A PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF ULTRATRACE IOBENGUANE I 131 IN PATIENTS WITH MALIGNANT RELAPSED/REFRACTORY PHEOCHROMOCYTOMA/PARAGANGLIOMA

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[redacted] MD
Executive Vice President Research & Development
Medical Monitor
Molecular Insight Pharmaceuticals, Inc.
[redacted]

Molecular Insight Pharmaceuticals, Inc.,
a subsidiary of Progenics Pharmaceuticals Inc.

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2. Protocol Approval

Study medication name:	Ultratrace Iobenguane I 131 (No-Carrier-Added Iobenguane I 131)
Project name:	Phase II Iobenguane for Pheochromocytoma

Protocol number:	MIP-IB12B
Original: Current Version:	January 14, 2009 March 21, 2014
Protocol title:	*A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients with Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma*

This protocol is approved by the undersigned:

Name: [redacted] MD
Title: Executive Vice President, Research & Development

Signature: [redacted] Date: [redacted]

Name: [redacted] DrPH
Title: Executive Director, Biometrics

Signature: [redacted] Date: [redacted]

Name: [redacted] DC
Title: Associate Director, [redacted] ce

Signature: [redacted] Date: [redacted]

3. ABBREVIATIONS

AE	Adverse Event/Experience
AESI	Adverse Events of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT/SGPT	Alanine aminotransferase/ serum glutamic pyruvic transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST/SGOT	Aspartate aminotransferase/ serum glutamic oxaloacetic transaminase
ßHCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
dL	Deciliter
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EENT	Eyes, Ears, Nose, and Throat
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG	Flurodeoxyglucose
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Gy	Gray
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High-density lipoprotein

HIV	Human Immunodeficiency Virus
HPF	High power field
Hr	Hour(s)
IATA	International Air Transportation
ICH	International Conference on Harmonization
IB	Investigator's Brochure
ID	Injected Dose
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intend to Treat
IUD	Intrauterine device
LDL	Low-density lipoprotein
MBq/mL	Megabecquerel per milliliter
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
MIBG	Metaiodobenzyl-guanidine
Min	Minute(s)
MIP	Molecular Insight Pharmaceuticals, Inc.
MIRD	Medical Internal Radiation Dose
mL	Milliliter
MR	Magnetic Resonance or Moderate Response (per context)
mSv	Millisievert
MTD	Maximum Tolerated Dose
mV	Millivolt
Nca	No Carrier Added
NET	Norepinephrine Transporter
NIH	National Institutes of Health
OS	Overall Survival
PD	Progressive Disease
PET	positron emission tomography
PR	Partial Response
PT	Prothrombin Time
q.s.	*Quantum Sufficiat* (as much as suffices)

QoL	Quality of Life
Rad	100 ergs per g or 0.1 joules per kg of irradiated material
RBC	Red Blood Cell Count (total erythrocyte count)
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	Region of Interest
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAER	Serious Adverse Event Report
SLD	Sum of Longest Diameters
SD	Standard Deviation or Stable Disease (per context)
SOP(s)	Standard Operating Procedure(s)
Study Agent	Compound Under Investigation
SUV	Standard Uptake Value
Sx	Signs and Symptoms
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VMA	Vanillylmandelic Acid
WBC	White Blood cell Count (total leukocyte count)

4. STUDY OUTLINE

STUDY OUTLINE: MIP-IB12B A PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF ULTRATRACE IOBENGUANE I 131 IN PATIENTS WITH MALIGNANT RELAPSED/REFRACTORY PHEOCHROMOCYTOMA/PARAGANGLIOMA	
Rationale:	Pheochromocytomas are rare tumors that arise from cells of the sympathetic nervous system and may secrete catecholamines. Such tumors are usually found within one or both adrenal glands (85%), but may arise in other areas of sympathetic nerve cells, and are then referred to as paragangliomas. About 15% are found to be malignant at the time, or immediately after, the primary tumor is discovered. Another 5% of individuals with pheochromocytomas are later found to have malignant or recurrent disease. Iobenguane is a guanethidine derivative structurally resembling norepinephrine, and is a substrate for the norepinephrine transporter (NET). It can be labeled with radioisotopes of iodine, suitable for both diagnostic and therapeutic applications. Carrier-added iobenguane I 131 is a systemically administered radiopharmaceutical that is therapeutically active at high doses as a single agent in malignant pheochromocytoma, paraganglioma and metastatic carcinoid, and has been used successfully in combination with surgery and/or myeloablative chemotherapy. Targeted radiotherapy with carrier-added iobenguane I 131 is therapeutically active in recurrent or metastatic pheochromocytoma, with 34% of patients showing objective tumor response and 50% showing biochemical response. Azedra™ (Ultratrace® iobenguane I 131), commonly referred to as Ultratrace iobenguane I 131, is a very high specific activity form of iobenguane I 131, produced using Molecular Insight's proprietary Ultratrace® platform. This technology avoids unlabelled or "cold" iobenguane being carried through from the production reaction to the final formulation, resulting in a product with no or dramatically reduced levels of cold iobenguane carrier and therefore very high specific activity. Based on the well characterized cellular active transport mechanism, the higher the specific activity of iobenguane I 131, the greater the cellular uptake of radioactivity and hence greater tumor uptake. In animal studies, Ultratrace iobenguane I 131 has shown increased uptake by the normal tissues that express theNET such as the heart. In murine xenografts, Ultratrace iobenguane I 131 demonstrated significantly higher radiopharmaceutical concentration tumors expressing the NET. The carrier molecule iobenguane is a synthetic bioactive amine, which can cause hypertension as well as nausea and vomiting when administered at high mass doses as is currently the standard for therapeutic doses of iobenguane I 131. Also, the specific active uptake by the NET, expressed on the surface of neuroendocrine tumor cells, is a competitive process.

	Thus, the presence of cold iobenguane molecules in the infusion solution can diminish the uptake of radioactivity in the target tumors. *In vivo* imaging and therapy studies in rodents confirm that target organ accumulation is more than 50% greater for no-carrier added iobenguane I 131 as that obtained with carrier added preparations, and tumor kill is dramatically enhanced due to the resulting greater radiation dose to tumor. This study is designed to study the efficacy of Ultratrace iobenguane I 131 monotherapy for the treatment of relapsed/refractory malignant pheochromocytoma and paraganglioma. The study was originally initiated in June 2009 and is being extended to complete patient enrollment.
Objectives:	*Primary Objective:* To determine the proportion of study subjects with a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least six months or two cycles, from two Therapeutic Doses each at 500 mCi (or 8 mCi/kg, for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 administered approximately three months apart. *Secondary Objectives:* • To evaluate the safety of Ultratrace iobenguane I 131 in subjects with malignant pheochromocytoma/paraganglioma, including human radiation absorbed dose estimates to normal organs. • To assess the proportion of subjects with overall tumor response of complete response (CR) or partial response (PR) per RECIST criteria • To assess the proportion of subjects with overall tumor response of CR, PR or MR (moderate response, i.e., decrease in the sum of the longest diameters of the target lesions of 15-30%, with no evidence of progressive disease [PD] in non-target lesions) per RECIST criteria • To assess bone lesion status on the Soloway Scale • To assess tumor marker response in 24 hr urine and other serum/plasma tumor markers associated with pheochromocytoma/paraganglioma • To describe changes from baseline in the overall quality of life through the EORTC QLQ-C30 questionnaire post-treatment • To describe changes from baseline in symptoms using the National Institute of Health (NIH) Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma post-treatment • To assess change in use of analgesics and pain medications • To describe Karnofsky Performance Status post-treatment • To assess overall survival, up to 5 years post-treatment
Study Design:	This is a multi-center, open-label, single arm study. It is anticipated that approximately 75 subjects will be enrolled to ensure fifty-eight subjects given two Therapeutic Doses each at 500 mCi (or 8 mCi/kg for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 will be evaluable for efficacy and safety. Prior to administration of the first Therapeutic Dose, subjects will be given an Imaging Dose (3 mCi – 6 mCi) of Ultratrace iobenguane I 131 and will undergo iobenguane I 131 scintigraphic scans to

	evaluate tumor avidity as well as to measure normal organ distribution and allow for the calculation of radiation dosimetry to normal organs. Both Therapeutic Doses for a subject will be appropriately decreased by the same amount if results of the dosimetry study indicate an adjustment is warranted. Tumors will be measured by computed tomography (CT) or magnetic resonance (MR) at baseline and at 3, 6, 9 and 12 months after the first Therapeutic Dose. A bone scan will be performed at Screening/baseline, and if probable metastatic disease is observed additional bone scans will be performed at Months 3, 6, 9, and 12. Overall tumor response at 3, 6, 9 and 12 months per RECIST criteria will be assessed centrally by independent, blinded readers. If the study site has the capability to perform flurodeoxyglucose (FDG) scans, they may be performed to assess viable tumor tissue at baseline and 3, 6, 9, and 12 months. Tumor markers [serum chromogranin A, plasma free metanephrines and normetanephrines, 24 hour urinary vanillylmandelic acid (VMA), plasma catecholamines (dopamine, epinephrine and norepinephrine), 24 hour urinary catecholamines (dopamine, epinephrine and norepinephrine) and urinary metanephrines and normetanephrines] will be evaluated by a central laboratory at intervals described in the protocol. Renal function will be assessed through either creatinine clearance or Glomerular Filtration Rate (GFR) at baseline and at the Months 6 and 12 Efficacy Visits. Evaluation of thyroid function (T3, T4 and TSH) and clinical evaluation of possible dry mouth will be performed at the 12 month Efficacy Visit. Use and dose of antihypertensive, pain and other medication required for tumor associated signs and symptoms will be recorded on an on-going basis, including on an outpatient basis. Subject-reported Quality of Life measurements will be obtained through the EORTC QLQ-C30 v3 and the NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma. The frequency of the procedures is summarized in the Schedule of Procedures. Safety will be assessed through analyses of treatment emergent adverse events (AEs), as well as baseline and pre- and post-infusion ECGs, physical examinations, vital signs measurements, laboratory measurements (including clinical chemistry, hematology and urinalysis), and human radiation absorbed dose estimates to target lesions and normal organs. After the 12 month assessment, subjects enter long-term follow-up. Subjects will be followed for adverse events including post radiation toxicity reported as Events of Special Interest (Appendix VI) collected after the Safety Phone Call at 16 Weeks after administration of the last Therapeutic Dose of Ultratrace iobenguane I 131 and will also be followed for overall survival for 5 years after receiving the first therapeutic dose. In years 2-5 post-treatment (or until a subject experiences disease progression, start of another anticancer therapy or death), data on tumor response, tumor markers and clinical benefit (including use of antihypertensive medication) will be collected through assessments provided as institutional standard of care. If standard of care is not providing such assessments, they will be offered by the study site.

Study Duration:	Subjects will attend study visits from the time of signed informed consent through 12 months after the first Therapeutic Dose of Ultratrace iobenguane I 131. They will then enter long-term follow-up, and remain in follow-up for 5 years after the first therapeutic dose.
Inclusion Criteria:	All subjects must: 1. Provide written informed consent (and assent for subjects less than 18 years of age) and be willing to comply with protocol requirements 2. Be at least 12 years of age 3. Have a documented (medical record) diagnosis of either pheochromocytoma or paraganglioma that was confirmed by histology or a physician using other supportive data (e.g., abnormal metaiodobenzyl guanidine (MIBG) diagnostic study, or elevated tumor markers). 4. Be ineligible for curative surgery for pheochromocytoma 5. Have failed a prior therapy for pheochromocytoma/paraganglioma or are not candidates for chemotherapy or other curative therapies 6. Be on stable antihypertensive medication regimen for tumor-related hypertension for at least 30 days prior to the first therapeutic dose. A stable antihypertensive medication regimen is defined as no addition or deletion of antihypertensive medication and no change in total daily dose or route of administration for currently used antihypertensive medication(s) in the 30 days prior to first therapeutic dose. 7. Have at least one tumor site by CT or MR or iobenguane I 131 scan 8. Have definitive MIBG tumor avidity 9. Have an expected survival period of at least 6 months as prognosticated by physician Female subjects must: 10. Have a negative pregnancy test within 48 hours prior to receiving Ultratrace iobenguane I 131 11. Agree to use an acceptable form of birth control (abstinence, IUD, oral contraception, barrier and spermicide or hormonal implant) during this study and for 6 months following Therapeutic Doses of Ultratrace iobenguane I 131. For those women who are sexually active and using oral contraceptives, a second form of barrier contraception is required or 12. Not be of childbearing potential as documented by history (e.g., tubal ligation or hysterectomy) or is post-menopausal with a minimum of 1 year without menses Male subjects must: 13. Agree not to father a child during the period beginning immediately after administration of the first Therapeutic Dose of Ultratrace iobenguane I 131 and ending six months after administration of the last Therapeutic Dose of Ultratrace iobenguane I 131. 14. Use an acceptable method of birth control (e.g., vasectomy or as

	described above) during the study and for six months following the Therapeutic Doses of Ultratrace iobenguane I 131.
Exclusion Criteria:	Subjects will be excluded if <u>any</u> of the following conditions are observed: 1. <50% of FDG (if data are available) positive lesions are MIBG avid 2. Pregnant or nursing females 3. Active central nervous system (CNS) lesions by CT or MR scanning within 3 months of study entry 4. New York Heart Association class IV heart failure, symptomatic congestive heart failure [New York Heart Association class IV with another medical disorder], unstable angina pectoris, cardiac arrhythmia 5. Received any previous systemic radiotherapy resulting in marrow toxicity within 3 months of study entry or have active malignancy (other than pheochromocytoma/paraganglioma) requiring additional treatment during the active phase or follow up period of the Ultratrace iobenguane I 131 trial. (Prior iobenguane I 131 therapy is allowed if not within 3 months prior to the first therapeutic dose). 6. Administered prior whole-body radiation therapy 7. Received external beam radiotherapy to > 25% of bone marrow 8. Administered prior chemotherapy within 30 days of study entry or have active malignancy (other than pheochromocytoma/ paraganglioma) requiring additional treatment. 9. Karnofsky Performance Status is < 60 10. Platelets < 80,000/μL 11. Absolute neutrophil count (ANC) < 1,200/μL 12. Total bilirubin > 1.5 times the upper limit of normal 13. AST/SGOT or ALT/SGPT > 2.5 times the upper limit of normal 14. Diagnosed with AIDS or HIV-positive per patient medical history 15. Active chronic alcohol abuse, chronic liver disease (excluding liver metastases), or hepatitis (A, B or C, detected by positive testing for HbsAg and anti-HCV as stated in patient medical history) 16. Renal dysfunction/impairment (defined as creatinine clearance of <30 mL/min or Glomerular Filtration Rate (GFR) of <30 mL/min) because of the possibility of delayed Ultratrace Iobenguane I 131 excretion and increased whole body dose 17. Known allergy to iobenguane that has required medical intervention 18. Received a therapeutic investigational compound and/or medical device within 30 days before admission into this study 19. Receiving a medication which inhibits tumor uptake of iobenguane I 131 as described in Appendix III of the protocol 20. Any medical condition or other circumstances (i.e., uncontrolled current illness including but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with the study requirements). 21. Any other condition, that in the opinion of the investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study

Study Drug:	Each subject will be administered 3 mCi to 6 mCi Ultratrace iobenguane I 131, referred to as the Imaging Dose, to confirm that subject meets radiological entry criteria and to establish dosimetry. All subjects meeting entry criteria will then receive the investigational product referred to as the Therapeutic Dose (500 mCi or 8 mCi/kg if the subject weighs 62.5 kg or less) of Ultratrace iobenguane I 131, followed by imaging within 7 days post infusion. The Therapeutic Doses will be adjusted equally if warranted by results of the dosimetry evaluation. At least 3 months later, subjects will receive the second Therapeutic Dose.
Imaging Parameters:	During the baseline period, a CT or MR scans of the chest, abdomen and pelvis with IV contrast (unless medical condition or allergy prevents its use) and a bone scan will be acquired to determine extent of disease. Obtaining renal volume for each kidney is required. Anatomical volumes may be measured for other organ and tissues to further evaluate absorbed dose. After the Imaging Dose (3 mCi to 6 mCi) of Ultratrace iobenguane I 131, subjects will have an Ultratrace iobenguane I 131 anterior and posterior planar whole body scan at 1 hour, 1-2 days and 2-5 days following the dose to evaluate biodistribution and (for the first dose) to confirm uptake in at least one known tumor that meets RECIST criteria. At least 18 hours separation between each of the three image acquisitions is required. The tumor to background ratio should be $\geq$2, and may be best visualized beginning at the 24 hour image to allow background clearance. For example, a liver lesion should be 2X background normal liver while soft tissue lesions would use background in surrounding soft tissue. Subjects will have an Ultratrace iobenguane I 131 whole body scan within 7 days following each Therapeutic Dose to further assess biodistribution. Subjects will have follow-up CT or MR scans at 3, 6, 9 and 12 months after the first Therapeutic Dose of Ultratrace iobenguane I 131 to assess tumor response. Subjects may also have optional follow up FDG scans at 3, 6, 9 and 12 months after the first Therapeutic Dose of Ultratrace iobenguane I 131. Bone scans will be performed at Month 3, 6, 9, 12, if probable metastatic disease is observed on the Screening bone scan. Subjects may undergo additional scans at unscheduled visits for confirmation of response. All images will be sent to the central imaging core lab for evaluation after anonymization. Off-site CT or MR assessment will be conducted by independent, CT and MR-experienced readers in accordance with the charter issued by the imaging core laboratory. These readers will be blinded to clinical subject information as described in the Imaging Charter. The readers will determine objective tumor response according to RECIST criteria. On-site interpretation of CT and MR images may also be performed, but only the results of the blinded read will be used for the objective tumor response evaluations. As part of long-term follow-up, a subject may receive additional scans to monitor disease status per institutional standard of care; these images will not be evaluated by a central laboratory.

