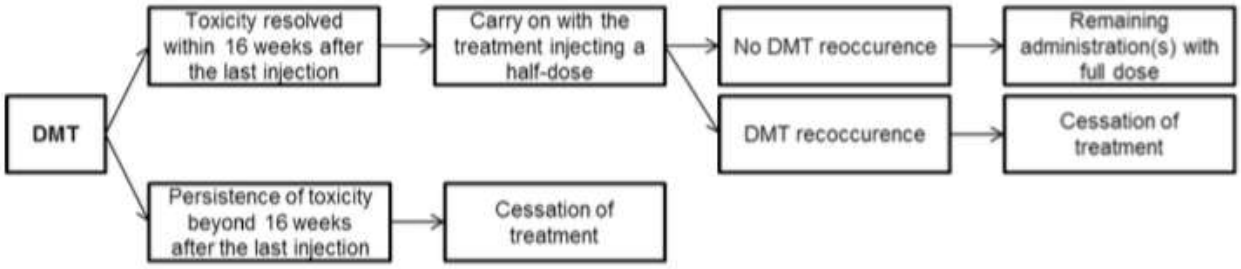
6.1.11 Lutathera Dose Modification

In some circumstances, it might be necessary to suspend treatment with Lutathera, adapt the posology (i.e. administer a half dose), or even definitively stop administration, as described in the following tables:

Table 9. When to adapt Lutathera posology?

<table>
<tr><th colspan="2">Adapt Lutathera posology according to the following actions in patients who have presented any of the following severe adverse reactions:</th></tr>
<tr><th>Severe adverse reactions / Dose-modifying toxicity (DMT) criteria</th><th>Action</th></tr>
<tr><td>Thrombocytopenia of grade 2 or superior (CTCAE).</td><td rowspan="5">1. Suspend treatment with Lutathera
2. Monitor biological parameters every 2 weeks, and eventually treat appropriately if needed; in case of renal failure, good hydration is recommended if not otherwise contraindicated.
a. <u>If the observed toxicity continues</u> beyond 16 weeks after the last infusion, treatment with LUTATHERA must be definitively stopped.
b. <u>If the observed toxicity resolves</u> within 16 weeks after the last infusion, it is possible to continue treatment with LUTATHERA by infusing a half dose (3.7 GBq instead of 7.4 GBq)*.
3. If the half dose is well tolerated (i.e. no DMT reoccurrence), the next remaining treatment administration(s) should continue with full dose (i.e. 7.4 GBq); but, if DMT recurs after treatment with a half dose, treatment with LUTATHERA must be definitively stopped.</td></tr>
<tr><td>Any hematologic toxicity of grade 3 or superior (CTCAE), except lymphopenia.</td></tr>
<tr><td>Renal toxicity defined as an estimated creatinine clearance < 40 mL/min, or a 40 % increase compare to the baseline serum creatinine level with a decrease of over 40 % compared to the baseline creatinine clearance.</td></tr>
<tr><td>Liver toxicity defined as either :
Bilirubinemia > 3 times the upper limit of normal,
Or hypoalbuminemia < 30 g/L with a decreased prothrombin ratio < 70%.</td></tr>
<tr><td>Any other CTCAE grade 3 or grade 4 toxicity (CTCAE) possibly related to LUTATHERA.</td></tr>
</table>

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* the concomitant amino acid infusion is always administered at full dose

Table 10. When to definitively stop treatment with Lutathera?

Definitively stop further Lutathera administrations in patients who have experienced or are at risk of any of the following conditions during treatment:
Severe heart failure (defined as grade III or IV of the NYHA classification)
Pregnancy
Hypersensitivity to the active substance or to any of the components of this radiopharmaceutical
– In case some specific adverse reactions to Lutathera persist or reoccur, see Table 9

Table 11. When to suspend treatment with Lutathera?

Suspend treatment with Lutathera in patients who have experienced or are at risk of any of the following conditions during treatment:	
Criterion	**Action**
Occurrence of an intercurrent disease (e.g. urinary tract infection…) which according to the physician opinion could increase the risks linked to Lutathera administration.	Suspend administration until resolution or stabilization. Treatment can be resumed after resolution or stabilization.
In case of some specific adverse reactions to Lutathera, see Table 9	See Table 9

6.1.12 Duration of Treatment

Duration of Lutathera (^{177}Lu-DOTATATE) treatment will be approximately 6 months. Lutathera will be administered intravenously once every 8 weeks ±7 days for up to a total of 4 doses or until disease progression, unacceptable toxicity, initiation of a different anti-meningioma therapy, or withdrawal of consent, whichever comes first.

To be evaluated in the study, a study subject must have received at least one dose of Lutathera.

6.1.13 Lutathera Dosimetry

Lutathera Dosimetry evaluation will be performed in the exploratory study cohort only. A whole body planar and organ specific (head) SPECT CT will be performed on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) at 4, 24, 72, and 192 hours post Lutathera administration. The dosimetry will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH).

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SPECT CT is the standard way of performing dosimetry analyses. The CT component is a low dose CT scan, and therefore, the radiation dose to which the patient is exposed is markedly decreased. The SPECT component to the study visualizes the gamma rays emitted from the patient and therefore does not add any additional external radiation exposure. For comparison; the Dose-Length Product (DLP) to the Effective Dose (ED) to which a patient is exposed from a full dose head CT is approximately 6-7 times higher when compared to the radiation from a SPECT CT of the head (1034 mGy versus 184 mGy).

6.2 Shipment, Dispensation and Return or Destruction of Lutathera

6.2.1 Shipment and Receipt of Lutathera

Advanced Accelerator Applications, Inc. will manufacture and package the Lutathera product. The product will be will be packaged and labeled as described in **Section 6.1.2** and shipped to the Nuclear Medicine Department at each study site in appropriate transport containers that are monitored with temperature control devices.

Customer Service informs customer via email the week before scheduled infusion date to remind the institution of upcoming scheduled doses. Doses arrive the day before scheduled infusion. Customer service will send a copy of batch release on the same day that the dose arrives.

Upon receipt of the study treatment supplies, an inventory must be performed and a study product receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

6.2.2 Dispensation of Study Drug

The designated Nuclear Medicine physician or other qualified individual will be identified at each site to prepare Lutathera for administration. Refer to **Section 6.1.7** for Lutathera administration instructions.

All study drug accountability records must be kept current. The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee. All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

6.2.3 Return or Destruction of Study Drug

Retention of Drug Product Vials:
All opened vials (full, partially full, and empty) may be destroyed at the site by the appropriate site personnel (e.g., designated Nuclear Medicine staff members) following local environmental requirements and institutional policies. All destruction must be fully documented at the time of destruction on the investigational product accountability log, or equivalent document at the time of destruction.

Alternatively, Advanced Accelerator Applications can provide a FedEx label to send back to Advanced Accelerator Applications if necessary.

All unopened vials must be destroyed at the end of the treatment period unless Advanced Accelerator Applications provides separate instructions for return.

Retention of supplies
Normal saline solution may be disposed of according to local site procedures. Other items used in the dose preparation and administration should be disposed of according to local site procedures.

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At the completion of the study, there will be a final reconciliation of study product shipped, study product consumed, and study product remaining. This reconciliation will be logged on the study product reconciliation form which will be signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. All unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Study product which is destroyed on site will be documented in the study files.

7 Study Schedule and Procedures

7.1 Study Schedule

7.1.1 Informed Consent

Prior to the performance of any protocol specific procedures, written informed consent must be obtained by signing an Institutional Review Board (IRB) approved Informed Consent Form (ICF). Results from laboratory test or radiographic evaluations performed prior to the date of informed consent, but within the allowed timeframe for screening procedures, can be used for determining the subject's eligibility if obtained as part of the subject's standard of care. If such results or evaluations are used in the determination of eligibility, this must be clearly documented in the subject's source documents. All materials (e.g., radiographic images obtained for this study) used for the baseline assessments and follow-up of subjects, or for the investigation of adverse events, may be duplicated and made available to the Sponsor and/or an authorized independent body for review.

Please see **Section 13.3** for further information regarding **Informed Consent Procedures.**

7.1.2 Baseline/Screening Procedures (Day -30 to Day 0)

After providing informed consent, study subjects will undergo screening for eligibility to participate in the study. Screening will start within 30 days prior to initiation of study treatment (first dose of Lutathera). Please also refer to the **Schedule of Events** (**Attachment 1**) for further details.