Endpoints:	*Primary Endpoint:* The primary endpoint for this trial is the proportion of study subjects with a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least six months or two cycles Ultratrace iobenguane I 131. The primary endpoint will be assessed at the time of study completion or discontinuation, whichever occurs first. *Secondary Endpoints:* • Proportion of subjects with overall tumor response of CR or PR per RECIST criteria, • Proportion of subjects with overall tumor response of CR, PR or MR (moderate response) per RECIST criteria • Bone lesion response per the Soloway Scale • Tumor marker response in 24 hr urine and other serum/plasma tumor markers associated with pheochromocytoma/paraganglioma • Status of hypertension and changes in blood pressure • Quality of Life per the recommended guidelines from the EORTC QLQ-C30 manual • Symptoms as evaluated through the NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma • Change in use of analgesics and pain medications • Overall survival (OS), defined as the time from the date of enrollment to the date of death from any cause. OS time will be censored at the last date the subject is known to be alive when the confirmation is absent or unknown. • Safety assessed by changes in lab values, physical exams or vital signs, and the occurrence of treatment emergent adverse events • Human radiation absorbed dose estimates to normal organs
Sample Size:	It is anticipated that approximately 75 subjects will be enrolled to ensure that 58 subjects receive two doses and are evaluable for safety and efficacy. The one-sided alternative hypothesis of the study is that the proportion of subjects experiencing a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least six months or two cycles is 0.25, against the null hypothesis that the proportion is 0.10. Sample size of 58 subjects in the Per Protocol Set was based on a one-sided significance level of $\alpha = 0.025$ and power of 0.90 (90%).
Statistical Methods:	Summary tables and listings of demographics and baseline characteristics for all enrolled subjects will be presented. Listings of laboratory test results collected at baseline and during the study will be generated. All subjects who received at least one Therapeutic Dose of Ultratrace iobenguane I 131 will be included in the Full Analysis Set; all subjects who received both Therapeutic Doses and who attended the 3 Month and 6 Month Efficacy Visits with no major Protocol violations will be included in the Per Protocol Set. For each of these populations, a point estimate (with a 95% confidence interval, using the normal approximation with a continuity correction) for the proportion of subjects experiencing a reduction in use of all antihypertensive medication by at least 50% for at least six months or two cycles will be calculated. This single arm trial will be considered a

	success if the lower limit of the two-sided 95% confidence interval for the Full Analysis Set exceeds 0.10 (10%). Secondary analyses of the primary efficacy endpoint and analyses of the secondary efficacy endpoints will be conducted as described in the protocol and Statistical Analysis Plan. Safety analyses will include treatment emergent adverse events, clinical laboratory measurements, vital signs measurements, and physical examination findings. Adverse events and incidence of overall toxicity, categorized by toxicity grades (severity), will be described. All subjects who received the Imaging Dose of Ultratrace iobenguane I 131 will be included in the analysis of any safety endpoint. Adverse events will be captured for all enrolled subjects and those prior to the Imaging Dose will be displayed in a separate listing.

Sponsor Contact Information

Main Telephone Number for Business Hours 8:30 AM – 5:00 PM EST	[redacted]
Worldwide Safety Hotline	[redacted]
[redacted] MD Executive Vice President, Research & Development Medical Monitor	[redacted]
[redacted] Clinical Trial Manager	[redacted]

5. TITLE OF STUDY

A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients with Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma

6. PROTOCOL AND EUDRACT NUMBER

This study is being conducted under protocol number: MIP-IB12B. The IND number is: [redacted] and the EudraCT number is 2008-001148-38. The study will be completed according to the guidelines of International Conference on Harmonisation Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

7. INTRODUCTION

7.1 Malignant Pheochromocytoma/Paraganglioma

Pheochromocytomas are rare tumors that arise from cells of the sympathetic nervous system and may secrete catecholamines. Such tumors are usually found within one or both adrenal glands (85%), but may arise in other areas of sympathetic nerve cells, and are then referred to as paragangliomas.[21] About 15% are found to be malignant at the time, or immediately after, the primary tumor is discovered. [17] Another 5% of individuals with pheochromocytomas are later found to have malignant or recurrent disease.

Common sites of metastatic disease include lung, lymph nodes, and bone. Although the effects of excessive catecholamine can be reduced by adrenergic blockade or blocking of catecholamine synthesis, these drugs do not halt tumor growth. Five-year survival has been 40%.[1] For malignant pheochromocytoma; radiation therapy has been palliative but not curative. Chemotherapy trials have failed to produce cures or significant remissions. A study of the CVD regimen (cyclophosphamide + vincristine + dacarbazine) in 14 patients with malignant pheochromocytoma reported a complete or partial response in 57% of patients (median duration, 21 months) in this very small patient study; importantly, disease progression occurred in 9 of the 14 patients and there were 6 deaths with short term follow-up.[2] Patients recently diagnosed with malignant pheochromocytoma have tumors that initially can be slow growing even though the survival rate is less than 50%; although some patients may experience minimal morbidity with survival for as long as 20 years.[3] Rather than newly diagnosed non-metastatic malignant pheochromocytoma, this study will focus on patients with metastatic malignant pheochromocytoma or paraganglioma who have failed other therapies or are not candidates for chemotherapy or other curative therapies.

In this setting of more rapidly growing and progressive lesions, survival is often 24 months or less.

7.2 Carrier-Added Iobenguane I 131

Iobenguane is a guanethidine derivative structurally resembling norepinephrine, and is a substrate for the norepinephrine transporter (NET). It can be labeled with radioactive isotopes of iodine, suitable for both diagnostic and therapeutic applications. Carrier-added iobenguane I 131 has been used in combination with surgery and/or myeloablative chemotherapy as therapy for neuroendocrine cancers, including pheochromocytoma. The term, "carrier added", refers to the fact that a significant quantity of non-radioactive or "cold" MIBG is present in the iobenguane I 131 patient administered dose. In therapeutic doses of carrier-added iobenguane I 131 the molar ratio of nonradioactive to radioactive MIBG molecules approaches 2000:1.

Sisson et al.[4] treated 5 malignant pheochromocytoma patients with carrier-added iobenguane I 131 at ten month intervals at a single institution in the US. Total administered activity was 484 mCi in 4 treatments over 15 months for the first patient, 373 mCi in 3 treatments over 8 months for the second patient, 410 mCi in 3 treatments over 17 months for the third patient, 270 mCi in 2 treatments over 3 months for the fourth patient, and 293 mCi in 2 treatments over 3 months for the fifth patient. The first two patients had predominantly soft tissue metastases and had responses in terms of disappearance of symptoms and a reduction in volume and function of tumors to < 50% of pretreatment values. These partial remissions lasted over 1 year to the date of publication. There was no significant toxicity reported. Tumor absorbed doses were stated to range between 13 and 120 Gy, but the dose estimation method was not elaborated.

Charbonnel et al.,[5] in France, reported treatments with carrier-added iobenguane I 131 in 7 patients with metastatic pheochromocytomas (3 with only soft tissue metastases, 1 with only bone metastases, and 3 with both soft tissue and bone metastases). Treatment was with 100-200 mCi every 3-6 months. There was a decrease in catecholamines of greater than 50% in all 7 patients and a decrease in tumor mass of greater than 50% in all 7 patients. Toxicity included moderate pancytopenia in one patient with diffuse osseous metastasis after the second carrier-added iobenguane I 131 therapy course; this resolved within 3 months but recurred after the third treatment, requiring blood and platelet transfusion (cumulative dose 394 mCi). A mild increase in blood pressure was noted in 3 patients 2-3 days after treatment that resolved over several days.

Limone et al.[6] and Konings et al.[7] each reported 1 patient with clinical improvement following carrier-added iobenguane I 131 treatment. The authors suggest that treatment results could be improved if carrier-added iobenguane I 131 were given to patients with low metastatic tumor burden.

Brendel et al.[8] in France reported 2 patients with malignant pheochromocytoma treated with carrier-added iobenguane I 131. One patient with bone and lung metastases received 2,030 mCi of carrier-added iobenguane I 131 over 10 courses at 3 month intervals; this resulted in remission in pain and asthenia, regression of > 50% in skull and lung tumors, and a decrease in VMA of 35%. The second patient received 950 mCi of carrier-added iobenguane I 131 over 5 courses at 3 month intervals. She had normalization of VMA levels and a > 50% reduction in the volume of metastatic lymph nodes. Side effects included transient leukopenia. One patient had unstable hypertension and nausea 48-72 hours after each treatment.

Troncone et al.[9] in Italy reported treatment with carrier-added iobenguane I 131 of 4 patients with advanced pheochromocytoma. One patient with residual tumor received 300 mCi in 3 courses

at 3 month intervals and had complete regression of tumor, normalization of catecholamine levels, and no evidence of disease 20 months after start of therapy. Another patient with metastases had an 18 month remission after 670 mCi carrier-added iobenguane I 131 over 9 courses at 3 month intervals, but refused further treatment and died 6 months later. The third patient died after 15 months stabilization of the disease following 340 mCi carrier-added iobenguane I 131 over 3 courses. No change was noted in the fourth patient with massive abdominal recurrence who received only 150 mCi carrier-added iobenguane I 131 and died 2 months later. There were no adverse reactions reported.

Shapiro et al.[10] investigated 28 patients at a single institution in the US. These patients had histologically-proven metastatic pheochromocytoma or invasive, unresectable pheochromocytoma, all of which were avid for tracer doses of carrier-added iobenguane I 131. Patients received 1 to 6 carrier-added iobenguane I 131 treatments, ranging from 97 to 301 mCi of administered activity; cumulative doses ranged from 111 to 916 mCi. Mild radiation sickness (nausea, vomiting and anorexia) occurred in 75.0% (21 of 28). Minor degrees of leukopenia and thrombocytopenia were observed in 10.7% (3 of 28). There were three cases of hypothyroidism but no significant hepatic, renal, adrenocortical, or autonomic nervous dysfunction. The authors found partial responses both in terms of tumor shrinkage and in terms of decreases in biochemical secretion. The tumor response (with 95% confidence interval, or CI) was 28.6% $\pm$ 16.7% (8 of 28 evaluable patients). The biochemical response (95% CI) was 42.9% $\pm$ 18.3% (12 of 28 evaluable patients).

Krempf et al.[11-12] studied 15 patients with malignant pheochromocytoma at 6 centers in France. Four patients had only soft tissue metastases, 4 had only bone metastases, and 7 had both bone and soft tissue metastases. Ages ranged from 28 to 75 years. Patients were administered 740 megabequerel/mg of carrier-added iobenguane I 131 every 3 months. The number of courses ranged from 2 to 11, administered activity per course ranged from 78.4 to 250.0 mCi, and cumulative activity ranged from 300.0 to 2,322 mCi. The cumulative absorbed dose in tumors ranged from 12 to 155 Gy. One patient with widespread bone metastases developed pancytopenia after three courses (348.6 mCi); however, this resolved after treatment was discontinued. The tumor response (95% CI) was 33.3% $\pm$ 23.9% (5 of 15 evaluable patients); duration of tumor response ranged from 29 to 54 months. The biochemical response (95% CI) was 46.7% $\pm$ 25.2% (7 of 15 evaluable patients); duration of biochemical response ranged from 5 to 48 months. All patients with a hormonal response had objective improvement in clinical status and blood pressure. Seven patients died during the 54-month follow-up period, 4 of whom never responded to treatment. The investigators reported finding no relationship between cumulative dose and response.

Schlumberger et al.[13] studied 11 patients with metastatic pheochromocytoma who received carrier-added iobenguane I 131 at a single institution in France between 1985 and 1990. Cumulative activity ranged from 100 to 711 mCi, in 1 to 6 courses. Moderate myelosuppression occurred in 4 patients. Symptoms improved in 55.6% (5 of 9). The tumor response proportion (95% CI) was 22.2% + 27.2% (2 of 9 evaluable patients); the tumor responses lasted 9 months and 28 months.

Loh et al.[14] reviewed the literature on carrier-added iobenguane I 131 treatment for malignant pheochromocytomas and extra-adrenal paragangliomas from 1983 through 1996 in 24 centers in

10 countries. They found a total of 116 evaluable patients. A majority of the patients were selected for treatment based upon positive tracer uptake studies. The cumulative dose of carrier-added iobenguane I 131 administered ranged from 96 to 2,322 mCi, with a mean (± SD) of 490 ± 350 mCi. The patients received a mean single therapy dose of 158 mCi and the number of doses administered ranged from 1 to 11, with a mean (± SD) of 3.3 ± 2.2 doses. Initial symptomatic improvement was achieved in 76% of patients, tumor responses in 30%, and hormonal responses in 45%. Five patients had complete tumor and hormonal responses, ranging from 16 to 58 months, which were sustained at the time of reporting. Patients with metastases to soft tissue had more favorable responses to treatment than those with metastases to bone. No difference was noted in the age between the responders and non-responders. Adverse effects, recorded in 41% of the treated patients, were generally mild except for one fatality from bone marrow aplasia. Among 89 patients with follow-up data, 45% of the responders had relapsed with recurrent or progressive disease after a mean interval of 29.3 ± 31.1 months (median 19 months). Of patients with an initial response to carrier-added iobenguane I 131, death was reported in 33% after a mean (± SD) of 23.2 ± 8.1 months (median 22 months) following treatment. Of non-responders, death was reported in 45% after a mean (± SD) of 14.3 ± 8.3 months (median 13 months). The reviewers concluded that carrier-added iobenguane I 131 therapy may be a useful adjunct in selected patients with malignant pheochromocytoma or paraganglioma.

Mukherjee et al.[15] reported carrier-added iobenguane I 131 treatment of 15 patients with metastatic pheochromocytoma or paraganglioma. The patients were treated repeatedly to a cumulative dose of 592 mCi; this ranged from 200 to 1,592 mCi. No patients had complete remissions, but 82% had stable disease. The overall 5-year survival was 85%. Hormonal control was attained in 53%.

Safford et al.[16] retrospectively report the experience of a single institution in the US in treating 22 patients with metastatic pheochromocytoma and 11 patients with paraganglioma over a 10-year period. Patients received a mean (± SD) administered activity of 388 ± 131 mCi. The investigators found that patients administered > 500 mCi on their initial course of carrier-added iobenguane I 131 had improved overall survival (3.8 years versus 2.8 years, $p = 0.02$). By univariate analyses, the authors also found that both symptom improvement ($p < 0.01$) and biochemical response ($p = 0.01$) were associated with increased overall survival.

Rose et al.[17] prospectively studied carrier-added iobenguane I 131 in 12 patients with malignant pheochromocytoma or paraganglioma at a single institution in the US. The disease was required to have been metastatic or unresectable at baseline. Patient age ranged from 10 to 58 years, with a median of 31 years. First, bone marrow/stem cells were harvested for all patients. Six patients received only 1 treatment, 5 patients received 2 treatments, and 1 patient received 3 treatments. Single treatment activity ranged from 5.6 to 18.3 mCi/kg, with a median of 11.5 mCi/kg. The activities of repeat treatments averaged within ± 2% of prior treatments. Grade 3 thrombocytopenia occurred following 15 of the 19 treatments (78.9%). Grade 3 neutropenia occurred following 10 of the 19 treatments (52.6%) and grade 4 neutropenia occurred following 4 of the 19 treatments (21.1%). One patient needed stem cell infusion and 1 developed primary ovarian failure. There were 2 complete and 2 partial responses by RECIST criteria; the response proportion (95% CI) was 36.4% ± 28.4% (4 of 11 evaluable patients). Duration of response ranged from 6 to 101 months, with a median of 15 months. Improvement of symptoms occurred among 90.0% ± 18.6% (9 of 10 evaluable patients). Duration of symptom improvement ranged

from 2 to 101 months, with a median of 43 months. No dose-response effect was seen in terms of either cumulative activity or cumulative activity per kilogram.

Fitzgerald et al.[18] prospectively studied carrier-added iobenguane I 131 in 30 patients with malignant pheochromocytoma or paraganglioma at a single institution in the US. For study entry, patients were required to have had unresectable tumors avid for carrier-added iobenguane I 131 or I 123. Eleven patients had pheochromocytoma and 19 patients had paraganglioma. Ninety percent had distant metastases, including 23 of 30 with bone lesions and 12 of 30 with liver lesions. All patients had prior surgery; 6 had prior radiation and 9 had prior chemotherapy. Ages ranged from 10 to 62 years, with a mean of 39 years. All patients had peripheral blood stem cells collected. Carrier-added iobenguane I 131 was infused over 2 hours at doses ranging from 557 to 1185 mCi (7.4 to 18.8 mCi/kg), with a mean of 833 mCi (12.6 mCi/kg). Hematologic toxicity included 19 patients needing platelet transfusions, 19 needing GCSF, 13 needing RBCs, and 3 needing peripheral blood stem cell infusions. Efficacy was assessed by both objective tumor response and biochemical response. Three patients had a durable complete response and 16 patients had a durable partial response, for an overall response proportion (95% CI) of 63.3% $\pm$ 17.2% (19 of 30 evaluable patients).

Gonias et al.[45] evaluated data for 50 patients with metastatic pheochromocytoma or paraganglioma, ages 10 to 64 years. The results for the first 30 patient in this study were analyzed by Fitzgerald[18] (see paragraph above). Thirty-four patients (69%) enrolled on the study were diagnosed with paraganglioma, whereas 15 patients (31%) were diagnosed with pheochromocytoma. Subjects were treated with [131I] MIBG doses ranging from 492 to 1,160 mCi (median, 12 mCi/kg). Cumulative [131I] MIBG administered ranged from 492 to 3,191 mCi. Sixty-nine [131I] MIBG infusions were given, which included infusions to 35 patients treated once and infusions to 15 patients who received two or three treatments. The overall complete response (CR) plus partial response (PR) rate in 49 evaluable patients was 22%. Additionally, 35% of patients achieved a CR or PR in at least one measure of response without progressive disease, and 8% of patients maintained stable disease for greater than 12 months. Thirty-five percent of patients experienced progressive disease within 1 year after therapy. The estimated 5-year overall survival rate was 64%.

Table 1 below summarizes dosing, objective tumor response proportions, and biochemical response proportions of published carrier-added iobenguane I 131 studies for malignant pheochromocytoma that included 5 or more patients each.

TABLE 1: SUMMARY OF CARRIER-ADDED IOBENGUANE I 131 THERAPY FOR 156 MALIGNANT PHEOCHROMOCYTOMA PATIENTS

Study	N	Tx type	Median Single Dose (Range)#	Tumor Response Proportion*	Biochemical Response Proportion**
Safford[16]	33	M	388 ± 131 (NR) mCi	NR	NR
Mukherjee[15]	15	M,C	592 (200-1592) mCi	0	53 ± 25
Schlumberger[13]	11	M,S,C	NR (100-711) mCi	22 ± 27	NR
Shapiro[10]	28	M	NR (111-916) mCi	29 ± 17	43 ± 18
Krempf[11,12]	15	M	NR (300-2322) mCi	33 ± 24	47 ± 25

Study	N	Tx type	Median Single Dose (Range)#	Tumor Response Proportion*	Biochemical Response Proportion**
Rose[17]	12	M	11.5 (5.6-18.3) mCi	36 ± 28	NR
Sisson[4]	5	M	373 (270-484) mCi	40 ± 43	NR
Fitzgerald[18]	30	M	825 (552-1160) mCi	63 ± 17†	NR
Charbonnel[5]	7	M	NR (100-200) mCi	100	100
Gonias[45]	49	M	818 (492-1,160) mCi^	57%^^	NR

Legend

Tx Type:	M = carrier-added iobenguane I 131, C = myeloablative chemotherapy, S = surgery.
#	Whole-body absorbed doses in Gy are not reported, so administered activity in mCi/kg or mCi is shown.
Response	Includes complete and partial responses.
*	Decrease in percent with 95% confidence interval using RECIST criteria
**	Decrease in percent with 95% confidence interval
†	Reported proportion is in consideration of both objective tumor response and biochemical response.
NR	Not reported.
^	First treatment range
^^	Overall complete response

The studies demonstrate the following:

- Median administered activity per study ranged from 373 to 825 mCi, with a median of 490 mCi.
- Objective tumor response proportions per study ranged from 0 to 100%, with a median of 34.5%.
- Biochemical response proportions per study ranged from 43 to 100%, with a median of 50%.
- One study[15] found an ^{131}I-iobenguane dose-response effect for overall survival (nominal p-value < 0.05).