The following procedures will be performed for the purpose of determining study eligibility or characterizing the baseline population:

- **Demography** including gender, date of birth, race
- **Disease history:**
  A full **disease history** outlining the course of the subject's meningioma, including date of first pathological diagnosis, date of any subsequent surgical resections (if applicable), dates of radiotherapy (if applicable), and dates of meningioma-directed medical therapy (if applicable) must be obtained.
- The subject must meet all **Subject Selection Criteria** per **Section 5**.
- A copy of the **pathology report** confirming the diagnosis of a WHO I-III meningioma
- **Medical history:** information about any other of the subject's past and present illnesses.
- **Concomitant medications**: Information regarding any concomitant prescription medications, over-the-counter medications and non-prescription medications must be obtained.
- **Physical examination:** Subjects will have a complete physical and neurological examination for eligibility within 30 days prior to initiation of study treatment (first dose of Lutathera). the following parameters will be documented in the CRF:

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- Vital signs: height (height is only required at screening), weight, temperature, resting blood pressure, pulse and respiration rate.
- The neurological examination will be documented using NANO **(Attachment 2**).
- Clinical performance status will be documented using KPS **(Attachment 3)** and ECOG criteria **(Attachment 4)**.

- **12-Lead ECG:** A standard 12-lead ECG will be required at screening only. The ECG strips or reports will be reviewed by the investigator (paper or electronic tracing) and will be retained with the source so that they are available for comparison with subsequent ECGs by the investigator if needed. The following parameters will be recorded on the CRF: PR Interval (msec), QRS Interval (msec), QT Interval (msec), Heart Rate (BPM; recorded from the ventricular rate).

- The following **Laboratory Studies** will be performed within 30 days prior to initiation of study treatment (first dose of Lutathera) and documented in the CRF:
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Urinalysis: glucose, blood, pH, specific gravity, ketones, and urine protein
  - Coagulation test (required at screening only): PT/INR, PT, PTT
  - Hepatitis B virus surface antibody, hepatitis B virus surface antigen, hepatitis B virus core antibody, and hepatitis C virus antibody
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential

- **Collection of archival tumor material** for research. Each study subject will be asked to arrange to provide archival tumor tissue (a paraffin-embedded archival tumor block sufficient to generate at least 8 unstained slides but preferably up to 25 unstained slides; or, if a paraffin tumor block is unavailable, at least 8 unstained slides but preferably up to 25 unstained slides) from the most recent resection.

- **Radiological Assessment**
  A gadolinium-enhanced MRI of the brain for baseline disease assessment (RANO) must be performed within 30 days prior to begin of Lutathera treatment.

- **^{68}Ga-DOTATATE PET MR imaging** must be performed within 30 days prior to begin of Lutathera treatment. The MRI brain as part of this study must contain gadolinium-enhanced T1 and MPRAGE sequences.

7.1.3 Cycle 1, Day 1 (C1D1)

After completion of screening procedures and subject registration, the clinical and laboratory procedures as outlined below should be performed within 7 days of Lutathera treatment initiation (C1D1). Evaluations performed at screening that fall within 7 days of treatment initiation will not need to be repeated.

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)

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- KPS/ECOG assessment
- Concomitant medications

- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential
- **Lutathera Administration**
  Lutathera will be administered intravenously as outlined in S**ection 6.1.7**.

Exploratory NYU cohort only.

- **Lutathera Dosimetry**
  A whole body planar and organ specific (head) SPECT CT will be performed on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) at 4 hours post Lutathera administration. Dosimetry calculations will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH).

7.1.4 Cycle 1, Day 2 (C1D2)

Exploratory NYU cohort only.

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
- **Lutathera Dosimetry**
  A whole body planar and organ specific (head) SPECT CT will be performed on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) at 24 hours post Lutathera administration. Dosimetry will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH).

7.1.5 Cycle 1, Day 4 (C1D4)

Exploratory NYU cohort only.

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
- **Lutathera Dosimetry**
  A whole body planar and organ specific (head) SPECT CT will be performed on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) at 72 hours post Lutathera administration. Dosimetry will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH). The

7.1.6 Cycle 1, Day 8 (C1D8)

Exploratory NYU cohort only.

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment

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- **Lutathera Dosimetry**
  A whole body planar and organ specific (head) SPECT CT will be performed on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) at 192 hours post Lutathera administration. Dosimetry will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH). The

7.1.7 Cycle 1, Day 14 (C1D14), Day 28 (C1D28), and Day 42 (C1D42)

The following **laboratory studies** will be performed for safety purposes every 14±5 days from date of the C1D1 Lutathera dose:

- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count

7.1.8 Cycle 2, Day 1 (C2D1)

C2D1 is to be scheduled 8 weeks from date of C1D1 Lutathera dose. The following procedures will be performed within a time window of ±7 days of the scheduled visit:

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications
- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential
- **Lutathera Administration**
  Lutathera will be administered intravenously (±7 days) as outlined in S**ection 6.1.7**.

7.1.9 Cycle 2, Day 14 (C2D14), Day 28 (C2D28), and Day 42 (C2D42)

The following **laboratory studies** will be performed for safety purposes every 14±5 days from date of C2D1 Lutathera dose:

- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- **NOTE**: At C2D28, corresponding to week 12 on study **(**±14 days), all patients must have radiological assessment of the tumor with a **gadolinium-enhanced MRI of the brain**. Tumor Assessments (RANO) with brain MRIs will be repeated every 12 weeks thereafter.

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7.1.10 Cycle 3, Day 1 (C3D1)

C3D1 is to be scheduled 8 weeks from date of C2D1 Lutathera dose. The following procedures will be performed within a time window of ±7 days of the scheduled visit:

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications
- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential
- **Lutathera Administration**
  Lutathera will be administered intravenously (±7 days) as outlined in S**ection 6.1.7**.

7.1.11 Cycle 3, Day 14 (C3D14), Day 28 (C3D28), and Day 42 (C3D42)

The following **laboratory studies** will be performed for safety purposes every 14±5 days from date of C3D1 Lutathera dose:

- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH).
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count.

7.1.12 Cycle 4, Day 1 (C4D1)

C4D1 is to be scheduled 8 weeks after date of C3D Lutathera dose.

The following procedures will be performed within a time window of ±7 days of scheduled visit:

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications
- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)

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- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
- Pregnancy test (urine or serum β-HCG) for women of child-bearing potential

- **Lutathera Administration**
  Lutathera will be administered intravenously (±7 days) as outlined in S**ection 6.1.7**.

The following radiological assessments will be performed within 14 days prior to the scheduled C4D1 visit:

- **^{68}Ga-DOTATATE PET MR imaging**. The MRI brain component must contain gadolinium-enhanced T1 and MPRAGE sequences.
- Radiological assessment of the tumor with a **gadolinium-enhanced MRI of the brain (RANO)**. Tumor Assessments with brain MRIs will be repeated every 12 weeks thereafter.

7.1.13 Cycle 4, Day 14 (C4D14), Day 28 (C4D28), and Day 42 (C2D42)

The following **laboratory studies** will be performed for safety purposes every 14±5 days from date of C4D1 Lutathera dose:

- Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
- Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count

7.1.14 End of Treatment (EOT)

The End of Treatment visit is to be scheduled 8 weeks after date of C4D1 Lutathera dose. The following procedures will be performed within a time window of ±7 days of scheduled visit:

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications
- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential

7.1.15 Follow up post-Lutathera treatment (after EOT)

All subjects who remain on study after the last (4th) Lutathera dose will be followed on study until progression of disease, unacceptable adverse event(s), initiation of a different anti-meningioma therapy, subject withdrawal of consent, death of the subject or up to 2 years or other event that meets criteria for subject withdrawal or treatment discontinuation as per guidelines outlined in **Section 5.7** and **Section 6.1.9**.

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All subjects will have the following clinical, laboratory and tumor (radiological) assessments every 12 weeks (±14 days)

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications

- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count

- **Radiological Assessment (RANO)**

A gadolinium-enhanced MRI of the brain for disease assessment will be obtained must be performed within 14 days prior to the scheduled visit.

7.1.16 End of Study Procedures

If subjects come off study due to progression of disease, unacceptable adverse event(s), initiation of a different anti-meningioma therapy, subject withdrawal of consent, death of the subject, or other event that meets criteria for subject withdrawal or treatment discontinuation as per guidelines outlined in **Section 5.7** and **Section 6.1.9**, then the End-of-Study procedures as outlined below will be performed within 14 days after decision to end study participation:

- **Clinical Assessments**
  - Vital signs (prior to any laboratory assessments and treatment procedures): Weight, temperature, resting blood pressure, pulse and respiration rate.
  - Adverse event assessment
  - Complete physical exam, including neurological exam (NANO)
  - KPS/ECOG assessment
  - Concomitant medications

- **Laboratory Procedures**
  - Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, and lactate dehydrogenase (LDH)
  - Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count
  - Pregnancy test (urine or serum β-HCG) for women of child-bearing potential

- **Radiological Assessment (RANO)**

If a study subject comes off within 12 weeks of begin of Lutathera treatment, a gadolinium-enhanced MRI of the brain for response assessment will be obtained within 30 days of coming off Lutathera treatment.

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7.1.17 Post Study Procedures

- **Post Lutathera Safety Procedures**
  All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 56 days of last study drug. After the last Lutathera dose, each subject will be followed for 56 days for adverse event and serious adverse event reporting. Assessments may continue for ongoing reportable adverse events. Participants removed from protocol treatment for unacceptable adverse events will be following until resolution or stabilization of the adverse event.

- **Extended Follow-up Post Study Participation**
  Subjects should be contacted every 3 months (±14 days) by phone for survival status and initiation of any new anti-cancer treatments until death, withdrawal of permission to record at least survival data, subject is lost to follow-up or up to 2 years. Contact may include clinic visit, telephone contact, e-mail, mail or medical record review. The date of death, initiation of any new anti-cancer treatments and date of last contact should be documented.

  If a subject withdraws permission to record at least survival data after coming off study, this must be documented along with the date the subject withdraws permission. Subjects will be considered lost to follow up if no medical records are available to be reviewed and two phone calls each to the subject and then the subject's next-of-kin (if the subject does not respond) are not returned over two consecutive 3-month periods.

7.2 Specific Study Procedures

7.2.1 Lutathera (^{177}Lu-DOTATATE) administration

Please see **Section 6.1.7, Section 6.1.8**, and **Section 6.1.11** for full details regarding the administration, dosing, and dose modifications of Lutathera.

7.2.2 Radiological Treatment Response Assessment

Objective tumor response to Lutathera treatment will be assessed by the investigator using gadolinium-enhanced MRI of the brain at baseline, 12 weeks after first dose of Lutathera, and **every 12 weeks** thereafter until progressive disease, initiation of a different anti-meningioma therapy, or study withdrawal. Clinicians may repeat response assessment more frequently as clinically indicated.

Objective tumor response assessments will only be performed on those study subjects who have measurable disease defined as at least one lesion measuring ≥10 mm (see Inclusion Criteria, **Section 5.1**) in at least one dimension *and* who received at least one Lutathera dose.

Tumor Response Categories

Complete Response
All of the following criteria must be met
- complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. A confirmatory scan 4 weeks later is mandatory.
- No new lesions (measurable and non-measurable)
- Stable or improved T2/FLAIR changes
- Stable or improved clinical signs and symptoms that were present and documented to be disease-related at baseline

Study subjects with non-measurable lesions cannot have a complete response. The best response is stable disease.

Partial Response
All of the following criteria must be met
- ≥50% decrease in the sum of the products of perpendicular diameters of all measurable tumors sustained for at least 4 weeks.
- No new lesions (measurable and non-measurable)

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- Stable or improved T2/FLAIR changes
- Clinically stable or improved clinical signs and symptoms that were present and documented to be disease-related at baseline

Study subjects with non-measurable lesions cannot have a partial response. The best response is stable disease

Stable Disease
All of the following criteria must be met
- Does not qualify for CR, PR, or progression.
- <50% decrease or <25% increase in the sum of the products of perpendicular diameters of all measurable tumors sustained for at least 4 weeks.
- Stable or improved clinical signs and symptoms that were present and documented to be disease-related at baseline

Progressive Disease (PD)
All of the following criteria must be met
- ≥25% increase in the sum of the products of perpendicular diameters of all measurable tumors.
- Any new contrast-enhancing measurable tumor
- Clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of treatment, cerebrovascular events, infection, etc.).
- The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days be considered neurologic deterioration.
- Failure to return for evaluation due to deteriorating condition or death.

Unknown Response Status
Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

^{68}Ga-DOTATATE (Netspot®) PET MR imaging NETSPOT, after radiolabeling with ^{68}Ga, is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

^{68}Ga-DOTATATE (Netspot®) clinical supply will be supplied by Advanced Accelerator Applications USA, Inc.

NETSPOT ordering: All orders must be made using the **Clinical Research Netspot Injection Order Form** provided by Advanced Accelerator Applications USA, Inc., and entered on the radiopharmacy's web-based ordering site or faxed to the dispensing radiopharmacy listed below. If the radiopharmacy does not receive this Form they will not fulfill the dose order.

Radiopharmacy Name: Nuclear Diagnostic Products of New York (NDP)
Web Address or Fax: https://adacap.checkappointments.com
Dispensing Pharmacy Phone # For Questions: 844-367-3222 or 844-DOSE-AAA

All study subjects will have a ^{68}Ga-DOTATATE PET MRI study at baseline/screening (see **Section 7.1.2**) prior to initiation of Lutathera treatment and 6 months (24 weeks). The second ^{68}Ga-DOTATATE PET MRI study ist to be performed within 14 days prior to the last Lutathera dose (see **Section 7.1.12**).

^{68}Ga-DOTATATE imaging will be performed using Netspot®, a single dose kit containing:
- **Vial 1** (reaction vial with lyophilized powder) containing 40 mcg of ^{68}Ga-DOTATATE
- **Vial 2** (buffer vial) containing 1 mL of reaction buffer solution

For full details regarding dosage and administration of Netspot® see the Netspot package insert.

Due to institutional differences in imaging technologies and when available, ^{68}Ga-DOTATATE PET should be performed as PET MRI from vertex-to-thighs concurrently with brain MRI without and with contrast. If the ^{68}Ga-DOTATATE PET MRI

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equipment is not available, ^{68}Ga-DOTATATE PET CT vertex-to-thighs should be performed and PET images of the brain should be fused with brain MR imaging without and with contrast that have been obtained within 7 days. Ideally post-contrast T1-weighted imaging, including magnetization-prepared rapid gradient-echo (MP-RAGE), would serve the best for the post-processing for the image fusion. Attenuation correction differences may lead to SUV alterations and possible SUV inconsistencies based on PET MRI and PET CT techniques. These will be addressed in the final assessment and each patient's scanning parameters will be provided in detail for reviewers in supplementary documents. If necessary, SUV lesion/liver or alternative internal references can be used, per consensus among nuclear medicine radiologists.

7.2.3 Research Specimen Procedures

For further details regarding background and rationale for the Research Specimen Procedures, please see **Section 3.3 Exploratory Objectives**, **Section 4.2.3 Exploratory Endpoints** and **Attachment 5.**

- **Archival Tumor Tissue**

Archival tumor tissue preferably from the most recent resection that demonstrates histopathological evidence of a WHO I-III meningioma as specified in the Inclusion Criteria (**Section 5.1**) must be submitted. Submission of a paraffin-embedded tissue block sufficient to generate at least 8 unstained slides but preferably up to 25 unstained slides; or, if a paraffin tumor block is unavailable, at least 8 unstained slides but preferably up 25 unstained slides is required. The tumor block should contain at least 50% viable tumor, i.e., a representative H&E slide should show that at least 50% of the specimen contains viable tumor.

- **Genome-wide DNA methylation profiling**

We will perform DNA methylation-based meningioma classification as described in [22] on all patients enrolled in the study and correlate DNA methylation-based subtype with outcome (PFS-6), SSTR2 expression, and baseline ^{68}Ga-DOTATATE uptake by PET MRI.

- **Whole exome next-generation sequencing**

We will perform whole-exome next-generation sequencing on all archival tumor specimens using the NYU genomics core.

- **Optional Tumor Tissue Post Treatment**

If study subjects undergo tumor resections or biopsies during the study period after treatment initiation, or after progression on Lutathera and if they give informed consent, a tumor specimen will be collected for research purposes. For details see **Attachment 5**. A FFPE block (sufficient to generate at least 8 unstained slides but preferably up 25 unstained slides; or, if a paraffin tumor block is unavailable, at least 8 unstained slides but preferably up 25 unstained slides is required) from the tumor surgery is preferred. The tumor block should contain at least 50% viable tumor, i.e., a representative H&E slide should show that at least 50% of the specimen contains viable tumor.

Send **Archival Tumor** and/or **Optional Tumor Tissue Post Treatment specimens** for research to:

Alexandra Miller, MD, PHD
ATTN: Ravesanker Ezhilarasan
Smilow Building, Room 806
522 First Avenue
New York, NY 10016
Phone: (212) 731-6267
Fax: (646) 754-9696
Alexandra.miller2@nyulangone.org

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8 Safety and Adverse Events

8.1 *Definitions*

8.1.1 Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay (In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer (see **NOTE** below).
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event - Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. Potential drug induced liver injury (DILI) is also considered an important medical event (see below for the definition of potential DILI).
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug.
- Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

Although pregnancy, study drug overdose, potential drug-induced liver injury (DILI), and development of another cancer are not always serious by regulatory definition, these events must be handled as SAEs.
Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

NOTE: Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Exceptions: Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)

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- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Progression of underlying malignancy
Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered a SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Potential Drug Induced Liver Injury (DILI)
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 8.4 for reporting details).

Potential drug induced liver injury (DILI) is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

1) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.1.3 Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others are defined as any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

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8.2 Classification of an Adverse Event

8.2.1 Severity of Event

The severity of AEs (including test findings classified as AEs) will be graded using the current version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 grading system.