An earlier literature review published in 1997 reported the experience of 116 patients with malignant pheochromocytoma. It found a mean administered activity of 490 mCi, an objective tumor response proportion of 30%, and a biochemical response proportion of 45%.[13]

7.3 No-Carrier-Added (Ultratrace®) Iobenguane I 131 Dosing Regimen

The carrier molecule, iobenguane is a bioactive amine, which can cause hypertension as well as nausea and vomiting when administered at high mass doses, which is currently the standard for therapeutic doses of iobenguane I 131. Also, the specific active uptake by the norepinephrine transporter (NET), expressed on the surface of neuroendocrine tumor cells, is a competitive process. Thus, the presence of cold "carrier" iobenguane molecules in the infusion solution can diminish the initial uptake in the target tissues, such as neuroendocrine tumors. *In vivo* imaging and therapy studies in rodents confirm that target organ accumulation is more than 50% greater for no-carrier added iobenguane as that obtained with carrier added preparations, and tumor kill is dramatically enhanced due to the resulting greater radiation dose to tumor.

A review of the published clinical experience with iobenguane I 131 for the treatment of metastatic pheochromocytoma shows that multiple cycles of iobenguane I 131 were well tolerated in patients.[14,16,18] From our (Phase I) dose escalation study with Ultratrace iobenguane I 131, we demonstrated that a single dose of 592 mCi/74 kg (296 mCi/m^2) was well tolerated with transient myelosuppression predicted by individual patient dosimetry. The transient myelosuppression resolved, returning to pre-treatment values by 8 weeks post-treatment.

For this study, subjects will receive two Therapeutic Doses of 500 mCi (or 8 mCi/kg if the subject weighs 62.5 kg or less) Ultratrace iobenguane I 131 approximately 12 weeks apart. Prior to the first Therapeutic Dose, we will perform dosimetry using an Imaging Dose (3 mCi – 6 mCi) of Ultratrace iobenguane I 131 followed by three I 131 scans, thereby ensuring that the Therapeutic Doses will not result in unacceptable toxicity to the subject. In those subjects where the dosimetry study suggests the potential of unacceptable toxicity, the doses will be adjusted downward equally as detailed in Section 10.2

7.4 Biomarkers for Pheochromocytoma and Paraganglioma

Pheochromocytomas and paragangliomas are rare tumors of chromaffin cells with pheochromocytomas arising from tissue of the adrenal medulla and paragangliomas located at extra-adrenal sites along the sympathetic or parasympathetic chain.[19] Pheochromocytoma and paragangliomas can synthesize, store and secrete catecholamines, and more rarely dopamine, causing a variety of clinical symptoms.[20,21] Even if they do not secrete hormones, pheochromocytomas synthesize catecholamines at increased rates that may be up to 27 times the synthetic rates of the normal adrenal medulla. Catecholamines are produced in quantities that exceed the vesicular storage capacity and accumulate in the cytoplasm of the tumor cells. Here they are subject to intracellular metabolism, and the excess catecholamines and metabolites diffuse out of the tumor cells into the circulation.[22]

Pheochromocytoma cells contain catechol-O-methyltransferase and therefore metabolize catecholamines locally releasing free metanephrines and other metabolites. This fact, combined with the usually low rates of extraneuronal catechol-O-methylation and the relatively large contribution of adrenal medullary cells to normally low plasma levels of free metanephrines, provides the extraordinary sensitivity of these measurements for detecting the presence of pheochromocytoma tumor cells. That is, the plasma level of these hormones is amplified by intratumoral formation of free metanephrines.[23,24] Secretion of catecholamines and other bioactive hormones into the plasma is episodic, and measurement of the parent compounds is therefore variable. However, metanephrines, the metabolites of catecholamines, are produced continuously within the pheochromocytoma tumor cells independent of catecholamine release,[21] and the production of O-methylated metabolites is independent of the highly variable release of catecholamines.[25]

Therefore, plasma free metanephrine measurement is a more sensitive test for detecting pheochromocytoma than measurement of the parent amines or other metabolites.[26,27,28] Increased sensitivity of metanephrine levels compared with catecholamines is due to the continuous production of O-methylated metabolites in tumors from catecholamines leaking from chromaffin stores.[29] Similarly, measurement of plasma methoxytyramine, the O-methylated metabolite of dopamine, provides a higher diagnostic accuracy than measurement of urinary dopamine.[20,25]

Chromogranin A is an acidic protein that is stored and released, along with catecholamines, from chromaffin granules of normal adrenal medulla and pheochromocytoma. Results of a study of samples from subjects with no tumors, with benign or with malignant pheochromocytoma demonstrate that measurement of serum chromogranin A is useful in the diagnosis of pheochromocytoma and assists in assessing the response to therapy for those with malignant disease. A progressive rise in serum chromogranin A was observed when levels from control subjects, those with benign pheochromocytoma and subjects with malignant pheochromocytoma was assessed along with a parallel rise in plasma norepinephrine. Serum chromogranin A elevation demonstrated the most significant difference between benign and malignant tumors, and in patients with benign or malignant pheochromocytoma, serum chromogranin A correlates with the weight of the excised tumor suggesting that levels reflect the tumor burden.[30] Indeed, chromogranin A can be used to monitor response to treatment and/or indicate relapse of disease[31] and correlates well with plasma metanephrines and tumor mass.[21, 32]

Similarly, plasma metanephrine concentration is a highly sensitive and specific diagnostic marker for pheochromocytoma and metanephrines strongly correlate with tumor mass.[20,21,23,33] Free metanephrines reflect continuous production by the tumor in contrast to the sporadic secretion of catecholamines, and repeated measurements of plasma metanephrines have been used to assess tumor recurrence.[34,35] Overall, the measurement of plasma or urinary metanephrines is superior to urinary catecholamines (sensitivity of 99% and 97% versus 86% and 84% when used for diagnosis)[35] and chromogranin A and metanephrine concentrations are proportional to the tumor mass.[20]

7.5 FDG Positron Emission Tomography

Diagnosis of pheochromocytoma, in part, relies on the biochemical demonstration of excessive catecholamines or their metabolites in blood and urine. In the drug development process the RECIST criteria for tumor evaluation are used to assess the efficacy of novel therapeutics in oncology. For example, a patient is said to have partial response (PR) for target lesions if the sum of the longest diameters of the target lesions decreases at least 30%. However, indolent slow growing tumors are usually comprised of a necrotic center surrounded by an area of hypoxic yet viable tissue. Since therapeutic agents will not reduce the size of the necrotic center and in some cases may increase the size of the necrotic region (anti-angiogenesis), disease status in some cases is quantified more accurately by a modality that assesses viable tumor tissue.

Positron emission tomography (PET) scanning with ^{18}F fluorodeoxyglucose (FDG) is becoming a more common imaging modality in the detection of viable tumor tissue. All tumors are under continuous oxidative stress due to their rapid metabolism and hypoxic nature. As a result of the combined hypoxia and oxidative stress there is increased glucose utilization by the tumor coupled with a concomitant over expression of glucose transporter proteins, elevated concentration of hexokinase and decreased rates of glucose-6-phosphate dephosphorylation.

MIBG is a guanethidine analogue that is transported into pheochromocytoma cells by the uptake-1 mechanism used by catecholamines allowing its accumulation in the tumor. When MIBG is labeled with ^{131}I it has the capability of eliciting a tumoricidal effect in viable neuroendocrine tumor tissue. For sites with FDG capability, FDG scans may be performed prior to therapy and

3, 6, 9 and 12 months post- ^{131}I-MIBG therapy and the tumor viability compared to pretreatment baseline. The FDG scans will be utilized as a surrogate for tumor variability to more accurately characterize the response to ^{131}I-MIBG therapy.

7.6 Ultratrace Iobenguane I 131 Clinical Trials

Ultratrace iobenguane I 131 has been evaluated in clinical trials for the treatment of neuroendocrine tumors in both pediatric and adult populations. The MIP-IB11 trial, which evaluated the dosimetry profile for Ultratrace iobenguane I 131 in adult patients with malignant pheochromocytoma/paraganglioma has been completed. The MIP-IB12 trial evaluating the maximum tolerated dose (MTD), dosimetry, safety and efficacy of Ultratrace iobenguane I 131 in patients with neuroblastoma has been completed. The treatment phase of the MIP-IB13 study which evaluated the MTD of Ultratrace iobenguane I 131 in pediatric and adult patients with malignant pheochromocytoma/paraganglioma is complete; however, subjects continue to be followed for development of secondary malignancy, last date alive, vital status, date of death and cause of death, where applicable.

7.6.1 Study MIP-IB11: A Phase I Study Evaluating the Safety, Distribution, and Radiation Dosimetry of Ultratrace® Iobenguane I 131 in Patients with Malignant Pheochromocytoma/Paraganglioma or Metastatic Carcinoid

The MIP-IB11 study, "A Phase I Study Evaluating the Safety, Distribution, and Radiation Dosimetry of Ultratrace® Iobenguane I 131 in Patients with Malignant Pheochromocytoma/Paraganglioma or Metastatic Carcinoid" is complete. This dosimetry study was designed to characterize dosimetry, pharmacokinetic parameters, and safety of 5 mCi (185 MBq) of Ultratrace® iobenguane I 131 supplemented with the mass of cold iobenguane equivalent to the maximum projected therapeutic dose (approximately 37 GBq, or 1 Ci) in 12 evaluable patients with malignant pheochromocytoma/ paraganglioma patients and 12 evaluable patients with metastatic carcinoid tumor. The study was halted once data for 7 carcinoid and 4 pheochromocytoma patients were obtained. The five organs absorbing the highest radiation doses are, in order, thyroid, salivary glands, lower large intestine wall, adrenal glands, and urinary bladder wall. Because renal toxicity is a key concern, the maximum administered activity each patient could receive was computed using kidney dose limits, and each patient's kidney dose values not adjusted for patient-specific kidney mass. Using 23 Gy as the limiting kidney radiation dose, the calculated average (of all eleven patients) maximum administered activity was 1,216 mCi (45 GBq) with a range from 568 mCi (21 GBq) to 1,568 mCi (58 GBq).[21] The most common reported adverse events were four patient reports of gastrointestinal disorders (diarrhea, abdominal pain and nausea) and two patient reports of a facial rash.

7.6.2 Study MIP-IB12: A Phase I-II Study Evaluating the Maximum Tolerated Dose, Dosimetry, Safety and Efficacy of Ultratrace® Iobenguane I 131 in Patients with Malignant Pheochromocytoma/Paraganglioma

The MIP-IB12 study, "A Phase I-II Study Evaluating the Maximum Tolerated Dose, Dosimetry, Safety and Efficacy of Ultratrace® iobenguane I 131 in Patients with Malignant Pheochromocytoma/Paraganglioma" has been completed. Twenty-one evaluable patients in this

study provided adequate safety and efficacy data to demonstrate a positive benefit for treatment of malignant pheochromocytoma/paraganglioma, and an acceptable safety profile. These patients received the highest dosage of Ultratrace iobenguane I 131 that did not exceed the protocol-mandated maximum radioactivity dosage of 450, 525, 600, or 675 mCi for patients at the planned 6, 7, 8, or 9 mCi/kg dose increments, respectively. The best response to treatment (partial response [PR] in 19% of patients) was observed for patients who received >500 mCi. The maximum dose level investigated was 9 mCi/kg, at which 2 patients experienced DLTs. The MTD was defined as the dose immediately below the level at which escalation was stopped due to the occurrence of ≥2 DLT's in a dose cohort, therefore, the MTD was determined to be 8 mCi/kg. Two other subjects also experienced hematological DLTs, one in the 7 mCi/kg dose cohort and one in the 8 mCi/kg dose cohort.

All 21 patients who received Ultratrace iobenguane I 131 had at least 1 treatment-related TEAE, for a total of 454 TEAEs reported. The majority of TEAEs (68.9%) were considered related to the administration of Ultratrace iobenguane I 131. Adverse events assessed as severe or life-threatening in severity were reported in 16 (76.2%) patients and were consistent with the anticipated hematologic consequences of bone marrow suppression (pancytopenia, thrombocytopenia, leukopenia, and neutropenia). A total of 15 (71%) of the 21 patients experienced 34 SAEs during the study. The majority of SAEs were not considered related to the administration of Ultratrace iobenguane I 131; SAEs of pancytopenia and dehydration (both SAEs occurred in 2 patients each), platelet count decreased (2 SAEs in 1 patient), and the single SAEs of febrile neutropenia, leukopenia, neutrophil count decreased, neutropenia, and white blood cell count decreased were considered related to study drug administration. There were 5 treatment-emergent deaths reported as AEs (hepatic failure, spinal disorder, thalamic infarction, pulmonary embolism, and metastasis). All deaths occurred from approximately 2.5 months to up to 22 months after the imaging dose and all were assessed as unrelated to study treatment.

7.6.3 Study MIP-IB13: A Phase 2a Study of Ultratrace® Iobenguane I 131 in Patients with Relapsed/Refractory High Risk Neuroblastoma

The treatment phase of study MIP-IB13, titled "A Phase 2a Study of Ultratrace® Iobenguane I 131 in Patients with Relapsed/Refractory High Risk Neuroblastoma", has been completed. Subjects are still being followed for development of a secondary malignancy, last alive date, vital status, date of death and cause of death, where applicable. The primary objective was to establish the maximum tolerated dose of Ultratrace iobenguane I 131 for patients with high-risk neuroblastoma. Secondary goals were to describe the safety profile, estimate tumor and normal organ dosimetry based on an imaging dose of Ultratrace iobenguane I 131, estimate tumor response, assess dose response, and investigate the effect of therapy on quality of life.

Fifteen eligible patients from 1 to 30 years old with confirmed relapsed or refractory high-risk neuroblastoma enrolled in this trial, each of whom first received a diagnostic imaging dose of Ultratrace® Iobenguane I 131 (1-5 mCi), followed by typically three dosimetry scans over 3-6 days. All patients demonstrated normal biodistribution and tumor uptake, and received their therapeutic dose (planned at 12.0, 15.0, 18.0, or 21.0 mCi/kg), within 7-28 days of the diagnostic imaging dose. To maximize patient safety, the dosimetry scan was used to calculate the therapeutic dose so that it would not exceed >23 Gy to the kidneys, >30 Gy to the liver, or >15 Gy to the lungs. A single imaging scan was obtained on Day 7 post therapy. On approximately

Day 14 post therapy, autologous stem cells were infused to initiate hematologic recovery following the administration of the radiolabeled therapeutic dose. Disease and final toxicity evaluation were to be performed 60 ±10 days post therapy.

Because no DLTs were observed, the MTD could not be determined. However, based on dosimetry results that indicating that the maximal dosage allowed to normal organs would be exceeded at a dose of 21.0 mCi/kg, an upper dosage limit was achieved: for all 15 patients, the greatest calculated therapeutic dose allowed was 19.7 mCi/kg. However, the highest dose actually administered during this study was 18.6 mCi/kg.

All 15 patients who received Ultratrace iobenguane I 131 had at least 1 treatment-related TEAE, for a total of 500 TEAEs reported. The most frequently reported TEAEs were hematologic abnormalities, including leukopenia and thrombocytopenia, each reported in all 15 patients. The majority of TEAEs (76.0%) were considered related to the administration of Ultratrace iobenguane I 131. Although twelve (80.0%) patients experienced at least one life-threatening event, the majority of events (76.6%) were mild or moderate in severity. A total of five subjects experienced seven SAEs during the study. Of the seven reported SAEs which included febrile neutropenia (2 patients), bacteremia, disease progression, infection, neutropenic infection, and upper respiratory tract infection, only febrile neutropenia (both events) and infection were considered to be related to study treatment. There were no treatment-emergent deaths reported on study.

8. STUDY OBJECTIVE

The primary and secondary objectives of this study are as follows.

Primary Objective:
To determine the proportion of study subjects with a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least six months or two cycles, from two Therapeutic Doses each at 500 mCi (or 8 mCi/kg, for subjects weighing 62.5 kg or less) of Ultratrace Iobenguane I 131 administered approximately three months apart.

Secondary Objectives:

- To evaluate the safety of Ultratrace iobenguane I 131 in subjects with malignant pheochromocytoma/paraganglioma, including human radiation absorbed dose estimates to normal organs.
- To assess the proportion of subjects with overall tumor response of CR or PR per RECIST criteria
- To assess the proportion of subjects with overall tumor response of CR, PR or MR (moderate response, i.e., decrease in the sum of the longest diameters of the target lesions of 15-30%, with no evidence of PD in non-target lesions) per RECIST criteria
- To assess bone lesion status on the Soloway Scale
- To assess tumor marker response in 24 hr urine and other serum/plasma tumor markers associated with pheochromocytoma/paraganglioma
- To describe changes from baseline in the overall quality of life through the EORTC QLQ-C30 questionnaire post-treatment
- To describe changes from baseline in symptoms using the NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma post-treatment
- To assess change in use of analgesics and pain medications
- To describe Karnofsky Performance Status post-treatment
- To assess overall survival, up to 5 years post-treatment

9. INVESTIGATIONAL PLAN

9.1 Study Design

This is a multi-center, open-label, single arm study. The study was originally initiated in June 2009 and is being extended to complete patient enrollment. It is anticipated that approximately seventy-five subjects will be given up to two Therapeutic Doses each at 500 mCi (or 8 mCi/kg, for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 to ensure that fifty-eight subjects receive both doses and are evaluable for efficacy and safety. Prior to administration of the first Therapeutic Dose, subjects will be given an Imaging Dose (3 mCi – 6 mCi) of Ultratrace iobenguane I 131 and will undergo iobenguane I 131 scintigraphic scans to evaluate tumor avidity as well as to measure normal organ distribution and allow for the calculation of radiation dosimetry to normal organs for both Therapeutic Doses. Both Therapeutic Doses for a subject will be equally decreased if results of the dosimetry study indicate an adjustment is warranted.

Use of antihypertensive medication will be measured through standard, ongoing reporting of concomitant medications throughout the study until completion of the follow-up period. Tumors will be measured by computed tomography (CT) with contrast or magnetic resonance (MR) imaging at baseline and at 3, 6, 9 and 12 months after the first Therapeutic Dose. Obtaining renal volume for each kidney is required at baseline. A bone scan will be performed at Screening/baseline and if probable metastatic disease is observed or suspected, additional bone scans will be performed at Month 3, 6, 9, 12. Overall tumor response at 3, 6, 9 and 12 months per RECIST criteria will be assessed centrally by independent, blinded readers. FDG scans may also be performed at baseline and 3, 6, 9, and 12 months to assess viable tumor tissue. Tumor markers [serum chromogranin A, plasma free metanephrines and normetanephrines, 24 hour urinary vanillylmandelic acid (VMA), plasma catecholamines (dopamine, epinephrine and norepinephrine), 24 hour urinary catecholamines (dopamine, epinephrine and norepinephrine) and urinary metanephrines and normetanephrines] will be evaluated by a central laboratory. Testing for tumor markers will occur at baseline, every two weeks for the first 24 weeks after the first Therapeutic Dose starting at Week 2, and monthly during months 7-12. Renal function will be assessed through either creatinine clearance or Glomerular Filtration Rate (GFR) at baseline and at the Months 6 and 12 Efficacy Visits. Evaluation of thyroid function (T3, T4 and TSH) and clinical evaluation of possible dry mouth will be performed at the 12 month Efficacy Visit. Use and dose of antihypertensive, pain and other medication required for tumor associated signs and symptoms will be recorded on an on-going basis throughout the study until completion of the follow-up period. Subject-reported Quality of Life measurements will be obtained through the EORTC QLQ-C30 v3 and the NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma. The frequency of the procedures is summarized in the Schedule of Procedures (Appendix VII). Subject may undergo additional assessments as warranted (for example, to confirm tumor response) at unscheduled visits.