AEs not listed in the NCI-CTCAE will be graded according to the following scale:

Grade 1 (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 (Life-threatening): Life-threatening consequences; urgent intervention indicated.

Grade 5 (Death): Death related to AE.

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

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- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent or listed in the Lutathera Investigator's Brochure.

Expected Adverse Events with Lutathera
Common and severe adverse reactions attributable to Lutathera are

- Nausea/vomiting
- Diarrhea
- Fatigue
- Myelosuppression including anemia, thrombocytopenia, neutropenia, and lymphopenia
- Secondary Myelodysplastic Syndrome and Leukemia
- Renal failure
- Transaminase elevation
- Cholestasis (increased GGT)
- Hyperglycemia
- Hypokalemia.

Please see **Section 2.4.1** and the **Lutathera Investigator's Brochure** for further details regarding the risks and **expected adverse events** associated with Lutathera.

8.3 Time Periods and Frequency of Event Assessments and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be

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notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protection (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection."

The following describes the NYULH IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

The NYU IRB address is:

NYULH IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly (no later than 5 working days)
Researchers are required to submit reports of the following problems promptly but **no later than 5 working days** from the time the investigator becomes aware of the event:

- **Unanticipated problems including adverse events that are unexpected and related**
  - Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to subjects or others, or placed them at increased risk

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

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Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.4.1 Adverse Event Reporting

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). Signs, symptoms, and abnormal diagnostic procedure results that are clearly related should be grouped under one diagnosis/AE and recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately (see **Section 8.4.2**).

Adverse Event Reporting Period
The study period during which adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 42 days following the last administration of Lutathera.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Abnormal lab values that are not clinically significant are not considered adverse events.

8.4.2 Serious Adverse Event Reporting

Reporting of all Serious Adverse Events (SAEs), related or unrelated, will begin with the date of informed consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported.

Investigators and the Study Sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 days of Study Sponsor notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see Adverse Event Definitions, **Section 8.1**)

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Serious adverse event reporting will begin in conjunction with the date of treatment administration. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the principal investigator, with a notification email sent to NYUPCCsafetyreports@nyulangone.org and recorded on the case report form. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyulangone.org whether full information regarding the event is known or not.

All other serious adverse events must be reported to the sponsor and DSMC's appointed medical monitor within 24 hours by email (NYUPCCsafetyreports@nyulangone.org). The Serious Adverse Event Form must also be emailed to the principal investigator and Clinical Trials Office (NYUPCCsafetyreports@nyulangone.org) , this documentation will be

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forwarded to the DSMC's appointed medical monitor within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

8.4.3 Unanticipated Problem (UP) Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the Study Sponsor.

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the Study Sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Study Sponsor within 5 calendar days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 55 business days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 Pregnancy reporting

Although pregnancy is not considered an AE, it is the responsibility of the Investigator to report to the Study Sponsor (or designee), by telephone or e-mail within 24 hours of becoming aware of any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 90 days of the last dose of study drug.

The investigator should discontinue Lutathera treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the pregnancy should continue until conclusion of the pregnancy.

Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. All pregnancy outcomes will be followed.

Any congenital anomaly/birth defect in a child born to a female subject or partner of a male subject exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (within one business day after learning of the event). Any spontaneous abortion should be reported in the same fashion.

8.5 Reporting Procedures – Notifying the Study Sponsor (NYULH)

The Investigator will complete a Serious Adverse Event (SAE) Form provided by the CTO QAU within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Study Sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.

- Other SAEs regardless of relationship will be submitted to the Study Sponsor within 24 hours of site awareness.

The following describes events that must be reported to the Sponsor (Overall PI) in an **expedited fashion (within 24 hours of awareness of the event)** using a SAE form provided by the CTO QAU:

- Unanticipated Problems related to study participation,
- Serious Adverse Events, regardless of whether they are unexpected,

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- Overdose of study drug (Lutathera), accidental or intentional overdose of at least 2 times the intended dose of Lutathera within the intended therapeutic window, irrespective of association with an AE.
- Pregnancy
- Exposure during Pregnancy or Breastfeeding (even if not associated with an AE)
- Occupational exposure (even if not associated with an AE)
- Potential Drug-induced Liver Injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator.

The Sponsor (Overall PI), must then inform the NYUSoM IRB (if reportable), PCC CTO, and DSMC within 24 hours of the event whether full information regarding the event is known or not.

All serious adverse events (SAEs) will be evaluated by the DSMC. If meeting the requirements for expedited reporting, the Sponsor (Overall PI) will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The Sponsor (Overall PI) is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Study Sponsor and should be provided as soon as possible.

As a **follow-up to the initial report**, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

New information available after 48 hours of initial event: within 24 hours of awareness of new information
If new information about a previously reported event becomes available 48 hours after the initial awareness of the event, this new Information should be reported within 24 hours of awareness of the new information. Any new follow-up information that is received or that the investigator is newly made aware of after the initial 48 hour reporting period should be reported within 24 hours from the time of awareness of the new information.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.
- **Withdrawal of IRB approval**

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

Contact information for submission of reportable events to the Study Sponsor (NYULH):

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NYUPCCsafetyreports@nyulangone.org

AND

Alexandra Miller, M.D., Ph.D.
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
530 1st Avenue, Suite 10W
New York, NY 10016
Tel: 212-731-6267
Fax: 646-754-9696
Email: alexandra.miller2@nyulangone.org

AND

PCC Assigned Medical Monitor

8.6 Sponsor Reporting Procedures – Notifying the FDA

The Study Sponsor (Overall PI) is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** (via telephone or facsimile report)
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** (via written report)
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Study Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafetyreports@nyulangone.org

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8.7 Investigator Reporting: Notifying the IRB

Federal regulations require timely **reporting by investigators to their local IRB** of unanticipated problems posing risks to subjects or others. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protection (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection." The following describes the NYUSoM IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYUSoM IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

At the time of each annual review any protocol deviations stated above, such as dose-reductions (even if done in accordance with protocol guidelines) must be reported to the IRB.

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8.8 Reporting Procedures – Notifying Co-Investigators

It is the responsibility of the Study Sponsor (NYULH) to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above in **Section 8.8**. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

8.9 Data Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of Adverse Events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan as detailed below. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team. The DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study at least semi-annually. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight for this investigator-initiated study will be under the direction of the DSMC of the New York University Langone Health Perlmutter Cancer Center.

The DSMC operates based on the 2017 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULH PCC that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYULH PCC Institutional Data Safety and Monitoring Plan, this 2-stage phase II clinical trial will be monitored by the DSMC semi-annually, additionally at time of interim analysis and decision to proceed to stage 2 (see **Statistical Considerations**, **Section 10**), and at the completion of the study prior to study closure. This DSMC review will include accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of this study. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will provide its input to the Principal and Co-investigators of this study. The DSMC will review safety data every 6 months.

DSMC Review of Serious Adverse Events (SAEs)
All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported via email to NYUPCCsafetyreports@nyulangone.org and reviewed by the DSMC within 24 hours.

Based on the DSMC review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next protocol review.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Clinical Monitoring will be performed as outlined below in **Section 12, Quality Assurance and Quality Contro**l.

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10 Statistical Considerations

10.1 Statistical Hypotheses

Primary Hypothesis

Lutathera will result in PFS-6 of at least 47% (target PFS-6) in patients with progressive or high-risk meningioma that have positive ^{68}Ga-DOTATATE uptake on PET-MRI.

Secondary Hypotheses

- Lutathera will be well tolerated by patients with progressive meningioma without neurotoxicity.
- Improved PFS-6 relative to historical control will translate to improved median PFS and improved landmark overall survival (OS-12).
- ^{68}Ga-DOTATATE uptake on MR-PET will serve as a predictive as well as a pharmacodynamic biomarker for Lutathera treatment in progressive or high-risk meningioma
- ^{68}Ga-DOTATATE uptake on MR-PET will serve as a non-invasive molecular diagnostic, correlating with tumor SSTR2 expression levels, molecular meningioma subtype as determined by DNA methylation array, and WHO grade.
- ^{177}Lu-DOTATATE (Lutathera) dosimetry calculated in the target lesions at at 4, 24, 72 and 192 hours will correlate with response to treatment.

10.2 Analysis Populations

The following Analysis Populations have been defined:

- The **Evaluable-for-Efficacy Analysis Population** consists of all subjects who are successfully screened and registered, receive at least one dose of Lutathera and have at least one post-baseline tumor response assessment by gadolinium-enhanced MRI.

- The **Safety Analysis Population** includes all subjects who are successfully screened and registered, and received at least one dose of Lutathera. All demographics, baseline characteristics and safety data will be analyzed using the Safety Analysis Population.

- The **Exploratory Study Population** comprises of all subjects who are successfully screened and registered, received at least one dose of Lutathera and underwent ^{177}Lu-DOTATATE dosimetry calculation at 4, 24, 72 and 192 hours after C1D1 Lutathera dose. All demographics, baseline characteristics and safety data will be analyzed using the Exploratory Study Population.

10.3 Description of Statistical Methods

10.3.1 General Approach

This is a single arm, open-label, multicenter, two-stage, phase 2 clinical study to evaluate the efficacy of Lutathera (^{177}Lu-DOTATATE) in patients with progressive or high-risk meningioma.

Simon's two-stage design will be used with α=0.05, β=0.2, and statistical power=0.8. All statistical tests will be performed with 2-tailed $p<0.05$ indicating statistical significance.

10.3.2 Analysis of the Primary Efficacy Endpoint

The Primary Efficacy Endpoint is Progression Free Survival at 6 months (PFS-6).

Six months will be defined as 24 weeks. PFS-6 is defined as the proportion of subjects who achieve a radiographic complete response (CR), partial response (PR), or stable disease (SD) at 6 months from start of Lutathera treatment. Radiographic response assessments will be performed by measuring the bidirectional tumor diameters on contrast-enhanced MRI in patients who received at least one dose of Lutathera compared to baseline measurements (see Efficacy Procedures, **Section 7.2.2**).

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Kaplan-Meier Analysis will be performed to estimate PFS-6 in the Evaluable-for-Efficacy Analysis Population (**see Section 10.2**). Subjects who are lost to follow-up or for whom radiographic response assessment data are missing, will be censored. PFS-6 in the Evaluable-for-Efficacy Analysis Population will be compared to a historical control PFS-6=0.26. The results of this analysis will be summarized using the estimate of PFS-6 and its associated 95% confidence interval.

10.3.3 Analysis of the Secondary Endpoints

The secondary endpoint variables will be summarized and analyzed descriptively as described below.

- **Safety and Adverse Events:** Safety will be assessed by reported/elicited AEs, laboratory assessments including hematology and chemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs, i.e., AEs occurring from the time the first dose of the study drug until 42 (±7) days after the last dose) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.

  The overall incidence of TEAEs and the proportion of patients who discontinue because of a TEAE will be summarized and analyzed descriptively. The number and percent of patients with new-onset TEAEs will be summarized according to the Medical Dictionary for Regulatory Activities system-organ-class (SOC) level and Preferred Term (MedDRA version 21) for all treated patients. The summary of TEAEs will be presented in the following categories:

  - Number and percentage of patients with any TEAEs by SOC and Preferred Term.
  - Number and percentage of patients with any SAEs by SOC and Preferred Term.
  - Number and percentage of patients with related TEAEs by SOC and Preferred Term.
  - Number and percentage of patients with TEAEs causing discontinuation of the study by Body System and Preferred Term.

  In addition, the number and percent of patients with TEAEs by grade will be summarized. Finally, the number of completed cycles will also be summarized and analyzed descriptively.

- **Objective Response Rate (ORR)** is defined as the best response [Complete Response (CR) + Partial Response (PR) + stable disease (SD)] recorded from the start of the study until the end of study in patients who received at least 1 dose of Lutathera. Radiographic response assessments will be performed by measuring the bidirectional tumor diameters on contrast-enhanced MRI in patients who received at least one dose of Lutathera compared to baseline measurements (see Efficacy Procedures, **Section 7.2.2**).

  The secondary endpoint variable of ORR will be summarized descriptively using its estimate and associated 95% confidence interval.

- **Overall Survival at 12 months (OS-12)** is defined as the proportion of subjects who are alive at 12 months from start of Lutathera treatment. Survival data will be captured by clinical follow-up every 8 weeks during treatment with Lutathera and by regular follow-up phone calls every 12 weeks for up to 2 years after completion of treatment with Lutathera (see section 7.1.14).

  The results of this analysis will be summarized using the estimate of OS-12 and its associated 95% confidence interval.

- **Progression Free Survival (PFS)** is defined as the number of days from the treatment start date to the date of documented disease progression or death due to any cause. Disease progression will be determined based on radiographic review.

  The secondary endpoint variable of PFS will be summarized and analyzed descriptively. Kaplan-Meier analysis will be performed and **median PFS** will be described along with 95% CI based on radiographic review.

- **Overall Survival (OS)** is defined as the number of days from the treatment start date to the date of death due to any cause.

  The secondary endpoint variable of OS will be summarized and analyzed descriptively. Kaplan-Meier analysis will be performed and **median OS** will be described along with 95% CI based on radiographic review.

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10.3.4 Safety Analyses

For details regarding Safety Analysis, see **Section 10.3.3, Secondary Endpoint Analyses, Safety and Adverse Events.**

10.3.5 Baseline Descriptive Statistics

Baseline characteristics, including demographics and laboratory measurements will be summarized descriptively. Exploratory Regression Analyses will be performed to evaluate possible associations of outcome variables with specific subgroups.

10.3.6 Planned Interim Analysis

A Simon's two-stage design [23] will be used for this phase II interventional study. In the first stage, 14 patients will be accrued and an interim analysis will be performed. If there are 3 or fewer PFS-6 events among these 14 patients, then the study will be stopped. Otherwise, the study will proceed to stage 2 and an additional 18 additional patients will be accrued for a total of 32 patients.

10.3.7 Exploratory Analyses

The following Exploratory Analyses are planned and will be analyzed and reported descriptively. For further details, please see **Section 3.3 Exploratory Objectives**, **Section 4.2.3 Exploratory Endpoints**, and **Attachment 5.**

- **^{68}Ga-DOTATATE PET MR Imaging**: We will perform 3D list mode ^{68}Ga-DOTATATE PET imaging combined with T1 DCE / T2* DSE perfusion MR imaging on all patients in the trial at baseline prior to initiation of Lutathera treatment and at 6 months within 14 days prior to the last Lutathera dose.

  Each subject's PET MR imaging will be post-processed with texture-based analysis as a part of the Artificial Intelligence initiative at NYU. We aim to detect statistical and structural features that would allow us recognize patterns of treatment response and failure at early time points.

  We aim to explore the
  - Association of pre-treatment ^{68}Ga-DOTATATE uptake on MR-PET with:
    - PFS-6
    - SSTR2 expression by IHC;
    - meningioma molecular subtypes determined by DNA methylation array [22];
    - WHO grade;
    - and DNA mutations (NF2, SMO, PI3K/Akt pathway, etc).
  - Association of change in 6-month post-treatment ^{68}Ga-DOTATATE uptake on MR-PET compared to baseline with:
    - PFS-6
    - SSTR2 expression by IHC
    - meningioma molecular subtypes determined by DNA methylation array [22];

- **SSTR2 Immunohistochemistry:** SSTR2 expression will be correlated with outcome (PFS-6), baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

- **Genome-wide DNA methylation profiling**: DNA methylation-based meningioma classification will be performed on all patients enrolled in the study and DNA methylation-based subtype will be correlated with outcome (PFS-6), SSTR2 expression, and baseline ^{68}Ga-DOTATATE uptake by PET MRI.

- **Whole exome next-generation sequencing:** We will perform whole-exome next-generation sequencing on all archival tumor specimens (NYU genomics core) to assess the association between recurrent mutations recently identified in meningiomas (e.g. NF2, SMO, PI3K/Akt pathway, etc) and outcome (PFS-6), SSTR2 expression, baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

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- **^{177}Lu-DOTATATE (Lutathera) dosimetr**y will be performed via whole body planar and SPECT CT imaging. Positive uptake is defined as uptake higher than the background and SUV ratios adjusted to the liver and spleen uptake (adopted from Krenning score).[25]

  The exploratory endpoint variable of ^{177}Lu-DOTATATE (Lutathera) dosimetry will be summarized and analyzed descriptively.

10.4 Sample Size

A recent meta-analysis of 47 publications on medical therapy for progressive meningioma showed a weighted average PFS-6 of 26% for WHO grades II/III meningioma. Across studies, it was demonstrated that PFS-6 was the most robust outcome measure available for patients with therapy-refractory meningiomas and the PFS-6 benchmark was recommended for future clinical studies [5]. Therefore, our PFS-6 historical control is 26%. A Simon's two-stage design will be used [23]. The null hypothesis that the true response rate (H_0) is 0.26 will be tested against a one-sided alternative response rate (H_1) of 0.47. In the first stage, 14 patients will be accrued. If there are 3 or fewer PFS-6 events among these 14 patients, the study will be stopped. Otherwise, 18 additional patients will be accrued for a total of 32 patients. The null hypothesis will be rejected if ≥13 achieve PFS-6 among the total of 32 patients. This design yields a type I error rate of 0.05 and a power of 80% when the true response rate is 0.47. The probability of early termination is 0.49 under the null hypothesis of a 26% PFS-6 rate, and only 0.18 under the alternative hypothesis of a 47% PFS-6 rate.