Safety will be assessed through analyses of treatment emergent adverse events (AEs), as well as baseline and pre- and post-infusion ECGs, physical examinations, vital signs measurements, laboratory measurements (including clinical chemistry, hematology and urinalysis), and human radiation absorbed dose estimates to target lesions and normal organs. Subjects will be monitored for serious and non-serious AEs, and Adverse Events of Special Interest see Section 12.

After the 12 month assessment, subjects enter long-term follow-up and remain in follow-up for 5 years following the first therapeutic dose. Subjects will be followed for overall survival for 5 years following the first therapeutic dose. In years 2-5 post-treatment (or until a patient experiences disease progression, start of another anticancer therapy or death), data on tumor response, tumor markers and clinical benefit (including use of antihypertensive medication) will be collected through assessments provided as institutional standard of care. If standard of care is not providing such assessments, they will be offered by the study site.

9.2 Study Design Rationale

This is a phase II study to evaluate the efficacy and safety of two Therapeutic Doses (each dose 500 mCi, or 8 mCi/kg for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 in subjects with malignant pheochromocytoma or paraganglioma. Prior clinical studies have investigated the value of carrier-added iobenguane I 131 in treating malignant

pheochromocytoma or paraganglioma.[3-18] Carrier–added iobenguane I 131 is approved for use in localization of pheochromocytoma and neuroblastoma.[36]

Higher specific activity of iobenguane I 131 (i.e., Ultratrace iobenguane I 131) may result in greater tumor uptake of radioactivity. In animal studies, the Ultratrace form of iobenguane I 131 has shown increased uptake by normal tissue expressing norepinephrine transporter (NET) such as the heart. In xenografts, the Ultratrace form demonstrated higher radiopharmaceutical concentration in UVW/NET transfected tumors and in SK-N-BE (2c) neuroblastoma.

Subjects will receive baseline assessments including CT or MR and bone scan imaging. Subjects will be administered a 3 to 6 mCi Imaging Dose of Ultratrace iobenguane I 131 to confirm uptake of the study agent by at least one tumor. Each subject will then receive two Therapeutic Doses (each infusion 500 mCi, or 8 mCi/kg for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 at least three months apart. Within 7 days after each Therapeutic Dose, each subject will have a whole body scan. Pre-infusion safety measurements are to serve as the within-subject control for assessing post-infusion measurements for effects of Ultratrace iobenguane I 131 therapy.

As detailed in Section 9.1 Study Design, efficacy will be assessed through monitoring of use of concomitant medications, analyses of objective tumor response via CT or MR imaging, FDG scans (if available), and analysis of tumor marker levels. Safety will be assessed through analyses of treatment emergent adverse events (TEAEs), as well as baseline and pre- and post-infusion ECGs, physical examinations, vital signs measurements, laboratory measurements (including clinical chemistry, hematology and urinalysis), and human radiation absorbed dose estimates to target lesions and normal organs.

9.3 Study Duration

Subjects will attend study visits from the time of signed informed consent through 12 months (efficacy portion) and a 5 year follow-up period after the first Therapeutic Dose of Ultratrace iobenguane I 131. Subjects will be monitored for AE/SAE and Adverse Events of Special Interest (including post radiation toxicity) as described in Section 12. Subjects may undergo additional assessments to confirm response, or as part of institutional standard of care during long-term follow-up. Figure 1 outlines the study period; a more extensive summary of study procedures is given in the Schedule of Procedures (Appendix VII).

FIGURE 1: STUDY DURATION

Signed informed consent, subject enters study
↓
Eligibility/dosimetry study
Imaging Dose (3 to 6 mCi) of Ultratrace iobenguane I 131 administered within 30 days of first therapeutic dose followed by three I 131 whole body scans to confirm uptake and to determine dosimetry
↓
First Therapeutic Dose of Ultratrace iobenguane I 131 administered day 0
↓
I 131 scan within seven days post first therapeutic infusion to assess biodistribution
↓
Safety visit 6 weeks post-first Therapeutic Dose
↓
Objective tumor response assessments 3 months post-Therapeutic Dose and prior to the second Therapeutic Dose
↓
Second Therapeutic Dose Ultratrace iobenguane I 131 administered starting at month 3, at least 12 weeks after the first Therapeutic Dose.
↓
I 131 scan within seven days after second Therapeutic Dose
↓
Safety visit 6 weeks post second Therapeutic Dose
↓
Tumor response assessments, tumor markers (every two weeks through week 24 and monthly from month 7-12), physical exam at months 3 (prior to the second Therapeutic Dose, if administered), 6, 9 and 12
Subject completes regularly scheduled study visits at month 12
↓
Long-term follow-up for adverse events of special interest, overall survival, tumor markers and disease status (inc. clinical benefit) through year 5

9.4 Study Population

It is anticipated that the study will enroll approximately seventy-five subjects to ensure a total of 58 subjects given two doses of Ultratrace iobenguane I 131 will be evaluable for efficacy and safety. All subjects who received at least one Therapeutic Dose of Ultratrace iobenguane I 131 will be included in the Full Analysis Set; all subjects who received both Therapeutic Doses and who attended the 3 Month and 6 Month Efficacy Visits with no major protocol violations will be included in the Per Protocol Set. The primary endpoint, proportion of subjects experiencing a reduction in use of antihypertensive medication for at least six months or two cycles, will be analyzed separately for each of these populations.

Safety analyses will include treatment emergent adverse events, clinical laboratory measurements, vital signs measurements, and physical examination findings. All subjects who received the Imaging Dose of Ultratrace iobenguane I 131 will be included in the analysis of any

safety endpoint. Adverse events will be captured for all enrolled subjects and those prior to the Imaging Dose will be displayed in a separate listing.

9.5 Inclusion Criteria

To participate in this study, subjects must meet all of the inclusion criteria listed below.

All subjects must:

1. Provide written informed consent (and assent for subjects less than 18 years of age) and be willing to comply with protocol requirements
2. Be at least 12 years of age
3. Have a documented (medical record) diagnosis of either pheochromocytoma or paraganglioma that was confirmed by histology or a physician using other supportive data (e.g. abnormal MIBG diagnostic study, or elevated tumor markers).
4. Be ineligible for curative surgery for pheochromocytoma
5. Have failed a prior therapy for pheochromocytoma/paraganglioma or are not candidates for chemotherapy or other curative therapies
6. Be on stable antihypertensive medication regimen for tumor-related hypertension for at least 30 days prior to the first therapeutic dose. A stable antihypertensive medication regimen is defined as no addition or deletion of antihypertensive medication and no change in total daily dose or route of administration for currently used antihypertensive medication(s) in the 30 days prior to first therapeutic dose.
7. Have at least one tumor site by CT or MR or iobenguane I 131 scan
8. Have definitive MIBG tumor avidity
9. Have an expected survival period of at least 6 months as prognosticated by physician

Female subjects must:

10. Have a negative pregnancy test within 48 hours prior to receiving Ultratrace iobenguane I 131
11. Agree to use an acceptable form of birth control (abstinence, IUD, oral contraception, barrier and spermicide or hormonal implant) during this study and for 6 months following Therapeutic Doses of Ultratrace iobenguane I 131. For those women who are sexually active and using oral contraceptives, a second form of barrier contraception is required. or
12. Not be of childbearing potential as documented by history (e.g., tubal ligation or hysterectomy) or is post menopausal with a minimum of 1 year without menses

Male subjects must:

13. Agree not to father a child during the period beginning immediately after administration of the first Therapeutic Dose of Ultratrace iobenguane I 131 during the study and ending six months after administration of the last Therapeutic Dose of Ultratrace iobenguane I 131.
14. Use an acceptable method of birth control (e.g., vasectomy or as described above) during the study and for six months following the Therapeutic Doses of Ultratrace iobenguane I 131.

9.6 Exclusion Criteria

Subjects will be excluded if any of the following conditions are observed:

1. <50% of FDG (if data are available) positive lesions are MIBG avid
2. Pregnant or nursing females
3. Active CNS lesions by CT or MR scanning within 3 months of study entry
4. New York Heart Association class IV heart failure, symptomatic congestive heart failure [New York Heart Association class IV with another medical disorder], unstable angina pectoris, cardiac arrhythmia
5. Received any previous systemic radiotherapy resulting in marrow toxicity within 3 months of study entry or have active malignancy (other than pheochromocytoma/paraganglioma) requiring additional treatment during the active phase or follow up period of the Ultratrace iobenguane I 131 trial. (Prior iobenguane I 131 therapy is allowed if not within 3 months prior to the first therapeutic dose).
6. Administered prior whole-body radiation therapy
7. Received external beam radiotherapy to > 25% of bone marrow
8. Administered prior chemotherapy within 30 days of study entry or have active malignancy (other than pheochromocytoma/paraganglioma) requiring additional treatment.
9. Karnofsky Performance Status is < 60
10. Platelets ≤ 80,000/μL
11. Absolute neutrophil count (ANC) ≤ 1,200/μL
12. Total bilirubin > 1.5 times the upper limit of normal
13. AST/SGOT or ALT/SGPT ≥ 2.5 times the upper limit of normal
14. Diagnosed with AIDS or HIV-positive per patient medical history
15. Active chronic alcohol abuse, chronic liver disease (excluding liver metastases), or hepatitis (A, B or C, detected by positive testing for HbsAg and anti-HCV as stated in patient medical history)
16. Renal dysfunction/impairment (defined as creatinine clearance of <30 mL/min or Glomerular Filtration Rate (GFR) of <30mL/min) because of the possibility of delayed Ultratrace iobenguane I 131 excretion and increased whole body dose
17. Known allergy to iobenguane that has required medical intervention
18. Received a therapeutic investigational compound and/or medical device within 30 days before admission into this study
19. Receiving a medication which inhibits tumor uptake of iobenguane I 131 as described in Appendix III of the protocol
20. Any medical condition or other circumstances (i.e., uncontrolled current illness including but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with the study requirements.)
21. Any other condition, that in the opinion of the investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study

9.7 Discontinuation Criteria

The reason for the subject's discontinuation will be clearly documented on the case report form (CRF). Discontinued subjects may be replaced with written authorization from MIP. Subjects will be discontinued from the study if the subject:

- withdraws consent
- experiences progressive disease
- receives another anticancer therapy
- is lost to follow up
- experiences an adverse event leading to discontinuation

If a subject discontinues the study within 6 weeks following a Therapeutic Dose infusion of Ultratrace iobenguane I 131, the Investigator will contact the subject via telephone or other appropriate means to follow up 6 weeks post-infusion.

9.8 Visits for Discontinued Subjects Not Withdrawing Consent

Unless consent has been withdrawn, discontinued subjects should continue to receive all scheduled assessments other than CT/MR/bone scans and tumor marker lab tests, and the subjects should also be entered on long-term follow-up to be followed for overall survival and late radiation toxicity.

Subjects who meet discontinuation criteria, but do not withdraw consent can continue to be followed as described below:

Subjects discontinuing within 6 weeks of either therapeutic iobenguane I 131 infusion are to be assessed at the Safety Visit. After this safety checkpoint, subjects can continue to be followed on the Efficacy Visit schedule until Month 12 receiving all scheduled assessments other than CT/MR/bone scans and tumor marker lab tests. After the Month 12 Efficacy Visit, the subject may enter the Long-Term Follow-Up (LTFU) to be followed another 4 years for a total of 5 years from the first therapeutic dose.

Subjects discontinuing during the Efficacy Visit Phase can continue to be followed on the Efficacy Visit schedule until Month 12 receiving all scheduled assessments other than CT/MR/bone scans and tumor marker lab tests. After the Month 12 visit, the subject may enter the LTFU period to be followed another 4 years for a total of 5 years from the first therapeutic dose.

For subjects wanting to withdraw consent during the efficacy portion of the study (the first 12 months), every effort shall be made to have these subjects return for a final visit and perform the procedures delineated for the Month 12 visit.

Subjects discontinuing during the Long-Term Follow-up period will only be followed for adverse event of special interest. The follow-up discussion may occur via telephone, for subjects who are being followed only for adverse events of special interest.

10. STUDY AGENT

10.1 Dosing Evaluations

Within 30 days prior to the first scheduled first Therapeutic Dose, subjects will be administered a 3 to 6 mCi Ultratrace iobenguane I 131 Imaging Dose. The imaging dose will be administered based on each subject's body weight. Subjects weighing at least 50 kg will receive 5 to 6 mCi of Ultratrace iobenguane I 131 for imaging. Subjects weighing 30 to 49 kg will receive 0.1 mCi/kg of Ultratrace iobenguane I 131 for imaging, and the Medical Monitor should be consulted for the appropriate imaging dose for subjects weighing less than 30 kg.

Three I 131 whole body scans will be performed to assess tumor uptake and biodistribution, as detailed in Section 11.6 Eligibility/Dosimetry scans. To be eligible to continue in the study, uptake of the study agent by at least one known measurable tumor on the Image 2 or Image 3 scan must be documented. Images 1, 2 or 3 will be evaluated centrally to confirm tumor uptake and biodistribution. The dosimetry study will be performed using these three Images. This will ensure that even a single dose of 500 mCi does not result in an absorbed dose exceeding 23 Gy to the kidney, 17.5 Gy to the lungs and 30 Gy to the liver. These limits are based upon the Emami Criteria.[44] Should the dosimetry study show that a reduction in the activity of Ultratrace iobenguane I 131 is warranted, both Therapeutic Doses to be administered will be equally adjusted to specified dose levels (see Section 10.2).

Approximately three months following the initial Therapeutic Dose of Ultratrace iobenguane I 131, the subject will be administered the second Therapeutic Dose. The hematological laboratory values must be reviewed by the Principal Investigator and MIP prior to administration of the second Ultratrace iobenguane I 131 for any subject. The determination whether to proceed with the second Therapeutic Dose of Ultratrace iobenguane I 131 will be made based on the hematological status following the first therapy dose. The dosimetry calculation done prior to the first therapeutic dose must demonstrate that the cumulative absorbed dose does not exceed specified absorbed dose levels for the specified organs. Additionally, the subject's hematological laboratory values must demonstrate full recovery to the normal range or the subject's baseline following the first dose of Ultratrace iobenguane I 131. If after the first dose of Ultratrace iobenguane I 131, the subject experiences any of the following hematological toxicities:

- Febrile neutropenia (temperature ≥38.5° C and ANC <1,000/μL); or
- CTCAE Grade 3 thrombocytopenia with active bleeding; or
- CTCAE Grade 4 hematological toxicity >1 week duration;

Then the subject's hematological laboratory values must return to baseline before receiving the second dose of Ultratrace iobenguane I 131. Additionally, any subject who experiences a hematologic toxicity as described above must receive a decreased second dose, as described in Section 10.2.

10.2 Dose Modification

Dosimetry will be calculated to confirm that the protocol-specified two administrations of 500 mCi (or 8 mCi/kg for subjects weighing 62.5 kg or less) of Ultratrace iobenguane I 131 does not exceed the specified absorbed dose levels (23 Gy to the kidney, 17.5 Gy to the lungs and 30 Gy

to the liver) over the entire treatment (two therapeutic doses). Additionally, subjects must have recovered from treatment side effects experienced during the initial dose and prior to administration of the second dose. Dose modification, if required, may be based on subject's body weight, estimated renal, hepatic or lung absorbed dose or hematological toxicity. Similarly, the Principal Investigator or designee may modify second dose scheduling, in consultation with the study medical monitor, due to medical condition and/or other logistic or personal reasons. In any case this delay of second therapeutic dose should not exceed 24 weeks from the first therapeutic dose. Specifically, if the total dose requires downward adjustment resulting from the dosimetry calculation, then both the first and second Treatment Doses will be decreased equally.

10.2.1 Dose modification due to renal, lung or liver absorbed exposure

The calculated cumulative dose for the study must be confirmed not to exceed 23 Gy exposure to the kidneys, 30 Gy to the liver, and 17.5 Gy to the lungs. If based on CT or MRI, the target organ does not contain tumor, then the dose will be decreased in a proportional fashion to fall below the theoretical organ tolerance. Should the organ estimate include tumor tissue, then a separate region of interest for 'non-involved' normal organ tissue will be computed and extrapolated to an equivalent total organ radiation dose assuming no internalized tumors. This radiation dose estimate represents the best estimate of the radiation dose to the 'non-involved' organ tissue and should be applied to the normal organ toxicity limits established. If this value exceeds the radiation limits, then the administered activity will be reduced proportionally to achieve an estimated normal organ total radiation dose per the limiting value. If the organ is diffusely infiltrated with tumor or contains large extensive metastatic lesions, then this will require careful review of the scans and dosimetry by the responsible dosimetrist, Principal Investigator and study medical monitor to determine the most accurate and safe dose adjustment. Whenever a dose adjustment is warranted, all scheduled doses will be adjusted equally.

10.2.2 Dose modification for hematologic toxicity

The subject's hematologic values must return to baseline levels prior to administration of the second Therapeutic Dose. The administration of the second Therapeutic Dose may be delayed for up to 4 – 12 weeks (i.e., 16 - 24 weeks following administration of the first Therapeutic Dose) to allow for adequate hematologic recovery. If recovery to baseline levels has not occurred within 24 weeks following the initial Therapeutic Dose, the subject should be discontinued from the study.

Additionally, if the subject has experienced:

- Febrile neutropenia (temperature ≥38.5° C and ANC <1,000/μL); or
- CTCAE Grade 3 thrombocytopenia with active bleeding; or
- CTCAE Grade 4 hematological toxicity >1 week duration at any time following administration of the initial Therapeutic Dose,

The second Therapeutic Dose should be decreased to 425 mCi (or 7 mCi/kg for subjects weighing less than 62.5 kg).

10.3 Study Agent Description

10.3.1 Ultratrace Iobenguane I 131

Each vial of Ultratrace iobenguane I 131 consists of a sterile, clear aqueous solution. The dose is provided in a glass vial capped with a gray septum and aluminum crimp. The primary container is shipped in a secondary lead shield container, to limit exposure. The Dosimetry and therapy doses are shipped frozen on dry ice. The product for both the imaging Ultratrace iobenguane I 131 and the therapy Ultratrace iobenguane I 131 will have the same formulation but a lower total radioactivity and radioactive concentration will be used for imaging. Excipients include ascorbic acid and gentisic acids. Please refer to the Investigator Brochure for a more complete description of the formulation. Radioactivity values are at Time of Calibration (TOC), see the Pharmacy Manual for further information. The Time of Expiration is eight days post manufacture. The drug should be stored at ≤-70°C with adequate shielding (e.g., lead pot, lead bricks, etc.).

10.4 Receipt and Storage of Drug Product

The storage condition and expiration of the Ultratrace iobenguane I 131 product are described in the Pharmacy Manual and must be strictly followed. The drug product contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use of the drug product is limited to a facility licensed by the Federal or State authorities. Unused or residual waste should be disposed of as radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidances.

10.5 Blinding and Randomization

This is an open-label, single arm study.

10.6 Handling and Preparation

Ultratrace iobenguane I 131 must be handled according to hospital policy for radioactive diagnostic isotopes. The Imaging and Therapeutic Ultratrace iobenguane I 131 must be used within the expiration dates as outlined in Section 10.3.1. The appropriate temperature and storage conditions will be further described in the Azedra Pharmacy Manual.

The contents are sterile and aseptic procedures should be employed during the withdrawal of doses for administration.

Care should be taken to equalize the pressure in the syringe and vial when drawing the drug from the vial. Use of a vent needle is recommended.

10.7 Administration

Before administration of Ultratrace iobenguane I-131, the subject's thyroid should be blocked with inorganic iodine. The site may use an institutionally approved thyroid blocking protocol or utilize the following recommendations adopted from the CDER potassium iodide thyroid blocking agent guidance.

The administration of potassium iodide should begin 24 hours prior to the administration of Ultratrace iobenguane I-131 and should continue for a total of 10 days. Children ages 12 through 18 years should receive 65 mg potassium iodide daily for a 10 day course of therapy. Adolescents approaching adult size (greater than or equal to 70 kg) should receive the full adult dose. Adults 18 years and older, should receive potassium iodide 130mg daily for a 10 day course of therapy. Potassium iodide can be diluted in milk, infant formula, juice or water. The product can be taken with food to minimize gastric irritation.

There are several commercially available products such as:

- Potassium iodide (SSKI 1gm/ml): 50-250 mg (1-5 drops SSKI), 1 drop = 50 mg (contains sodium thiosulfate)
- Lugol's solution: potassium iodide (100 mg/ml)
- Pima syrup: 325 mg/5ml (black raspberry flavor)
- ThyroShield: 65 mg/ml (30 ml black raspberry flavor)
- Iosat: 130mg tablet
- ThyroSafe: 65 mg tablet (equivalent to iodine 50mg)

To minimize irradiation of the urinary bladder, the subject should be encouraged to increase fluid intake and to void frequently through the first day after administration.

Prophylactic antiemetic therapy is recommended prior to the administration of therapeutic Ultratrace iobenguane I 131 to reduce or eliminate nausea and vomiting. Investigators may use the antiemetic guidelines as prescribed by their institution, typically starting the day of therapeutic Ultratrace iobenguane I 131 administration and continuing 2-5 days, depending upon the subject's antiemetic history and Investigator's evaluation.

Salivary gland stimulation should be encouraged for subjects in order to prevent or decrease the possibility of radiation sialadenitis. Subjects may be advised to hydrate well by ingesting at least 2 liters of liquid per day and stimulate salivation by chewing gum or sucking hard candy (sour candy with citric acid or equivalent is best) while awake for one week following Ultratrace iobenguane I 131 therapy.

Careful attention to hydration status, particularly in the setting of gastrointestinal intolerability is required. Ensuring optimal hydration status before therapy is an important component of subject preparation.

Prior to Ultratrace iobenguane I 131 imaging injection, an indwelling intravenous catheter will be inserted into the antecubital vein (or an equivalent venous access). The radiopharmaceutical will be injected through the indwelling catheter. The Imaging Dose will be administered slowly over a period of approximately 60 seconds.

The first Therapeutic Dose of Ultratrace iobenguane I 131 will be administered after the dosimetry calculations are complete. The first therapeutic infusion may be administered up to 30 days after the Imaging dose if subject scheduling or product availability causes a delay in therapy.

The subject will be weighed before the Therapeutic Dose is drawn. If the subject's weight has changed by more than ± 2 kg since the calculation of the Therapeutic Dose of Ultratrace iobenguane I 131, the dose will be recalculated.

Please refer to the Ultratrace iobenguane I 131 Therapeutic Dose Infusion System Clinical Manual and the Pharmacy Manual when preparing and administering a therapeutic dose. Both manuals provide recommendations for the preparation and administration of the drug that may be modified in accordance with each institution's standard operating procedures. The recommended infusion rate of the Therapeutic Dose is 50 mL over a period of 15 to 60 minutes. At infusion intervals that are less than 30 minutes, some patients receiving the infusion via peripheral venous access have reported infusion site discomfort. Therefore, MIP recommends a peripheral infusion rate of less than or equal to 50 mL over 30 minutes (100 mL/hour). If needed, infusion site discomfort may be managed by slower infusion rates or by stopping the infusion temporarily. Ultratrace iobenguane I 131 Therapeutic Dose Infusion System Clinical Manual can be consulted for further details.

Following completion of each administration (imaging or therapy) of Ultratrace iobenguane I 131, 10 mL of normal saline will be delivered through the catheter.

An interruption in a therapeutic infusion is allowed to accommodate subject issues (e.g., toilet, nausea, vomiting, anxiety, etc.). Most of these are avoidable by good subject education and dose planning. The subject's infusion should not be discontinued unless the Investigator determines that continuing would represent an unacceptable risk, undue safety hazard, or if subject's medical condition deteriorates rapidly and the infusion cannot continue or would interfere with medical or surgical care. As long as infusion is expected to finish on the day scheduled, it may proceed even with interruptions.

Investigators will be made aware that a theoretical risk for hypertensive crisis, most commonly seen after hepatic embolization, cannot be excluded after therapeutic Ultratrace iobenguane I 131 infusion. Phentolamine or other acute therapeutic measures and physicians trained in managing hypertensive crisis or severe cardiovascular adverse events should be readily available during each infusion.

Any misadministration of any infusion (e.g., overdose, observable extravasation, medication error) will be recorded in the subject's source records and transcribed onto the case report form (CRF) and reported within 24 hours using the SAE form for initial communication. Therapeutic over dosage or under dosage may also require a separate report to the competent regulatory authority governing the use of medical radioactive material.

Investigators will follow radiological isolation procedures after the therapeutic dose of Ultratrace iobenguane I 131 as governed by institutional and local radiological authorities.

10.8 Calculation of Administered Activity

The dose of radioactivity will be determined by measuring the amount of radioactivity in the syringe (for imaging) or the container housing the Therapeutic Dose pre- and post-infusion. A properly calibrated radioisotope dose calibrator will be used for both measurements. Calibrations of the dose calibrator and calculation of the delivered radioactivity in the dose will be performed according to the Ultratrace iobenguane I 131 Dose Calibrator Correction Factor Manual.

10.9 Accountability

In accordance with International Conference of Harmonisation (ICH) and United States Food and Drug Administration (FDA) requirements, the Investigator and/or drug dispenser must at all times be able to account for all study drugs provided to the institution. The appropriate site personnel must sign, date and forward to the sponsor documentation that the drug was received.

No study agent is to be used outside of this study. Record the use of the study agent on the appropriate Drug Accountability record. All study agents must be accounted for, whether used or unused, during the course of and at the conclusion of the study. The shipment of drugs from the Sponsor to the Investigator or other designated persons cooperating with the Investigator will be accompanied by a receipt form that indicates the lot number(s) and the amount of drug provided for the study. Documentation of the receipt of drug must be signed, dated and returned to the Sponsor.

The Investigator is responsible for ensuring that deliveries of study drugs are correctly received and recorded, and handled and stored safely and properly in accordance with the Code of Federal Regulations (CFR), local/state laws and used in accordance with this protocol.

Unused product will be disposed of according to institutional regulations. Record the use and/or disposal of the study agent on the drug accountability record. This drug accountability record should account for the receipt and disposition of all clinical supplies shipped to the Investigator and must be available for review by the study monitor.

11. METHODOLOGY

A table summarizing the study procedures described in this section is presented in Schedule of Procedures (Appendix VII).

11.1 Written Informed Consent / Assent

Written informed consent or assent will be obtained from the subject at the time of enrollment. Subjects will be given a copy of the signed informed consent or assent form.

11.2 Subject Numbering

MIP or its designee will assign a six-character subject number for each subject for whom written informed consent has been obtained. The first two characters of the subject number will be used to specify the study indication. The third and fourth characters of the subject number will be the investigational site numbers. The fifth and sixth characters will be a number starting with 01 for the first subject enrolled at the site and incrementing by "1" for each sequential subject.

Subject numbers will never be reassigned. In the event that a subject withdraws from the study, the number assigned to that subject is retired and the next subject receives the next sequential number.

11.3 Screening / Baseline

All subjects will be screened to ensure that all inclusion and exclusion criteria are met. Baseline procedures (detailed in Section 11.5 below) include a medical history, physical examination, measurement of vital signs, CT or MR scans, bone scans, FDG scans (if available), laboratory tests and completion of quality of life questionnaires. If the subject has not been assessed for renal function through either a 24 hour urine creatinine clearance or Glomerular Filtration Rate (GFR using ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) analysis) within four weeks of screening, one of these procedures will be performed during the screening/baseline period. A serum pregnancy test for all females of childbearing potential will be performed following informed consent and prior to each administration of study drug. Renal volume will be obtained. An assessment of tumor markers, blood pressure and heart rate will be performed during the baseline/screening period. If Screening/Pre-Screening procedures are completed as standard of care within 48 hours prior to obtaining informed consent, these procedures do not need to be repeated as Screening assessments specifically for this study. The data from these assessments will be collected in the appropriate CRF location.

11.4 Evaluation of Antihypertensive Status

The evaluation of each subject's antihypertensive status from the screening/baseline period throughout the study by the Principal Investigator and/or sub-Investigator and subject's referring physician is required. It is imperative that the site staff determine at screening if the subject's referring physician is willing and able to provide ongoing evaluation of the subject's antihypertensive medications. The Principal Investigator and/ or sub-Investigator will be responsible for communication with the subject's referring physician throughout the trial and provide supporting documentation in the subject's study file. These investigators will also provide representative algorithms (see Section 11.5.12), for the subject and their primary care physician to guide them through the considerations of antihypertensive medication adjustment(s). The site monitor will review the documentation regarding the status of antihypertensive medication for each subject.

11.5 Subject Evaluations

11.5.1 Medical History

A complete medical history will be obtained during the screening period prior to the imaging dose of Ultratrace iobenguane I 131. The subject's medical history will be recorded on the

medical history section of the case report form (CRF). Historical information concerning allergies (classification as food, drug and/or environmental) will also be obtained. The medical history must include any treatments for cancer.

11.5.2 Adverse Events

Non-serious adverse events and serious adverse events are defined in Section 12. Data will be collected for any non-serious or serious adverse events that occur from the time of signed informed consent through a Safety Phone Call at 16 weeks after the last therapeutic dose. If the timepoint of the 16 week Safety Phone Call falls within 2 weeks of a scheduled visit, the AE/SAE assessment can be performed at that visit instead of through a Safety Phone Call. The Investigator will contact the subject via telephone or follow-up by other appropriate means at six weeks following each Therapeutic Dose of Ultratrace iobenguane I 131 if the subject does not return for a safety visit. All adverse events will be recorded in the AE section of the CRF as specified in Section 12. Only post-dose untoward medical events will be assessed as relevant to the safety profile of Ultratrace iobenguane I 131. As part of long-term follow-up, data on occurrence of adverse events of special interest (Appendix VI) will be collected as described in Section 12.

11.5.3 Concomitant Medications

Subjects taking medications known or expected to affect the uptake of MIBG, as described in Appendix III, will not be enrolled in the protocol. A complete history of all chemotherapy and radiotherapy received before the Imaging Dose of Ultratrace iobenguane I 131 will be recorded in the CRF.

Except as specified below, all medications including herbal, prescription and over-the-counter taken from signing informed consent throughout the study will be recorded in the concomitant medication section of the CRF. All antihypertensive medication ongoing/ending within 30 days prior to informed consent will be recorded in the CRF. Additionally, any modifications to the total daily dose or newly prescribed pharmacological treatments in this section will be recorded throughout the study. The concomitant medication list will be reviewed at each study visit.

Subjects must be off any medication listed in Appendix III for at least 5 half lives of the restricted medication prior to receiving the Imaging dose. The subject must remain off of the restricted medication until 48 hours after the first therapeutic infusion and then can restart the medication if medically indicated. The subject must also be off the restricted medication for 5 half lives prior to the second therapeutic infusion and can restart the medication listed in Appendix III, 48 hours after the second therapeutic infusion if medically indicated. Labetolol is excluded throughout the study. Subjects on labetolol must discontinue the drug within 30 days prior to the first therapeutic dose.

A listing of examples of analgesics, pain and antihypertensive medications is provided in Appendix V of the protocol.

11.5.4 Laboratory Evaluations

Blood and urine samples will be collected for hematology, clinical chemistry and urinalysis as described in Table 2, at the following time points:

- at the screening/baseline period
- within 24 hours prior to the imaging and first therapeutic Ultratrace iobenguane I 131 infusion
- within 48 hours prior to the second therapeutic Ultratrace iobenguane I 131 infusion
- weekly starting with Week 2 until 24 weeks following administration of the first Therapeutic Dose of Ultratrace iobenguane I 131 and continued for at least 12 weeks following administration of the second Therapeutic Dose. Note: the first blood sample following each therapeutic Ultratrace iobenguane I 131 infusion is not required until 2 weeks post-infusion
- The blood draw and urine collection do not need to be repeated at Month 3 if the visit is within a week of the Week 12, Week 13, Week 14 or Week 15 blood draw
- The blood draw and urine collection do not need to be repeated at Month 6 if the visit is within a week of the Week 24 visit, Week 25, Week 26, Week 27, Week 28, Week 29 blood draw. (Week 25, Week 26, Week 27, Week 28, Week 29 blood draws are only performed if the second therapeutic dose is delayed)
- Monthly, 7 through 12 months after the first Therapeutic Dose of Ultratrace iobenguane I 131.
- TSH, T3 and T4 analysis will only be performed at screening/baseline and at the Month 12 Efficacy Visit

TABLE 2: LABORATORY ANALYTES

Hematology	**Clinical Chemistry**		**Urinalysis**
Hematocrit	Sodium	AST/SGOT	pH
Hemoglobin	Potassium	ALT/SGPT	Specific gravity
RBC count	Chloride	Alkaline Phosphatase	Protein
WBC count	Glucose	Cholesterol	Glucose
Differential WBC count	Urea nitrogen	Total protein	Ketones
Platelet count	Creatinine	Albumin	Blood
PT or INR	Total bilirubin	LDL	WBC/HPF
	Triglycerides	HDL	RBC/HPF
	Calcium	Phosphorus	Crystals
	TSH*	T3/T4*	

*TSH, T3 and T4 analysis will only be performed at screening/baseline and at the Month 12 Efficacy Visit.

11.5.5 Laboratory Evaluation of Renal Function

Either a 24 hour urine creatinine clearance or Glomerular Filtration Rate (GFR using ^{99m}Tc diethylenetriaminepentaacetic acid [DTPA] analysis) will be assessed for all subjects who have not had one of these assessments within four weeks of screening/baseline. Additionally, for all subjects, renal function will be assessed at the Month 6 and 12 Efficacy Visits using the same methodology used to evaluate renal function at screening/baseline.

11.5.6 Physical Examination and Clinical Status Evaluation

A physical examination will be performed during the screening period, prior to the administration of the first Imaging Dose of Ultratrace iobenguane I 131, prior to each Therapeutic Dose, at the 6 week safety visit following each therapeutic Ultratrace iobenguane I 131 infusion and at Months 3 (prior to the second Therapeutic Dose, if administered), 6, 9 and 12. The Physical Exam performed 6 weeks after each Therapeutic Dose administration may occur within ±10 days of the Week 6 window to accommodate potential blood count nadir or travel restrictions. Clinical evaluation for possible dry mouth will be performed at the Month 12 Efficacy Visit. All pertinent findings will be recorded on the appropriate CRFs. Any adverse event as described in Section 12 will be recorded in the CRF.

Subject's weight should be measured and recorded at screening/baseline and prior to each dose.

11.5.7 Pregnancy Test

If the subject is female, the possibility of pregnancy must be excluded:

- by testing on site at the institution (serum βHCG) at screening
- testing on site at the institution within 48 hours (urine pregnancy test) prior to the start of each Ultratrace iobenguane I 131 administration, if of child bearing potential, or
- by medical history (e.g., post-menopausal with a minimum 1 year without menses, tubal ligation or hysterectomy)

11.5.8 CT/MR Scanning

Each subject will receive a baseline CT or MR scan of the chest, abdomen and pelvis with IV contrast unless medical condition or allergy prevents its use. Obtaining renal volume for each kidney is required at baseline. Anatomical volumes may be measured for other organ and tissues to further evaluate absorbed dose. Subjects will have follow-up CT or MR scans at 3, 6, 9 and 12 months following the first therapeutic Ultratrace iobenguane I 131 infusion. For each subject, the same modality (CT or MR) and the same technique used for the baseline assessment should be used in all subsequent assessments. The images will be evaluated by a central core imaging laboratory to quantify the extent of tumor. For all MIBG avid lesions observed in the Imaging/Dosimetry evaluations, a CT or MR scan must be obtained for baseline information. If a subject has known lesion(s) outside of those captured by the baseline CT or MR of the chest, abdomen and pelvis, these images need to be submitted for evaluation to the Central Imaging vendor. All images submitted at baseline, should be followed at each subsequent timepoint throughout the study and submitted for evaluation.

Subjects achieving a CT or MR scan showing PR or CR must have this response confirmed by a follow up CT or MR obtained no less than four (4) weeks from the initial scan demonstrating response.

11.5.9 FDG PET Scans

To assess viable tumor tissue, subjects may receive however, it is not required, an ^{18}F Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) scan at baseline and at 3, 6, 9 and 12 months following the first therapeutic Ultratrace iobenguane I 131 infusion. If the subject does receive an ^{18}F FDG PET scan it should be performed per institution's nuclear medicine department SOPs or the following procedure. All subjects will fast a minimum of 4 hours and have serum glucose levels no greater than 140 mg/dL. After positioning the subject based on findings on CT and MIBG scintigraphy, administer 10 mCi of FDG intravenously and perform dynamic images for 1 hr post-injection followed by a whole body image. Images will be attenuation corrected using a germanium 68 transmission scan or CT if a PET/CT device is used. Region of interests are drawn and SUV's determined for suspect lesions and target organs.

11.5.10 Tumor Markers

Each subject will receive a baseline evaluation of tumor markers (serum chromogranin A, plasma free metanephrines and normetanephrines), 24 hour urinary vanillylmandelic acid (VMA), plasma catecholamines (dopamine, epinephrine and norepinephrine), 24 hour urinary catecholamines (dopamine, epinephrine and norepinephrine) and urinary metanephrines and normetanephrines, during the screening/ baseline period. Additional laboratory testing for tumor markers will include measurements every two weeks during weeks 2-24, monthly during Months 7 through 12 following the first therapeutic Ultratrace iobenguane I 131 infusion and during the

long-term follow-up through assessments provided as institutional standard of care (Section 11.5.17). All tumor markers will be evaluated by a central laboratory.

Although not a requirement, it is suggested that patients refrain from smoking or eating for at least 4 hours prior to blood draws for tumor markers to ensure reliable test measurements Subjects should sit quietly for 10-20 minutes before the phlebotomy. For dietary/medication considerations before tumor marker collection please refer to the guidelines provided in the Study Manual Binder.

11.5.11 Bone Scans

A bone scan will be performed at Screening/Baseline and if probable metastatic disease is observed, additional bone scans will be performed at Month 3, 6, 9, 12. If a subject did not have a bone lesion on the Screening bone scan, but shows possible bone involvement on CT/MR at a follow-up time point, a bone scan should be performed. If metastatic disease is suspected on this bone scan, a bone scan should be collected at this visit and from that time point forward for all efficacy visits (e.g., Month 6, Month 12) through the Month 12 time point.