11 Source Documents and Access to Source Data/Documents

Source Data and Source Documents
Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

Electronic Database Capture System
An electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The CTO quality assurance specialists will monitor this trial every 6-8 weeks for data entry accuracy.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into any electronic medical record or *electronic data capture system*. Relevant source documentation to be reviewed by the CTO QAU Specialists throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

Access to Study Records
Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents,

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data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial, which will also include a centralized review of data for quality, trends, consistency and general safety review. Monitoring visits are done remotely unless otherwise specified, via remote EMR access. A quality assurance specialist will regularly review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms and source data verification.

During scheduled monitoring visits, the investigator and the investigational site staff must be discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

Monitoring of Other Participating Institutions
Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with the Site Investigator and staff. If remote EMR access is not available, then the Site Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), before emailing all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high-priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO and the Study Sponsor of any audit requests by health authorities, and will provide the Study Sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient’s authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient’s personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

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(1) **Principal Investigator**: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) **DSMC**: Data Safety Monitoring occurs every 6 months

(3) **Institutional Review Board (IRB):** An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will provide interim monitoring, which begins within the first 6-8 weeks of first subject enrollment and every 6-8 weeks thereafter. Specialist will also verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The Informed Consent Form (ICF) used for this study is submitted with this protocol.

13.3.2 Consent Procedures and Documentation

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULH PCC CTO.

Informed Consent Procedures
A participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the potential participant; also must address any questions/concerns prior to obtaining written informed consent for participation and HIPAA authorization can also obtain consent.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

The Investigator will explain to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, potential compensation and or costs incurred by the patient and any discomfort this trial may entail. This informed consent should be given by means of standard written statement, written

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in non-technical language. All patients will be required to sign a written informed consent prior to being registered on this study. No patient can enter the study before his/her informed consent has been obtained. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

Non-English Speaking Patients
For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYULH PCC CTO guidelines and policies.

Patients who cannot read
For patients who cannot read, a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

Documentation of Consent
The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

Patient Informed Consent at Additional Sites
The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULH policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials, unless Fellows are listed as co-investigators.

The Investigator must ensure that each participant is fully informed about the nature and objectives of the study and possible risks associated with participation. All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

All parties will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, NYULH Perlmutter Cancer Center (PCC) will maintain high standards of confidentiality and protection of participant personal data.

The informed consent form must be in compliance with ICH/GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and NYULH before use.

13.4 Participant and Data Confidentiality

The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYULH will only be labeled with an assigned protocol-subject identification number without patient identifiers. Systems used for electronic data capture are compliant with HIPAA and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document.

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Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYULH. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYULH research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYULH.

13.4.1 Research Use of Stored Tumor Specimens and Subject Data

Please see **Section 7.2.4 Research Specimen Procedures** and **Section 13.5 Future Use of Stored Specimen** for details regarding use and storage of tumor specimen and subject data obtained during this study.

13.5 Future Use of Stored Specimens

At the time of informed consent to participate in this trial, patients will have the option to allow all research samples (archival tumor sample, research blood samples, and optional tumor biopsy sample) remaining after completion of the study and protocol-specified correlative biomarker research to be banked for future research studies. Future studies may include, but are not limited to, genetic, epigenetic, and molecular studies with the overall goal of correlating any scientific findings with the patients' outcome to protocol treatment. Leftover samples will be stored in a repository in the NYULH Center for Biospecimen Research and Development (CBRD) and labeled with an assigned protocol-patient identification number without subject identifiers. The assigned protocol-patient identification numbers will be stored in a central database on a password-protected NYULH server. This central database will contain the key to decoding assigned protocol-patient identification numbers used for sample labeling and patient's identifiable medical information (PHI). Only the Overall PI will have the linking key to the subject identifiers.

For each leftover research sample, key clinical information including, but not limited to, gender, age at diagnosis, tumor location, prior treatment and histology will be abstracted from the medical record and recorded with the assigned protocol-patient identification number on a separate database from the central database containing the identifiable PHI. This de-identified database will also be on a password-protected NYULH server and will be administered by the overall PI. Only

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the Overall PI and IRB-approved study investigators with permission from the Overall PI will have access to this de-identified database.

The de-identified samples and data may be made available to researchers at NYULH (NYU Langone Health), NYU SoM (NYU School of Medicine), and other NYULH affiliates, as well as researchers outside of NYU. De-identified samples may be shared with for-profit companies that are working with NYULH, NYU SoM or other NYULH affiliate researchers on a specific IRB-approved research project. De-identified specimens may also be made available to other researchers through research organizations whose mission focuses on the acquisition, authentication, production, preservation, development and/or distribution of data and materials for research in the life sciences, such as The Cancer Genome Atlas, a collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI).

Patients not agreeing to allow their leftover samples/data to be stored for future use will be able to fully participate in the study with no restrictions. The central database and de-identified database maintained for at least 5 years after termination of the study.

If a result from a genetic test on mandatory or leftover research samples is deemed by the Study Sponsor/Overall PI to be important to report to the subject, the Subject may elect at the time of informed consent to receive results of genetic tests. If results are shared with the subject, the genetic test result will be validated with a repeat genetic test prior to sharing the information with the subject. The subject must consent to have a consultation with a genetic counselor at the participating institution at the time results are released. The costs associated with the genetic counselor involved with the disclosure of these potentially clinically important results may be billed to the subject's insurance company or other third parties, if appropriate, and the subject may also be responsible for some of them. The funding source (Advanced Accelerator Applications) will not pay for costs for the genetic counselor involved with the disclosure of these potentially clinically important results.

Subjects can withdraw their samples/data from future use at any time. The subject may contact the Study Sponsor/Overall PI or designee to express his or her wish to withdraw leftover samples from storage.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant’s official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster, a 21 CFR Part 11-compliant data capture system provided by DataCore. The data system includes password protection and internal quality checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Only the Overall PI, and IRB-approved study investigators at NYULH and at collaborating sites specified on the protocol, will have access to this limited data set, with permission from the Overall PI. The limited data set will be shared under a Data Use Agreement between NYU Langone Health and Yale’s Associate Professor of Neurology (Neuro-Oncology), Sylvia Kurz, M.D.

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14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to the Study Sponsor.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act (FDAA) of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee’s responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

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- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

Funding for conducting the trial will be provided by Advanced Accelerator Applications. The investigational agents Lutathera (^{177}Lu-DOTATATE) and Netspot (^{68}Ga-DOTATATE) will be provided to patients enrolled on this study by Advanced Accelerator Applications.

15.2 Costs to the Participant

There are no additional costs to the study participants other than costs associated with standard of care procedures which may be covered by the participants' health insurance.

15.3 Participant Reimbursements or Payments

There are no participant reimbursements or payments for participation in this research study.

16 Study Administration

16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study Chairman (the PI of the Coordinating Center), the study Co-Chairs, and the PI of the clinical sites. The Steering Committee will meet in person or via teleconference at least monthly, these meetings are facilitated by CTO's quality assurance specialists.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NYULH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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19 Attachments

19.1 Attachment 1. Schedule of Events

	Screening / Baseline	Treatment Cycles	Disease Assessment Cycles		End of Study / Follow-up[7]
Study team procedures	**Within 30 days of Treatment**	**Every 8 weeks (56 ±7 days)**	**Every 12 weeks (±14 days)**	**Week 24 (±14 days)**	
Informed Consent	X				
Demographics	X				
Inclusion/Exclusion Criteria	X				
Medical/Disease history	X				
KPS/ECOG/NANO assessments[1]	X	Every 8 weeks[1] →			
Physical exam, Neurologic exam[1]	X	Every 8 weeks[1] →			X
Vital signs[1]	X	Every 8 weeks[1] →			X
Concomitant medications[2]	X	→			
Adverse Event Assessment[3]	X	→			
LUTATHERA administration[4]		X			
Disease assessment (Brain MRI)[5]	X		X		
^{68}Ga-DOTATATE PET-MRI[6]	X			X	
Disease status and survival[7]			X		X
Laboratory/Cardiology assessments					
Hematology[8]	X	Every 2 weeks ±5 days [8] →			X
Serum chemistries[9]	X	Every 2 weeks ±5 days [9] →			X
Coagulation tests[10]	X				
Pregnancy test[11]	X				X
Hepatitis B and C[12]	X				
12 Lead ECG	X				
Archival tumor tissue[13]	X				

1. Vital signs, physical/neurological exams, and KPS/ECOG/NANO assessments: Height (required only at screening), weight, blood pressure, respiration, pulse, and oral temperature will be performed at screening/baseline and **every 8 weeks until week 32, then every 12 weeks until off study**.
2. Concomitant medication recording will be ongoing throughout the course of the study. Record concomitant medications from within 30 days before starting study treatment up to the 30-Day Post Drug Visit.
3. All adverse events will be recorded from the time the date of initiation of study therapy through 42 days following the last dose of Lutathera and at each examination. Serious Adverse Events will be followed through 42 days following the last dose of Lutathera.
4. **LUTATHERA administration**. All subjects will receive their first dose of intravenous LUTATHERA [7.4 GBq (200 mCi) of ^{177}Lu-DOTATATE] on Cycle 1 Day 1 and then **every 8 weeks (±7 days) for a total of 4 doses**. Subjects without progressive disease after the 4th and final dose of Lutathera will be followed on study until progression of disease, unacceptable adverse event(s), initiation of a different anti-meningioma therapy, subject withdrawal of consent, or other event that meets criteria for subject withdrawal or treatment discontinuation as per guidelines outlined in Section 5.7 and Section 6.1.9.