11.5.12 Changes in antihypertensive medication post Ultratrace iobenguane I 131 therapy

At each subject visit a current list of antihypertensive medication doses and compliance history will be obtained. Following Ultratrace iobenguane I 131 therapy, the potential for a decrease or normalization in the subject's pre-treatment hypertension exists.

For this situation, guidance on decreasing the dose of a specific antihypertensive medication, decreasing the number of different antihypertensive medication (e.g., two antihypertensive medications reduced to one), or total discontinuation of antihypertensive medication is as follows:

- A target blood pressure goal is systolic BP <140 mm Hg and diastolic BP as <90 mm Hg. If the subject's systolic and diastolic values are less than 140 mm Hg and less than 90 mm Hg respectively, a change in antihypertensive medication should be considered.
- Follow up blood pressure evaluations should be performed by health care professional in the manner described below within 7 to 10 days.
- The subject should measure and routinely record their blood pressure. Recordings should be at least 1-2 times/week at the same time of day [e.g., evening before supper or before bedtime] and preferably no more than 7 days between measurements. This provides a mechanism to recognize any potential increase in blood pressure after decreasing or discontinuing antihypertensive medications or, conversely, allows recognition of overmedication of antihypertensive medication. The subject will be instructed to communicate any blood pressure changes or questions to their physician.

If the subject remains within a normotensive range (systolic BP <140 mm Hg and diastolic BP as <90 mm Hg), consideration for further reduction or discontinuation of antihypertensive medication as noted above should be considered.

Presentation of tiredness, fatigue or orthostatic hypotensive signs or symptoms several weeks or more following a therapeutic dose of Ultratrace iobenguane I 131 could be an indication of excessive antihypertensive medication. In this situation, evaluation of blood pressure as noted above is suggested.

As an alternative, a 20-30 mm Hg drop of either systolic and/or diastolic blood pressure versus baseline, but still above the normotensive values noted above, may also represent an opportunity for antihypertensive medication dose decrease based upon clinical judgment.

11.5.13 Vital Signs Measurements

Vital signs (blood pressure, pulse, temperature and respiration) will be collected at the time points listed below.

During Screening Period

Pre-dose: Within 4 hours prior to each administration of Ultratrace iobenguane I 131 (Imaging and Therapeutic)

Post-dose: Within 4 hours after each Ultratrace iobenguane I 131 administration

Both the professional staff (site staff or visiting nurse) and each subject will be obtaining blood pressure measurements for this study. The professional staff (site staff or visiting nurse) will measure heart rate and blood pressure using a manual mercury sphygmomanometer (or other device approved by MIP) at screening/baseline, twice weekly in the first 6 weeks following each therapeutic dose, weekly through Week 24 (at weeks when not collected twice weekly), and monthly at Months 7 through 12 as listed in the Schedule of Procedures (Appendix VII). If the second therapeutic dose is delayed, the twice weekly or weekly blood measurements may occur past Week 24. The twice weekly measurements will occur for at least 6 weeks after the second therapeutic dose and the weekly measurements will continue until at least 12 weeks past the second therapeutic dose. In addition, blood pressure and heart rate will be measured every time antihypertensive therapy is changed. If possible, the same site staff will measure the blood pressure for the subject's duration of the clinical trial. If it is not possible for the same personnel to measure the blood pressure for all determinations, care and accuracy of the blood pressure measurement will be emphasized.

The study subjects will be instructed to measure their blood pressure at least 1-2 times/week at the same time each day [e.g., evening before supper or before bedtime] and preferably no more than 7 days between measurements, from screening/baseline to the 12 month visit (Table 3). Subjects will be provided an Omron blood pressure monitor for blood pressure monitoring. Subjects will be trained by site staff to obtain their blood pressure measurements using the procedure outlined below.

TABLE 3: BLOOD PRESSURE MEASUREMENTS

(Blood pressure measurements should be obtained approximately the same time as baseline values throughout the study)	**Screening /Baseline**	**First 6 weeks following therapeutic dose(s) (dose 1 and dose 2)**	**Through week 24 (at weeks when not collected twice weekly)**	**Months 7-12**
Site staff or visiting nurse[a] (blood pressure and heart rate)	X	2X a week[b]	1X a week[b]	1X a month
Subject	From screening/baseline through 12 month visit at least 1-2X per week (no more than 7 days between measurements)			

[a] Blood pressure and heart rate will be measured every time antihypertensive therapy is changed

[b] If the second therapeutic dose is delayed ,the twice weekly or weekly blood measurements may occur past 24 weeks. The twice weekly measurements will occur for at least 6 weeks after the second therapeutic dose and weekly measurements will continue until at least 12 weeks past the second therapeutic dose

Prior to obtaining the blood pressure measurements, the subjects should sit quietly after resting for 5 minutes, with the arm supported on a flat surface, such that the upper arm is supported at the level of the heart. The subject's back should be supported, and both feet should be flat on the floor. An appropriately sized cuff should be placed on the subject's non-dominant arm. Within thirty minutes prior to the blood pressure measurement, subjects should refrain from smoking, drinking coffee or other caffeinated beverage, or exercising. At least two, and preferably three, readings should be taken at each sitting with at least a one minute interval between readings. A summary of recommendations for Home Blood Pressure Monitoring will be included as part of the Study Manual Binder.

If a subject develops symptoms consistent with orthostatic hypotension (light headedness, dizziness or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and heart rate should be collected. An evaluation of orthostatic hypotension should be performed to determine if the cause could be from excessive antihypertensive medication versus some other clinical explanation (e.g., dehydration). Whenever possible, blood pressure measurements should be obtained at approximately the same time as baseline values (e.g., morning).

11.5.14 Symptom and Quality of Life Evaluations

Two questionnaires and two clinical evaluations will be employed to evaluate the clinical status of each subject.

Quality of Life will be measured by subject report using the EORTC QLQ-C30 v.3 (Appendix IV). Also, the NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma (Appendix IV) will be used to evaluate symptoms specific to pheochromocytoma or paraganglioma. Both of these subject-reported questionnaires will be administered at Screening/Baseline (twice) before the first therapeutic dose, Week 3, Week 6, Week 10, Week

12, Week 15, Week 18, Week 22, and monthly from 6-12 months following the first Therapeutic Dose.

The Karnofsky Performance Status Scale (Appendix I) will be completed by the Investigator at screening/baseline, the day of each Therapeutic Dose, at the safety visits 6 weeks after each Therapeutic Dose and at the efficacy visits in months 3, 6, 9 and 12 post the first Therapeutic Dose. The Karnofsky Performance Status Scale administered at 6 weeks after each Therapeutic Dose administration may occur within ±10 days of the Week 6 window to accommodate potential blood count nadir or travel restrictions. The Investigator will evaluate the subject's clinical status at each timepoint as compared to baseline measurement.

11.5.15 Electrocardiograms

Electrocardiograms (ECGs) will be taken at the following time points, using a Holter monitor for measurements during the isolation periods:

- Pre-Imaging Dose: three 12-lead ECGs at least 5 minutes apart within 2 hours prior to the Imaging Dose administration
- Post-Imaging Dose: immediate (up to 2 minutes post-administration) and at 10± 2 minutes, 15 ± 2 minutes and 20 ± 2 minutes post-administration
- Post-Imaging Dose: within 15 minutes prior to the second and third post-Imaging Dose I 131 scans
- Pre-Therapeutic Dose: 24-hour Holter monitor, initiated between 100 minutes before to 45 minutes before each therapeutic Dose administration
- Post-Therapeutic Dose: continuation of Holter monitor for approximately 23 hours
- Post-Therapeutic Dose: 12-lead ECG within 7 days after each therapeutic dose

Rhythm, RR-, HR-,PR-, QT-, QTc- and QRS-intervals, and ST-segment will be assessed at each time point that a 12-lead ECG is recorded. The on-site Investigator will comment on any findings considered to be clinically significant. Any adverse events (see Section 12) will be reported in the CRF. An independent cardiologist at a core ECG lab will also read all ECGs for issues of safety.

11.5.16 Ultratrace iobenguane I 131 Scans

After thyroid blocking, it is anticipated that subjects will have a total of five Ultratrace iobenguane I 131 scans for this study. Three scans will be performed for the assessment of dosimetry, biodistribution and tumor uptake prior to the first Therapeutic Dose of Ultratrace iobenguane I 131.

- **Image 1:** Imaging will start within an hour of the end of the imaging infusion of 3 to 6 mCi Ultratrace iobenguane I 131 **prior** to subject voiding.
- **Image 2:** One to two days after administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.
- **Image 3:** Two to 5 days after the administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.

Subjects will have one additional scan within seven days following **each** of the two Therapeutic Doses of Ultratrace iobenguane I 131, to further assess biodistribution.

Anterior and posterior whole body images from head to toe will be performed. For any particular subject, the same gamma camera must be used for all scans. At least 18 hours separation between each of the three imaging acquisitions is required. Regions of Interest (ROI) of visualized major organs and target lesions will be performed by the Central Imaging vendor at all imaging time points. It is important to include the imaging standard (section 11.6) with Image 1, 2, 3.

11.5.17 Long-Term Follow-Up

Subjects will be followed for Events of Special Interest (Appendix VI), which includes post radiation toxicity as outlined in Section 12. Thereafter, subjects enter long term follow up and remain in follow up for 5 years after the first Therapeutic Dose of Ultratrace iobenguane I 131. During this period, subjects will be followed for adverse events of special interest and overall survival and concomitant medication usage. In years 2-5 post-treatment (or until a subject experiences disease progression, start of another anticancer therapy or death), data on tumor response, tumor markers and clinical benefit (including use of antihypertensive medication) will be collected through assessments provided as institutional standard of care. If standard of care is not providing such assessments, they will be offered by the study site.

11.5.18 Assessment Windows

The following windows are allowed from the study schedule to accommodate subject scheduling flexibility and other hardships:

- ±Weekly assessments through 24 week post first therapy dose

Week	Visit to occur between these days	Week	Visit to occur between these days
Week 1 Window	Day 0-Day 7	Week 2 Window	Day 8-Day 14
Week 3 Window	Day 15-Day 21	Week 4 Window	Day 22- Day 28
Week 5 Window	Day 29-Day 35	Week 6 Window	Day 36-Day 42
Week 7 Window	Day 43-Day 49	Week 8 Window	Day 50-Day 56
Week 9 Window	Day 57-Day 63	Week 10 Window	Day 64-Day 70
Week 11 Window	Day 71-Day 77	Week 12 Window	Day 78-Day 84
Week 13 Window	Day 85-Day 91	Week 14 Window	Day 92-Day 98
Week 15 Window	Day 99-Day 105	Week 16 Window	Day 106-Day 112
Week 17 Window	Day 113-Day 119	Week 18 Window	Day 120-Day 126
Week 19 Window	Day 127-Day 133	Week 20 Window	Day 134-Day 140
Week 21 Window	Day 141-Day 147	Week 22 Window	Day 148-Day 154
Week 23 Window	Day 155-Day 161	Week 24 Window	Day 162-Day 168

If past Week 24 please continue to have windows occur within the respective week window.

- Monthly assessments through month 12 post therapy dose: ±10 days

Month	Visit to occur between these days	Month	Visit to occur between these days
Month 3	Day 81-Day 101	Month 6	Day 173-Day 193
Month 7	Day 203-Day 223	Month 8	Day 233-Day 253
Month 9	Day 264-Day 284	Month 10	Day 294-Day 314
Month 11	Day 325-Day 345	Month 12	Day 355-Day 375

- Long-term follow-up assessments from Month 12 through Year 5: ±30 days

Any additional deviations from the assessment windows described must be approved in writing by MIP or designee prior to assessment.

11.6 Eligibility/Dosimetry Scans

An imaging standard will be prepared by adding Ultratrace iobenguane I 131 to a saline infusion bag and imaged simultaneously with the subject using the same protocol. Consult the Site Imaging Manual for details about the standard preparation, camera set up and scanning procedures. Acquire anterior and posterior whole body images from head to toe for assessment of biodistribution and tumor uptake. For any particular subject, the same gamma camera must be used for all scans. Regions of Interest (ROI) of visualized major organs and target lesions will be performed by the Central Imaging vendor at all imaging time points:

- **Image 1:** Imaging will start within an hour of the end of the imaging infusion of 3 to 6 mCi Ultratrace iobenguane I 131 **prior** to subject voiding.
- **Image 2:** One to two days after administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.
- **Image 3:** Two to five days after the administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.

There needs to be at least 18 hours between each of the three image acquisitions. The tumor to background ratio should be ≥2, and may be best visualized beginning at the 24 hour image to allow background clearance. For example, a liver lesion should be 2X background normal liver while soft tissue lesions would use background in surrounding soft tissue.

Any uptake to be designated as tumor on the Ultratrace iobenguane I 131 scan must correspond to a known measurable target lesion on the most recent CT or MRI scan.

11.6.1 Assessment of Biodistribution of Ultratrace Iobenguane I 131

The biodistribution of Ultratrace iobenguane I 131 should be assessed by visual examination of whole body scan. The scans will be evaluated by a qualified interpreter of nuclear medicine scans at the clinical trial site. Two time points will be used for the visual assessment, using the one hour post imaging (Image 1) as baseline and (Image 2), taken at 1 to 2 days after imaging dose administration. Further visual evaluation will be performed using (Image 3), taken 2 to 5 days after the administration of 3 to 6 mCi Ultratrace iobenguane I 131.

If the biodistribution of Ultratrace iobenguane I 131 is inconsistent with the expected organ or tissue distribution of iobenguane, the investigator must contact MIP to discuss and decide the appropriate course of action.

Whole body and renal radiation absorbed dose estimates will be calculated by a qualified independent expert using the internal absorbed radiation dose OLINDA/EXM dosimetry software.[39] If the calculated renal absorbed dose exceeds 23 Gy to the kidney, 17.5 Gy to the lungs and 30 Gy to the liver then the injected activity will be modified not to exceed the dose limits specified, as described in Section 10.2.

11.6.2 Image Acquisition

Imaging will be performed according to the Imaging Manual provided by MIP or its designee.

Gamma camera setup and acquisition parameters (such as the correct scan speed) will be set according to the Site Imaging Manual. At the recommended imaging times below, position the subject supine on the bed of a multi-head gamma camera equipped with high energy collimators. The same camera and collimators will be used for each imaging scan for a particular subject. Care will be taken to position the top of the head at a fixed position for each scan and to ensure that the subject's body is parallel to the scanning axis and centered. A 15% window will be centered on the 364 keV photopeak of I 131. The following serial simultaneous anterior and posterior whole body images will be acquired:

- **Image 1:** Imaging will start within an hour of the end of the imaging infusion of 3 to 6 mCi Ultratrace iobenguane I 131 **prior** to subject voiding.
- **Image 2:** One to two days after administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.
- **Image 3:** Two to five days after the administration of the Ultratrace iobenguane I 131 imaging dose and immediately **following** subject voiding.

All images will be sent to a central core lab after anonymization. Image standards prepared by adding Ultratrace iobenguane I 131 to saline infusion bags will be imaged using the same protocol. The Site Imaging Manual/Pharmacy Manual further describes the procedure and preparation and use of the standard.

11.6.3 Image Assessment

Two independent readers will determine if there is visible uptake of Ultratrace iobenguane I 131 in target lesions. Target lesions are measurable lesions with at least one diameter ≥ 20 mm.

A qualified person will draw regions of interest (ROI) and obtain ROI counts according to the instructions provided by MIP or its designee. In brief, for each image (anterior and posterior) obtained, ROIs will be drawn over tissues or organs that visibly accumulate radioactivity. Such organs may (but do not necessarily) include: the whole body, red marrow, brain, breasts, gut, heart, kidneys, liver, lungs, muscle, pancreas, salivary glands, skeleton, spleen, testes, thyroid, and urinary bladder contents. Once ROIs have been created, they will be kept constant for subsequent time points. The sizes of the various ROIs (number of pixels) will be determined and counts in the posterior and anterior views will be obtained for each image. In the case of other overlapping organs, a correction will be made by choosing a small ROI, within the organ ROI that does not overlap. The counts/pixel within this small region will be scaled up to represent the full organ ROI. The radioactivity (cpm)/pixel will be calculated from the geometric means of the ROIs from each view. Background will be identified as an area adjacent to the organ of interest ROI.

The time of the first whole body scan will be used as the reference time for decay correction of all subsequent whole body data. The geometric mean count of the first whole body studies (obtained prior to excretion) will be taken as representing 100% of administered activity. Data from subsequent time points will be related to this figure to obtain retention data in terms of percentage of administered activity at the various scanning times.

An independent expert will calculate radiation absorbed doses for normal organs. Images will be quantified in terms of percent of injected activity in the various source organs.

11.6.4 Dosimetry

The data will be evaluated by an independent expert to determine human radiation absorbed dose estimates to normal organs in accordance with Medical Internal Radiation Dose (MIRD).[37] For estimating internal absorbed radiation dose OLINDA/EXM dosimetry software will be used.[38] Subject-specific kidney or other organ measurements will be used for dosimetry estimates.

11.7 CT or MR Image Evaluation

Off-site CT and MR assessment will be conducted by independent, CT and MR-experienced readers in accordance with the charter issued by the imaging core laboratory. These readers will be blinded to clinical subject information as described in the Imaging Charter. The readers will determine objective tumor response according to RECIST criteria. On-site interpretation of CT and MR images may also be done, but only the results of the blinded read will be used for the objective tumor response evaluations.

12. REPORTING SAFETY INFORMATION

The site staff will screen subjects for adverse events during scheduled visits, non-scheduled visits or safety call at 16 weeks after the last therapeutic dose (see Section 11.5.2). Any untoward medical event that is discovered from the time of signed informed consent until the last day of week 15 from the last infusion of therapeutic administered Ultratrace iobenguane I 131 will be collected and reported as an adverse event. Thereafter, adverse events of special interest (AESI), will be collected starting 16 weeks after the last therapeutic administration of Ultratrace iobenguane I 131 until completion of the follow up period.

12.1 Adverse Events

12.1.1 Definitions

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, at any dose, which does not necessarily have a causal relationship with the treatment

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A **serious adverse event (SAE)** is any untoward medical occurrence that at any dose falls into one or more of the following categories:

- results in death
- is life-threatening
  - i.e., an event which, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred and does not include an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization.
  - For the seriousness criterion of inpatient hospitalization to apply, an overnight stay in the hospital is required. Admission to an ER and release without an overnight stay would not satisfy the inpatient hospitalization seriousness criterion.
- results in persistent or significant disability/incapacity
  - where disability is defined as a substantial disruption of a person ability to conduct normal life functions, either reported or defined as per clinical judgment
- is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome to the child)

- is any other important medical event
  - may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the serious definitions above. An important medical event may include development of drug dependency or drug abuse.

12.1.2 Reporting Serious Adverse Events

Serious is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining the sponsor's regulatory reporting obligations (i.e., to the applicable regulatory authorities). Adverse event severity and seriousness should be assessed independently by investigators.

MIP, as Sponsor of the study, is responsible for reporting relevant SAEs as safety reports to the FDA, Health Canada and other applicable regulatory authorities, and participating Investigators, in accordance with the US Code of Federal Regulations (CFR) Title 21 CFR 312.32 and 312.33, European Clinical Trials Directive, ICH guidelines, Health Canada guidelines, Good Clinical Practice and/or local regulatory requirements.

The Investigator must report all SAEs to MIP designee within 24 hours, by telephone, email or fax, and confirm that the information was received (see Appendix VIII).

A Serious Adverse Event Report (SAER) must be completed by the Investigator or designee and faxed or emailed to MIP's designee within 24 hours after the Investigator first becomes aware of the serious event. A separate SAER will be needed for each reported SAE so that the onset, resolution date causality and outcome can be assessed for each event. Any source documents relevant to the event should be forwarded to MIP's designee with the SAER form. The SAER form must be signed and dated by the Investigator. The Original copy must remain on site with the CRF.

In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to MIP's designee, together with the SAER. If an autopsy is performed, a copy of the autopsy report should be actively sought by the Investigator and sent to the Sponsor or designee as soon as available. A copy of the autopsy report must remain on site with the CRF.

All deaths will be reported as SAEs regardless of their relationship to disease progression and reported via an SAER form from the time of signed informed consent until completion of the follow up period. All other SAEs will be reported until the last day of Week 15 following the last administration of Ultratrace iobenguane I 131, and reported via an SAER form to MIP's designee.

A new follow-up SAER form will be filled in by the Investigator if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow up SAER must be signed and dated by the Investigator. The follow-up form and any additional source documentation regarding the event will be sent to the sponsor, or designee, as described above.

If a serious medical occurrence or death is reported to the Investigator outside the follow up window, which is believed to be related to the administration of the investigational product, it is the Investigator's responsibility to report this occurrence to MIP's designee. Such occurrences will be reported using a SAER form or other form of communication deemed appropriate by the Investigator and MIP.

Sites must contact MIP's designee to report all SAEs within 24 hours, by telephone, email or fax.

Contact Information in the US, UK and Canada, see Appendix VIII.

Sites must also report all pregnancies, overdoses and extravasations to MIP's designee. In the case of pregnancy, the pregnancy will be followed until the pregnancy outcome is known. The form must be completed and submitted to MIP's designee. Additional information, including source documentation, may be requested as follow up to any pregnancy.

12.1.2.1 Reporting Adverse Events of Special Interest

Definition:
An **adverse event of special interest (AESI)** is a serious or nonserious event of scientific and medical concern specific to Ultratrace iobenguane I 131. The event may require further investigation, and depending on the nature of the event, submission to the FDA, Health Canada and other applicable regulatory authorities. For the purposes of this trial AESI have been predefined by MIP (See Appendix IV) to identify any signs of late stage radiation toxicity in the study population. Additionally, if an investigator determines an event, not listed within the appendix, is medically significant and may be causally related to the study product, the event will be reported to MIP's designee (see Appendix VIII), expeditiously, for real-time monitoring. Adverse events of special interest would only be classified as SAEs if the Investigator determined that they met established regulatory criteria as outlined above for serious events or, if upon further review by the sponsor, the events meet SAE criteria.

All adverse events of special interest will be reported starting 16 weeks after the last therapeutic dose until completion of the follow-up period, on a Serious Adverse Event Report (SAER) form and must be completed by the Investigator or designee and telephoned, emailed or faxed to MIP's designee within 24 hours after the Investigator first becomes aware of the adverse event (see Appendix VIII). A separate SAER will be needed for each reported AE of interest so that the onset, resolution date, outcome and causality can be assessed for each event. Any source documents relevant to the event should be forwarded to MIP's designee with the SAER form. The SAER form must be signed and dated by the Investigator. The Original copy must remain on site with the CRF.

A new follow-up SAER will be completed by the Investigator if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow up SAER form must be signed and dated by the Investigator. The follow-up form and any additional source documentation regarding the event will be sent to MIP, or designee, as described above.

12.1.3 Breaking the Study Blind

This is a single arm, open label study.

12.1.4 Data Collection

The Investigator will elicit information through non-leading questioning and examination of the subject about the occurrence of adverse events from the time of informed consent until the Safety Phone Call 16 weeks after the last dose of study drug.

For each event, the following information will be recorded in the subject's records and transcribed onto the AE section of the CRF according to the instructions described below.

- **Classification of the Event as serious or non-serious:** Classify the event as either serious or non-serious (see definitions in Section 12.1.1).
- **Classification of the Event as an adverse event of special interest (AESI):** Determine if the event is an AESI (see Appendix VI).
- **Description of Signs or Symptoms**: Whenever possible, record a specific diagnosis for the event. If a diagnosis cannot be made, then record each sign or symptom separately, (e.g., record nausea and vomiting as two events).
- **Onset Date and Time:** Record the date and time the event started (e.g. if a laboratory test is reported as an AE, record the start date as the date of collection of the first lab sample that shows the change.)
- **Stop Date and Time:** Record the date and time the event resolved.
- **Grade:** Refer to the common terminology criteria for adverse events (CTCAE, version 3).

Relationship to the Study Drug: Make every effort to evaluate the relationship between the study drug and the AE as determined by the investigator per the definitions below:

Related	The event is reasonably suspected of a causal relationship to the study drug and/or causality cannot definitively be ruled out.
Not Related	The event is definitely due to causes separate from the administration of the study drug, i.e., • documented pre-existing condition • technical and manual procedural problems • concomitant medication • subject's clinical state

- **Action Taken with Study Drug:**
  1. Dose not changed (no action taken)
  2. Dose reduced
  3. Drug withdrawn
  4. Not applicable

- **Adverse Event Outcome:**
  1. **Recovered/ Resolved without sequelae**
  2. **Recovered/Resolved with sequelae**
  3. **Not recovered/Not resolved**, event is on-going at the end of the AE collection period.
  4. **Death (fatal)** the event description must be the primary cause of death. Disease progression is not considered an acceptable cause of death for purposes of this study.
  5. **Unknown**

12.1.5 Subject Follow-up

Every attempt will be made to follow the subject until the AE is resolved or until the Investigator determines the subject has returned to an acceptable state of health.

12.2 Laboratory Evaluations

12.2.1 Reporting and Evaluation of Local Laboratory Test Results

The Investigator will review laboratory values promptly upon receipt of the laboratory report. After the review is completed, the Investigator will sign and date each laboratory report. The laboratory will provide normal reference ranges for the laboratory tests on the laboratory results report. A value is **normal** when it falls on or within the upper and lower limits of the reference range. A value is **abnormal** when it falls outside the upper or lower limit of the reference range. The Investigator will review all laboratory results for clinical significance and note the clinical significance of all abnormal laboratory findings in the subject's source records.

The Investigator must evaluate any change from pre-dose to post-dose in a laboratory test which represents a worsening of the subject's clinical state as to whether it meets the definition of an AE or SAE. Any change determined to meet the definition of an AE or SAE will be recorded in the AE section of the CRF, and an SAER form will be forwarded to MIP's designee if appropriate (see Appendix VIII).

12.2.2 Additional procedures by site

For this study, specific sites may collect additional data that may represent investigator or institutional standard of care. For example, pre- or post- treatment evaluations or any other pre- or post- treatment laboratory, imaging or other ancillary studies, obtained for pheochromocytoma or paraganglioma subject management. MIP may collect data or procedure information related to the subject's enrollment, diagnosis or inclusion decision. The same confidentiality afforded to protocol defined data will be respected. The criteria for additional data collection, if any, would be to enhance study analysis and data understanding.

12.2.3 Repeat Testing

At the discretion of the Investigator, additional blood or urine samples may be collected to repeat the evaluation of any lab test that yields an abnormal result post-dose that was not abnormal pre-dose. Parameters will be monitored, as clinically indicated, until the value returns to the pre-dose level or clinically stabilizes, or until the Investigator or physician of record determines that further follow-up is unnecessary.

12.3 Electrocardiogram evaluation

If a worsening from pre-dose to post-dose is observed, the ECG may be repeated at the discretion of the Investigator, in addition to obtaining an ECG at the other post-dose time points required by the protocol. The Investigator will assess any worsening from pre-dose to post-dose in the ECG for clinical relevance (i.e., to determine whether it meets the definition of an AE). Any changes determined to meet the definition of an AE will be reported in the AE section of the CRF.

12.4 Physical Examinations

If a worsening from pre-dose to post-dose is observed, the physical examination may be repeated at the discretion of the Investigator, in addition to obtaining a physical examination at the other post dose time points required by the protocol. Any change from pre-dose to post-dose will be documented in the subject's source records and transcribed onto the physical examination section of the CRF. The Investigator will evaluate any worsening at the post-dose physical examination for clinical relevance and to determine whether an AE has occurred. Any changes determined to meet the definition of an AE or SAE will be recorded on the AE section of the CRF, and an SAER form will be forwarded to the MIP's designee if appropriate (see Appendix VIII). Specific observations (signs), symptoms and/or laboratory information supporting these changes will also be documented.

12.5 Vital Signs

If a worsening from pre-dose to post-dose is observed, vital signs measurements may be repeated at the discretion of the Investigator, in addition to obtaining vital sign measurements at the other post dose time points required by the protocol. The Investigator will evaluate any worsening in vital signs for its clinical relevance as to whether it meets the definition of an AE or SAE. Any changes determined to meet the definition of an AE or SAE will be recorded in the AE section of the CRF, and an SAER form will be forwarded to MIP's designee if appropriate (see Appendix VIII).

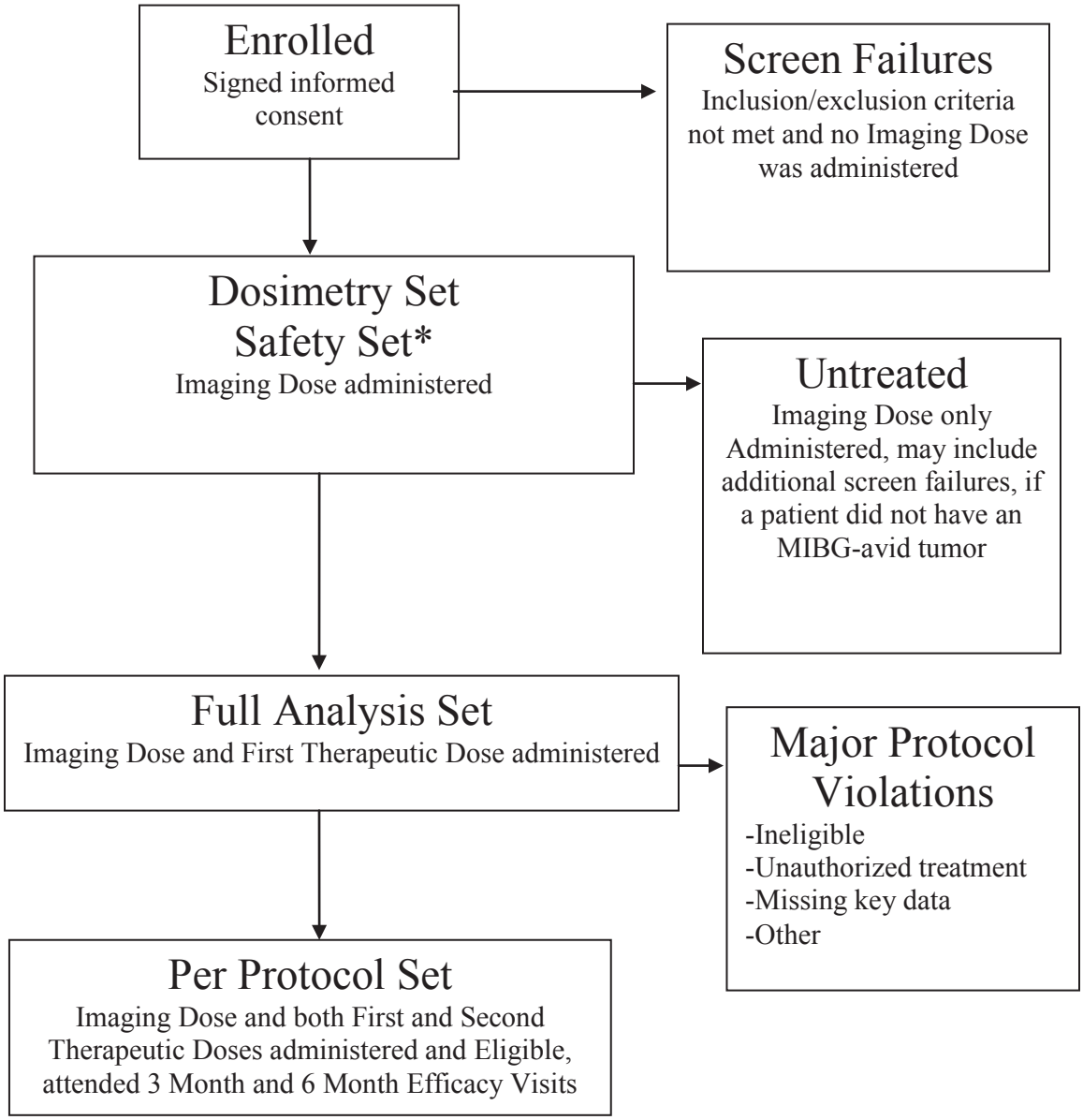
13. STATISTICAL METHODS

The detailed prospective procedures for data analysis are described in the Statistical Analysis Plan. Any changes in the original statistical methodology will be documented in the final Clinical Study Report. All statistical analyses, except those for dosimetry, will be performed using SAS® statistical analysis software version 9.1 or greater.[39]

13.1 Analysis Sets

Figure 2 is a flow diagram of the protocol defined analysis sets. The Enrolled Set includes all subjects who have provided signed informed consent. The Dosimetry Set and Safety Set include all subjects who received the Imaging Dose. Adverse Events prior to the Imaging Dose will be captured for all enrolled subjects and reported separately from treatment-emergent AEs. The Full Analysis Set is a subset of the Dosimetry Set / Safety Set, excluding subjects who did not receive at least the first Therapeutic Dose. Subjects whose therapeutic dose is decreased below 500 mCi, based on results of the dosimetry study or hematological dose modifications are included in the Full Analysis Set. The Full Analysis Set will be used for the primary analysis of efficacy. The Per Protocol Set is a subset of the Full Analysis Set, excluding subjects who received only one Therapeutic Dose, who did not attend the 3 Month and 6 Month Efficacy Visits, or with major protocol violations. Major protocol violations are defined as those that could impact the efficacy evaluation such as a subject is ineligible, missing key data, received an unauthorized treatment, etc. Only subjects receiving both Therapeutic Doses and with sufficient follow-up for efficacy will contribute to the Per Protocol Set. Key efficacy endpoints, including the primary endpoint of the proportion of subjects experiencing a reduction in use of all antihypertensive medication for at least six months or two cycles, will be analyzed on the Per Protocol Set (in addition to the Full Analysis Set).

FIGURE 2: SCHEMATIC OF PROTOCOL DEFINED POPULATIONS



* Adverse Events prior to the Imaging Dose will be captured for all enrolled subjects and reported separately from treatment-emergent AEs.

13.2 Sample Size

The sample size for this study is 58 subjects in the Per Protocol Set, for which it is estimated that approximately 75 subjects may be enrolled. The one-sided alternative hypothesis of the study is that the proportion of subjects experiencing reduction in use of all antihypertensive medication by at least 50% for at least six months or two cycles is 0.25, against the null hypothesis that the proportion is 0.10. Sample size of 58 was based on a one-sided significance level of $\alpha = 0.025$ and power of 0.90 (90%).

13.3 Statistical Methods

13.3.1 Descriptive and summary statistics

Summary tables and listings will be provided for demographic and baseline characteristics, including age, race, sex, height, weight, medical history, and prior medications. Summary tables and listings will also be provided for the number of subjects who have been enrolled and were administered imaging and therapy doses according to protocol guidelines.

Appropriate descriptive statistics will be generated for each endpoint of interest. In particular, mean, median, standard deviation and range will be computed for each continuous variable whilst counts and percentages will be computed for each categorical variable.

13.3.2 Efficacy Analysis

13.3.2.1 Primary Analysis: Reduction in use of antihypertensive medication

The primary endpoint in this study is the proportion of subjects, after a Therapeutic Dose of Ultratrace iobenguane I 131, with a reduction (including discontinuation) of all antihypertensive medication by at least 50% for at least six months or two cycles. The duration of benefit is measured by maximum duration as follows. A benefit duration period commences when the subject's medication is reduced to a level at or below 50% of baseline, and continues until the subject's medication rises above 50% of baseline. For purposes of illustration, the following examples are provided (Month refers to the number of months after the first Therapeutic Dose).

- Example 1: A patient experiences the clinical benefit from the beginning of Month 2 to the beginning of Month 4, and then again from the beginning of Month 5 to the beginning of Month 12. Since the maximum duration of the benefit was 7 months, the subject is considered a success on the primary endpoint.

- Example 2: A patient experiences the clinical benefit from the beginning of Month 2 to the beginning of Month 4, and then again from the beginning of Month 6 to the beginning of Month 11. The patient begins another anticancer treatment at Month 15 and is discontinued. Even though the patient experienced the clinical benefit for a total of 7 months, the maximum duration of the benefit was only 5 months, so the subject is considered a failure on the primary endpoint.

- Example 3: A patient experiences the benefit from the beginning of Month 2 to the beginning of Month 9. At Month 10, the patient receives another anticancer treatment and is discontinued from the study. Since the maximum duration of the benefit was 7 months, prior to discontinuation, the patient is considered a success on the primary endpoint.

For the primary analysis of the primary endpoint, a point estimate (with a 95% confidence interval, using the normal approximation with a continuity correction) for the proportion of subjects experiencing a reduction (including discontinuation) of all antihypertensive medication

by at least 50% for at least six months or two cycles will be calculated. This single-arm trial will be considered a success if the lower bound of the two-sided 95% confidence interval exceeds 0.10 (10%). The Full Analysis Set will be used for the primary analysis, but this same analysis will be repeated for the Per Protocol Set.

13.3.2.2 Secondary Analyses

13.3.2.2.1 Overall Tumor Response per RECIST Criteria

Objective tumor response and overall tumor response will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).[43] Tumor size measurements will be obtained by CT or MR at baseline and at 3, 6, 9, and 12 months post-treatment. For each subject, the same modality (CT or MR) and the same technique used for the baseline assessment will be used in all subsequent assessments.

Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan. Non-measurable lesions are all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), or bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

At baseline, all measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (SLD) for all target lesions will be calculated and reported as the baseline SLD. The baseline SLD will be used as reference by which to characterize the objective tumor. All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted at each follow-up.

Objective tumor response criteria for target lesions are as follows:

Complete Response (CR)	Confirmed* disappearance of all target lesions
Partial Response (PR)	Confirmed* decrease of at least 30% in the SLD of target lesions, taking as reference the baseline SLD
Moderate Response (MR)	Confirmed* decrease of at least 15% but at most 29% in the SLD of target lesions, taking as reference the baseline SLD
Stable Disease (SD)	Changes do not meet the criteria for CR, PR, MR or PD
Progressive Disease (PD)	At least a 20% increase in the SLD of target

lesions, taking as reference the smallest SLD recorded since the treatment started or the appearance of one or more new lesions

Objective tumor response criteria for non-target lesions are as follows:

Complete Response (CR)	Confirmed* disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Overall tumor response combines assessment of target lesions and non-target lesions. At each assessment, overall tumor response is that shown in the "Overall Response" column below.