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5. Neuroimaging (disease assessments). Contrast-enhanced MRI will be performed at time of study enrollment and then then every 12 weeks (+/- 14 days) thereafter until patients come off study.
6. ^{68}Ga-DOTATATE imaging will be performed at baseline pre-treatment and at 22 to 24 weeks (two total scans).
7. If subjects come off study due to progression of disease, unacceptable adverse event(s), initiation of a different anti-meningioma therapy, subject withdrawal of consent, or other event that meets criteria for subject withdrawal or treatment discontinuation as per guidelines outlined in Section 5.7 and Section 6.1.9, then the **End-of-Study procedures** will be performed **within 14 days** after decision to end study participation. **All subjects will be followed post-study** until death, withdrawal of permission to record at least survival data, or subject is lost to follow-up every 3 months (±14 days) after coming off study for up to 2 years.
8. Hematology: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, hematocrit, and platelet count at baseline and then **every 2 weeks until week 40** (which is 8 weeks after the last LUTATHERA dose, which is at C4D1/week 32), **then every 12 weeks until off study**.
9. Serum chemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, random glucose, albumin, total protein, creatinine, blood urea nitrogen (BUN), uric acid, ALT, AST, total bilirubin, direct and/or indirect bilirubin, alkaline phosphatase (ALP), amylase, lactate dehydrogenase (LDH) at baseline and then **every 2 weeks until week 40** (which is 8 weeks after the last LUTATHERA dose, which is at C4D1/week 32), **then every 12 weeks until off study**.
10. Coagulation tests (required at screening only): PT/INR, PT, PTT at baseline/screening only.
11. Pregnancy Test – baseline within 30 days of start of treatment and at end of study - urine or serum β-HCG in women of child bearing potential.
12. Hepatitis B virus surface antibody, hepatitis B virus surface antigen, hepatitis B virus core antibody, and hepatitis C virus antibody at screening/baseline only.
13. Availability of a paraffin-embedded archival tumor block sufficient to generate at least 8 unstained slides but preferably up 25 unstained slides; or, if a paraffin tumor block is unavailable, at least 8 unstained slides but preferably up 25 unstained slides.

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19.2 Attachment 2. Neurological Assessment in Neuro-Oncology (NANO)

Reference: Nayak et al. Neuro Oncol 2017;19(5):625-635.

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Patient Identifier: _____
Date Assessment Performed (day/month/year): _____
Study time point (i.e. baseline, cycle 1, day 1, etc):_____
Assessment performed by (please print name): _____

Domains	**Key Considerations**
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb
Ataxia (upper extremity) 0 ☐ Able to finger to nose touch without difficulty 1 ☐ Able to finger to nose touch but difficult 2 ☐ Unable to finger to nose touch ☐ Not assessed ☐ Not evaluable	• Non-evaluable if strength is compromised • Trunk/lower extremities assessed by gait domain • Particularly important for patients with brainstem and cerebellar tumors • Score based on best response of at least 3 attempts
Sensation 0 ☐ Normal 1 ☐ Decreased but aware of sensory modality 2 ☐ Unaware of sensory modality ☐ Not assessed ☐ Not evaluable	• Recommend evaluating major body areas separately (face, limbs and trunk) • Score should reflect worst performing area • Sensory modality includes but not limited to light touch, pinprick, temperature and proprioception • Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

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Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check 1 answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately due to pre-existing conditions, co-morbid events and/or concurrent medications.

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile and difficulty elevating eyebrows

Language

- 0 ☐ Normal
- 1 ☐ Abnormal but easily conveys meaning to examiner
- 2 ☐ Abnormal and difficulty conveying meaning to examiner
- 3 ☐ Abnormal. If verbal, unable to convey meaning to examiner. OR non-verbal (mute/global aphasia)
- ☐ Not assessed
- ☐ Not evaluable

- Assess based on spoken speech. Non-verbal cues or writing should not be included.
- **Level 1**: Includes word finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech.

Level of Consciousness

- 0 ☐ Normal
- 1 ☐ Drowsy (easily arousable)
- 2 ☐ Somnolent (difficult to arouse)
- 3 ☐ Unarousable/coma
- ☐ Not assessed
- ☐ Not evaluable

- None

Behavior

- 0 ☐ Normal
- 1 ☐ Mild/moderate alteration
- 2 ☐ Severe alteration
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition and confusion
- Consider subclinical seizures for significant alteration

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19.3 Attachment 3: Karnofsky Performance Status (KPS) Scale

KPS (%)	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

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19.4 Attachment 4: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair.
5	Dead.

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19.5 Attachment 5: Background and Rationale for Exploratory Study Objectives

1. ^{68}GA-DOTATATE PET/MR

We will explore the parameters of ^{68}Ga-DOTATATE PET MR imaging and its potential as a pharmacodynamic biomarker for Lutathera in meningioma. We hypothesize that patients with tumors that have the greatest baseline uptake of 68Ga-DOTATATE on PET MRI will respond to treatment. To test this, we will perform 3D list mode ^{68}Ga-DOTATATE PET imaging combined with T1 DCE / T2* DSE perfusion MR imaging on all patients in the trial at baseline prior to initiation of Lutathera treatment and 6 months. The latter ^{68}Ga-DOTATATE PET will be performed within 14 days of the last Lutathera dose (C4D1).

^{68}Ga-DOTATATE PET MR imaging is a hybrid functional and structural imaging technology with proven value as a prognostic tool in GEP NETs and head and neck paragangliomas, however it has yet to be evaluated prospectively in meningiomas. MRI is currently the standard of care for disease assessments for all brain tumors including meningiomas. However, MRI lacks specificity in distinguishing between progression and pseudoprogression (i.e., treatment effect). Previous studies have shown that ^{68}Ga-DOTATOC/DOTATATE PET imaging can accurately discriminate between progressive meningioma and tumor-free tissue. In addition, the 3D list mode capability of our PET MRI scanner will allow us to extract the dynamic imaging parameters of ^{68}Ga-DOTATATE that have not yet been addressed in the literature. Upon the completion of the study, each subject's PET MRI will be postprocessed with texture based analysis as a part of the Artificial Intelligence (AI) initiative at NYU. We aim to detect statistical and structural features that would allow us recognize patterns of treatment response and failure at early time points.

2. SSTR2 IMMUNOHISTOCHEMISTRY

We hypothesize that SSTR2 expression will correlate with outcome (PFS-6), baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

3. GENOME-WIDE DNA METHYLATION PROFILING:

A recent large analysis of ~500 meningiomas demonstrated that a DNA methylation-based meningioma classification has significantly greater power for predicting tumour recurrence and prognosis than the WHO classification, thus identifying more aggressive tumors with greater accuracy [22]. We hypothesize that a subset of patients will have the greatest response to Lutathera in this trial, and that response will correlate with DNA methylation-based meningioma subtypes. To test this, we will perform DNA methylation-based meningioma classification on all patients enrolled in the study and correlate DNA methylation-based subtype with outcome (PFS-6), SSTR2 expression, and baseline ^{68}Ga-DOTATATE uptake by PET MRI.

4. WHOLE EXOME NEXT-GENERATION SEQUENCING:

We will perform whole-exome next-generation sequencing on all archival tumor specimens (NYU genomics core) to assess the association between recurrent mutations recently identified in meningiomas (e.g. NF2, SMO, PI3K/Akt pathway, etc) and outcome (PFS-6), SSTR2 expression, baseline ^{68}Ga-DOTATATE uptake by PET MRI, and molecular subtype by DNA methylation array.

5. ^{177}LU-DOTATATE (LUTATHERA) DOSIMETRY:

We will perform ^{177}Lu-DOTATATE (Lutathera) dosimetry in an exploratory cohort of 10 patients. ^{177}Lu-DOTATATE administered dose will be calculated with MIM SurePlan™ MRT (MIM Software Inc., Cleveland, OH) following whole body planar and organ specific (head) SPECT CT on Symbia™ T6 Siemens (Siemens Medical Solutions USA, Hoffman Estates, IL, USA) on 4, 24, 72 and 192 hours post Lutathera administration.

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19.6 Attachment 6: Determination of LUTATHERA Administered Radioactivity

Determination of LUTATHERA Administered Radioactivity

The total amount of radioactivity administered to the patient is determined by measuring the radioactivity present in the LUTATHERA (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, Infusion Solution) Vial before and after administration. The procedure is as follows:

A. Measurement of LUTATHERA Vial radioactivity *before* LUTATHERA administration:

1) remove the LUTATHERA Vial from the original package;
2) place the LUTATHERA Vial in the dose calibrator (activimeter) chamber;
3) select the Lu-177 setting on the dose calibrator;
4) press the “measure” button (or equivalent function button);
5) record the measured radioactivity, and the time of measurement;
6) remove the LUTATHERA Vial from the dose calibrator chamber;
7) return the LUTATHERA Vial to its original package or prepare the Vial for patient administration.

B. Measurement of LUTATHERA vial radioactivity *after* LUTATHERA administration:

1) remove needles and tubing attached to the LUTATHERA Vial (NB: The physician must confirm that there is no significant residual radioactivity remaining in delivery needles and tubing after administration (< 0.1% of original Total Radioactivity in LUTATHERA Vial);
2) if the dose calibrator is in a different location, place the LUTATHERA Vial in the original package so that the material can be moved safely – otherwise go to step 4;
3) remove the LUTATHERA Vial from the original package;
4) place the LUTATHERA Vial in the dose calibrator chamber;
5) select the Lu-177 setting on the dose calibrator;
6) press the “measure” button (or equivalent function button);
7) record the measured radioactivity, and the time of measurement;
8) remove the LUTATHERA Vial from the dose calibrator chamber and dispose according to national and local regulations for disposal of radioactive waste;

C. Calculation of Total Administered and Residual Radioactivity:

1) Total Administered Radioactivity
   = (amount of radioactivity in LUTATHERA Vial before administration minus amount of radioactivity in LUTATHERA Vial after administration) times vial geometry correction factor
   $= (A.5 - B.7)\ x\ Correction\ Factor;$

2) Residual Radioactivity = amount of radioactivity remaining in LUTATHERA Vial after administration times vial geometry correction factor
   $= B.7\ x\ Correction\ Factor;$

3) record Total Administered Radioactivity and Residual Radioactivity.

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19.7 Attachment 7: Examples of Infusion Methods

Example 1: Two Pumps Method

Two infusion pumps (pump 1 and pump 2) infuse the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acids solution. A standard infusion set is connected to each pump and allows the infusion of the two pharmaceuticals products (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and amino acid solution) independently one each other.

The infusion set consists of:

1- a pre-filled, sterile container (glass bottle) of physiological solution that permit the fluid to flow one drop at a time, making it easy to see the flow rate (and also reducing air bubbles);

2- a long sterile tube with a clamp to regulate or stop the flow;

3- connectors to allow "piggybacking" of another infusion set onto the same line. This second line is connected to the amino acids solution bottle (pump 1) and to the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate vial (pump 2).

By means of a 3 way cock another sterile tube guarantees the connection of the tube coming from the physiological solution bottle and the tube coming from the second bottle (amino acid solution in the case of the pump 1 or ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in the case of pump 2) to the device (the infusion pump) that allows precise control over the flow rate and total amount of products delivered. The confluence of the two fluids that flows into the l vein infusion tube is allowed by another cock.

A scheme of the pumps infusion method is shown in Figure 1.

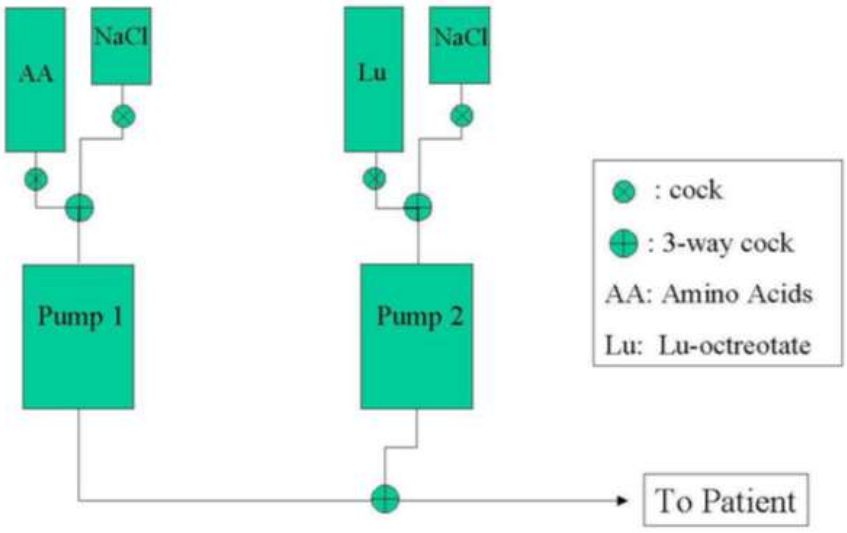


Figure 2. Two Pumps Infusion Method.

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Example 2: Flebo Infusion Method

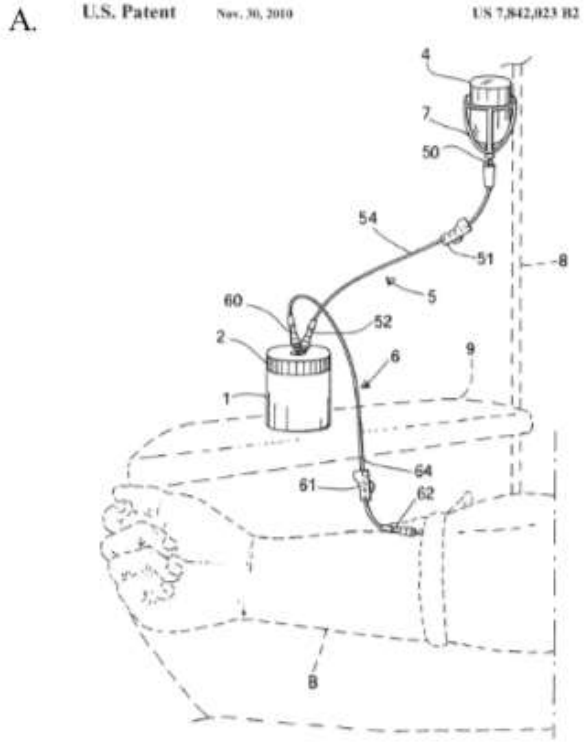
The Flebo infusion method is schematically presented in Figure 2. It consists of a container for a vial of radiopharmaceutical made of polymethyl methacrylate with a cavity capable of containing the vial of radiopharmaceutical, and of a lid screwed onto the receptacle for closing the container, said lid presenting a central through-hole. A set, in combination with this container with the vial of radiopharmaceutical, consisting of a bottle of saline solution and two infusion catheters, enhances the radioprotection during the infusion of a radiopharmaceutical in an infusion operation.

In an infusion operation, saline bottle **4** is conventionally suspended in a cradle **7** attached to a stand **8**, equipped with a support shelf **9**. The first infusion catheter is inserted with the first needle **50** in the cap of bottle **4**, while the second needle **52** is inserted, via flared portion and central through-hole of lid **2**, into the cap of radiopharmaceutical vial **3** in such a way as not to be immersed in the pharmaceutical.

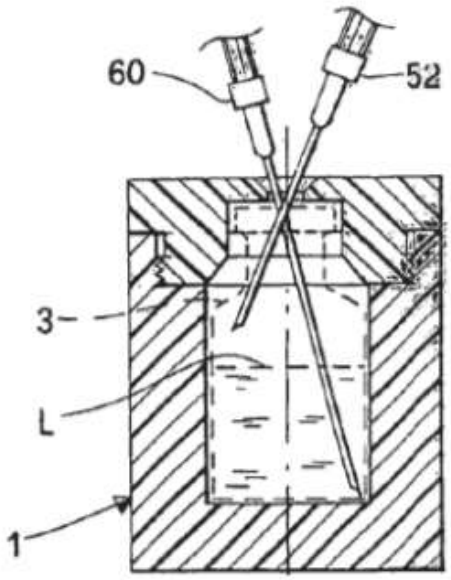
The second infusion catheter **6** also has its first needle **60** inserted via flared portion and through-hole of lid **2**, into the cap of the vial of radiopharmaceutical, whereas the second needle **62** is inserted in the brachial vein B of a patient. The first needle **60** is long enough to touch the bottom of the vial of radiopharmaceutical, where it must be held in place for the complete extraction of the radiopharmaceutical, as shown in Figure 2B.

The provision of flow via the bottle of saline solution **4**, the first infusion catheter **5**, vial **3** in container **1-2**, and the second infusion catheter **6** allows the radiopharmaceutical to be delivered by gravity. The saline solution is fed from bottle **4** into radiopharmaceutical vial **3** with flow regulation by means of flow-regulator **51**. The influx of saline brings about an increase in pressure in radiopharmaceutical vial **3** which has its entire contents aspirated by the second infusion catheter **6**, the flow rate of which is regulated by flow-regulator **61** (See US Patent 7842023) .

A.



B.



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C.



D.



Figure 3. Flebo Infusion Method (A) Showing Operations Details (B, C, D)

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