Target lesions	Non-Target Lesions	New Lesions	Overall Response
CR*	CR*	No	CR
CR*	Incomplete response/SD	No	PR
PR*	Non-PD	No	PR
MR*	Non-PD	No	MR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* To be assigned a status of CR, PR or MR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

For each post-therapy visit where objective tumor response is evaluated, each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) moderate response, 4) stable disease, 5) progressive disease, or 6) unknown (not assessable, insufficient data) based upon the independent, central evaluation of scans. An overall response of CR, PR or SD meets the secondary endpoint criterion for overall tumor response. RECIST tumor measurements will be listed by target, non-target, and bone (also considered non-target) lesions, for each RECIST reviewer, and the adjudicator, if there was a discrepant result for the overall tumor response. A summary table will be provided showing by nominal time point, target, non-target, bone, and overall response. Figures will also be constructed showing the sum of the longest diameter (SLD) over time since therapeutic dose.

13.3.2.2.2 Tumor Marker Response Proportion

Tumor markers will be assessed as stated in the Schedule of Procedures (Appendix VII). For all tumor markers, a significant increase in test value is indicative of progression, and a significant decrease is indicative of a response.

For each individual tumor marker, response criteria are defined as follows:

Complete Response (CR)	normalized, at or below ULN
Partial Response (PR)	≥50% decrease in baseline value
Stable Disease (SD)	any response other than CR, PR or PD
Progressive Disease (PD)	≥50% increase in baseline value

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

13.3.2.2.3 Bone Lesion Status

Results of bone scans will be scored using the Soloway Scale (Appendix II).

13.3.2.2.4 Quality of Life (QoL)

The EORTC QLQ-C30v.3[40] will be used to evaluate Quality of Life (QoL). The results of QoL, and changes from baseline, will be summarized by domain.

13.3.2.2.5 Symptom Response

A symptom response instrument will be used to evaluate symptoms specific to NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma as a secondary endpoint. Changes in symptoms over time will be evaluated by subject and across the Full Analysis Set in aggregate.

13.3.2.2.6 Analgesics and pain medicine

Changes in total dose of any single medication used to control tumor pain, and changes in potency within a symptom treatment (e.g., conversion of narcotic to NSAID) will be evaluated by subject and across the Full Analysis Set.

13.3.2.2.7 Karnofsky Performance Status

Karnofsky Performance Status will be evaluated by subject and across the Full Analysis Set in aggregate.

13.3.2.2.8 Overall survival (OS)

Overall survival is defined as the time from the date of enrollment to the date of death from any cause. OS time will be censored at the last date the subject is known to be alive when the confirmation is absent or unknown.

13.3.2.2.9 Viable tumor tissue (exploratory)

Results of available FDG assessments will be described, and exploratory analyses conducted across the Full Analysis Set.

13.3.3 Safety Analysis

13.3.3.1 Safety Indicators

Safety analyses will include treatment emergent AEs, clinical laboratory measurements, vital signs measurements, ECGs and physical examination findings. The Safety Set will be used in all analyses of safety. However, for computing percentages of patients experiencing adverse events or laboratory toxicities, the denominator will not include those in the Safety Set who are lacking follow-up for safety, because their inclusion would dilute the percentages.

All treatment emergent AEs, clinical laboratory measurements, vital signs measurements, ECG results and physical examination findings will be summarized and listed. Changes from baseline will be summarized as appropriate; for example, for clinical laboratory results with CTC grade, tables will indicate shifts from baseline. Changes in vital signs or ECG measurements of potential clinical significance will be flagged.

Study drug administration will be summarized by Imaging Dose and Therapeutic Dose for the Safety Set. A listing of the study drug administration data will be presented. The amount of Therapeutic Dose will be presented as absolute amount of radioactivity (mCi), as body weight normalized (mCi/kg), and as body surface area (BSA) normalized (mCi/m^2). The amount of the Imaging Dose will be presented as absolute amount of radioactivity (mCi).

13.3.3.2 Dosimetry

Separate comprehensive analyses plans will be generated to report dosimetry results.

13.4 Procedures for Handling Missing, Unused and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed in any primary analysis.

Subjects who receive the Imaging Dose or a Therapeutic Dose but have no follow-up for safety will not be included when computing percentages of subjects experiencing adverse events or laboratory toxicities, because their inclusion would dilute the percentages.

Data that are potentially spurious or erroneous will be examined using standard data management operating procedures, prior to database lock and statistical analysis.

13.5 Procedures for Reporting Deviations to Original Statistical Analysis Plan

Any changes from the statistical analysis described in this Protocol will be documented in the final Statistical Analysis Plan. Any deviations from the final Statistical Analysis Plan will be provided in the final clinical study report.

13.6 Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be established for this study to safeguard integrity of the study and the interests of the trial participants, potential participants, investigators, and sponsor. Furthermore, the DMC will assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct, and protect its validity and credibility.

The detailed procedures and composition of members is described in the MIP-IB12B Data Monitoring Committee Charter.

14. ETHICS

14.1 Ethical Considerations

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the Declaration of Helsinki.

14.2 Informed Consent /Assent

All subjects must sign and personally date an approved informed consent form or assent after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the study agent. An assent will be required for subject's age 12 to 18 years of age and informed consent from the subject's parent/legal guardian as per institutional guidelines. An informed consent form will be required for subjects 18 years of age and above. This must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP), and requirements of Title 21 CFR 50.20 through 50.27.

The subject must be made aware and agree that personal information may be scrutinized during audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

Prior to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) submission, the Investigator must send a copy of the informed consent form to be used at their institution to MIP or its agent for review to assure compliance with the ICH and CFR requirements.

14.3 Institutional Review Board/Independent Ethics Committee Approval

The protocol, informed consent form, and any advertisement for the recruitment of subjects must be reviewed and approved by an appropriately constituted IRB/IEC, as required in Title 21 CFR 56.107 through 56.115 and in chapter 3 of the ICH E6 Guideline. Written IRB/IEC approval must be obtained by MIP prior to shipment of study agent or subject enrollment.

The Investigator is committed in accordance with local requirements to inform the IRB/IEC of any emergent problem, SAEs, and/or protocol amendments.

15. ADMINISTRATIVE CONSIDERATIONS

15.1 Regulatory Requirements–Sponsor/Investigator Obligations

The principal investigator agrees that the study will be conducted according to the principles of the ICH E6 Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the World Medical Association Declaration of Helsinki. The principal investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. To ensure compliance the Investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals.

The Investigator must conduct the trial as outlined in the protocol and in accordance with (as applicable) Title 21 CFR 21 CFR 56 – Institutional Review Boards and (as applicable) the Declaration of Helsinki, as well as all applicable government regulations.

15.2 Protocol Amendments

No change to the protocol may be made without the joint agreement of both the Investigator and MIP. Any amendment to the original protocol will be signed by both parties and submitted to the IRB for approval or notification.

15.3 Curriculum Vitae

All persons listed on the site's 1572 form must provide MIP with current copies of their own curriculum vitae.

15.4 Administrative Structure

The administrative structure of the study (e.g., monitoring and vendor personnel, statistician, and laboratory facilities) and a complete and controlled list of the Investigators participating in this study will be in the study file maintained by the Sponsor or its agent.

15.5 Monitoring Procedures

15.5.1 Study Monitoring

An appropriate representative of MIP (Study Monitor) will maintain contact with the Investigator and will visit the study site for the purpose of overseeing the progress of the study, and ensuring it is conducted, recorded and reported in accordance with the protocol, SOPs, GCP and applicable regulatory requirements.

An initiation visit will be made by the Study Monitor to discuss the protocol and the obligations of both the Sponsor and the Investigator. The Investigator must allow the Study Monitor to perform periodic, interim monitoring visits. The purposes of these visits are to verify that written informed consent was obtained prior to each subject's participation in the trial and to:

- assess the progress of the study
- review the compliance with the study protocol
- determine whether all AEs were appropriately reported
- determine whether the Investigator is maintaining the essential documents
- discuss any emergent problem
- check the CRF for legibility, accuracy and completeness
- validate the contents of the CRF against source
- assess the status of drug storage, dispensing and retrieval
- retrieve study data

All data required by the protocol must be reported accurately on the CRF and must be consistent with the source documents. Source documents are original documents, data and records (e.g., 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 or other diagnostic images, subject's files, pharmacy records and laboratory records). The Investigator will make available the source documents for inspection. This information will be considered as confidential.

The Study Monitor will perform a closeout visit at the conclusion of the Investigator's involvement in the study.

15.5.2 Case Report Form

Case Report Forms (CRFs) must be completed for each subject in accordance with the Data Management Plan and any CRF Completion Guidelines.

15.5.3 Auditing

The Investigator will make all pertinent records available including source documentation for inspection by regulatory authorities and for auditing by the Sponsor. This information will be considered as confidential.

15.6 Archiving of Records

Copies of the protocol, subject identification codes, CRF, source data, informed consent form and other documents pertaining to the study conduct must be kept for the maximum period of time as required by the study center. This time period must be at least two years after the last approval of the marketing application of the study agent in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the study agent.

No study document will be destroyed without prior written agreement between MIP and the Investigator.

Originals of all documentation and copies of outgoing correspondence concerning the study will be stored and retained in a safe area under the control of MIP for the lifetime of the product. In particular, the final report must be retained by MIP, or the subsequent owner, for five years beyond the lifetime of the study agent.

15.7 Final Report

MIP or its designee will write the final report of the trial.

15.8 Use and Publication of Study Results

All unpublished documentation (including the protocol, CRF and Investigator's Brochure [IB]) given to the Investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of MIP. The submission of these documents to the IRB is expressly permitted. The Investigator agrees that MIP maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by MIP in accordance with the guidelines set forth in the applicable publication or financial agreement.

15.9 Financial Disclosure

The Investigator must adhere to regulations regarding financial disclosure in accordance with Title 21 CFR 54.2 to 54.6.

15.10 Termination of the Study

If MIP and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the Investigator terminates the study, an explanatory letter will be provided to MIP.

MIP also reserves the right to discontinue this study for administrative reasons at any time.

15.11 Information Material

Before the beginning of the study the Investigator will be given the last updated investigator brochure. If the investigator brochure is revised during the study, the Investigator will receive a copy of the revised version. The investigator brochure and the protocol are confidential communications of MIP. Acceptance constitutes the agreement by the recipient that no unpublished information therein contained will be published or disclosed without MIP's prior written approval except that these documents must be submitted in accordance with the SOPs of the IRB and other applicable oversight committees with the agreement these committees are required to keep the information confidential.

16. CONFIDENTIALITY

All information that is provided to the Investigator dealing with the study agent is regarded as confidential. The members of the research team agree to share the information on a need-to-know basis and not to discuss such information in any way without prior written permission from MIP.

17. INVESTIGATOR STATEMENT

STUDY TITLE: A Phase II Study Evaluating the Efficacy and Safety of Ultratrace Iobenguane I 131 in Patients with Malignant Relapsed/Refractory Pheochromocytoma/Paraganglioma

STUDY NUMBER: MIP-IB12B (v. March 21, 2014)

I acknowledge that I have read the attached protocol as amended and I agree that it contains all information necessary to conduct the study. I also agree to and will comply with all provisions set forth therein and herein, and certify as follows:

I will comply with all Health Authority regulations/guidelines relevant to the conduct of human clinical trials, as set forth in 21 CFR Parts 50, 54, 56, and 312 part D as they may be amended or supplemented from time to time. I will not initiate the study until I have obtained written approval from the appropriate Institutional Review Board/Independent Ethics Committee and have complied with all financial and administrative requirements of the governing body of my clinical institution. I will obtain written informed consent from all study participants prior to performing any screening procedures.

I understand that my signature (or that of a Sub-Investigator) on a case report form indicates that the data therein have been reviewed and are deemed to be complete, accurate, and acceptable to me.

I have not been disqualified by any regulatory authority or otherwise disqualified from serving as a Principal Investigator, or debarred by the U.S. FDA or any other regulatory authority. In the event that during the term of the study, I become debarred, or receive notice of an action by a health authority or threat of an action with respect to my conduct of clinical research, I shall immediately notify Molecular Insight Pharmaceuticals, Inc. In the event I become debarred, I shall immediately cease all activities relating to the study.

I understand and acknowledge that confidential information related to this study includes, but is not limited to, (1) this document, (2) the Protocol for the study, (3) the data derived from the study and (4) my impressions of the progress or results of the study ("Confidential Information") all of which is the proprietary and sole property of Molecular Insight Pharmaceuticals Inc. I will comply with the terms of the Confidentiality and Non-Disclosure Agreement and Clinical Trial Agreement, which stipulate that no Confidential Information will be disclosed or generally described to anyone other than Molecular Insight Pharmaceuticals, Inc. personnel or designees, participating study staff, regulatory authorities with appropriate jurisdiction, or members of the responsible Institutional Review Board/Independent Ethics Committee. I will not use such Confidential Information for any purpose other than the evaluation or conduct of the clinical investigation. I am not presently, nor will I be during the term of the study, a consultant or advisor to any division of any financial or securities firm.

_____ _____

Investigator Signature Date

_____ _____

Investigator (Printed Name) Site Name

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19. APPENDICES

APPENDIX I

KARNOFSKY PERFORMANCE STATUS

Do not enter subjects with a Karnofsky status < 60.

KARNOFSKY PERFORMANCE STATUS	
No symptoms, fully active, able to work.	100
Able to carry on normal activity; minor signs or symptoms of disease.	90
Able to carry on normal activity with effort; some signs or symptoms of disease.	80
Cares for self, but unable to carry on normal activity or do active work.	70
Requires occasional assistance but is able to care for most of own needs.	60
Requires considerable assistance and frequent medical care.	50
Disabled; requires special care and assistance.	40
Severely disabled; hospitalization indicated, although death not imminent.	30
Very ill; hospitalization necessary; active supportive treatment required.	20
Moribund, fatal processes progressing rapidly.	10
Dead	0

APPENDIX II

SOLOWAY SCALE FOR EXTENT OF DISEASE IN THE BONE

0 No lesions
1 1-5 lesions
2 6-20 lesions
3 $\geq$ 21 lesions but not a superscan
4 Superscan.

APPENDIX III

This is a list of excluded medication that are currently known to potentially interact with Ultratrace iobenguane I 131, however, the list may not be exhaustive.

EXCLUDED MEDICATIONS DUE TO DRUG INTERACTIONS WITH ULTRATRACE I-131-MIBG	
Drug Class	**Generic Drug Name Within Class**
CNS Stimulants (Norepinephrine Reuptake Inhibitor)	Cocaine
	Dexmethylphenidate
	Methylphenidate
CNS Stimulants (Norepinephrine and Dopamine Reuptake Inhibitor)	benzphetamine
	Diethylpropion
	Phendimetrazine
	Phenteramine
	Sibutramine
Monoamine Oxidase Inhibitors	Isocarboxazid
	Linezolid
	Phenelzine
	selegiline (MAOa at doses > 15 mg qd)
	Tranylcypromine
Central Monoamine Depleting Agent	Reserpine
Non-select Beta Adrenergic Blocking Agents	labetolol
Opiod Analgesic	Tramadol
Sympathomimetics : Direct Alpha 1 Agonist (found in cough/cold preps)	Pseudoephedrine
Sympathomimetics: Amphetamines	amphetamine (various salts)
	Dextroamphetamine
	methamphetamine (desoxyephedrine)
	Lisdexamfetamine

APPENDIX III (continued)

EXCLUDED MEDICATIONS DUE TO DRUG INTERACTIONS WITH ULTRATRACE I-131-MIBG	
Drug Class	**Generic Drug Name Within Class**
Sympathomimetics: Alpha 1 Adrenergic Agonists (found in cough and cold preps)	Phenylephrine
Sympathomimetic: Alpha/Beta Agonist	Ephedrine
	Phenylpropanolamine
Sympathomimetics: Alpha 2 Adrenergic Agonists (found in eye drops and nasal sprays)	I-desoxyephedrine
	naphazoline
	Oxymetazoline
	Propylhexedrine
	Tetrahydrozoline
	Xylometazoline
Tricyclic Antidepressants and Norepinephrine Reuptake Inhibitors	Amitriptyline
	Amoxapine
	Atomoxetine
	Bupropion
	Clomipramine
	Desipramine
	Desvenlafaxine
	Doxepin
	Duloxetine
	Imipramine
	Maprotiline
	Mirtazapine
	Nefazodone
	Nortriptyline
	Protriptyline
	Trimipramine
	Venlafaxine

APPENDIX III (continued)

EXCLUDED MEDICATIONS DUE TO DRUG INTERACTIONS WITH ULTRATRACE I-131-MIBG	
Drug Class	**Generic Drug Name Within Class**
*Herbal therapy (Inhibits Reuptake of One or More; NE, 5HT, DA)	Ephedra
	ma huang
	St John's Wort
	Yohimbine
*may consider avoiding all herbal therapy unless the mechanism of action is well established.	

APPENDIX IV

QUALITY OF LIFE AND SYMPTOMS QUESTIONNAIRES

NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma

Subjects sometimes report that they have the following symptoms or problems related to their pheochromocytoma or paraganglioma. Please indicate the extent to which you have experienced these symptoms or problems related to your pheochromocytoma or paraganglioma during the last two weeks. Please answer by circling the number that best applies to you.

During the last two weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
1) Have you experienced an increase in your blood pressure?	1	2	3	4
2) Have you experienced a decrease in your blood pressure?	1	2	3	4
3) Have you experienced an increase in your heart rate?	1	2	3	4
4) Have you experienced a decrease in your heart rate?	1	2	3	4
5) Have you experienced anxiety or nervousness?	1	2	3	4
6) Have you experienced any sweating?	1	2	3	4
7) Have you experienced paleness?	1	2	3	4
8) Have you experienced any hot flashes or flushing?	1	2	3	4
9) Have you experienced any headaches?	1	2	3	4
10) Have you experienced any dizziness?	1	2	3	4
11) Have you experienced any panic attacks also known as 'sudden experience of intense anxiety'?	1	2	3	4
12) Have you experienced any tremors or shaking?	1	2	3	4
13) Have you experienced any numbness?	1	2	3	4
14) Have you experienced any nausea?	1	2	3	4
15) Have you experienced any vomiting?	1	2	3	4

NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma (continued)

During the last two weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
16) Have you experienced any weakness?	1	2	3	4
17) Have you experienced any fatigue?	1	2	3	4
18) Have you experienced increase in energy level?	1	2	3	4
19) Have you experienced a decrease in energy level?	1	2	3	4
20) Have you experienced any increase in weight?	1	2	3	4
21) Have you experienced any decrease in weight?	1	2	3	4
22) Have you experienced any warmth or heat intolerance?	1	2	3	4
23) Have you experienced any visual changes?	1	2	3	4
24) Have you experienced any changes in bowel function?	1	2	3	4
25) Have you experienced any seizures?	1	2	3	4
26) Have you experienced any pain (other than chest pain)?	1	2	3	4
27) Have you experienced chest pain?	1	2	3	4
28) Have you experienced palpitations?	1	2	3	4

At Screening #2 the additional question will be asked:

Thinking about the questions you have just answered do you think your health and quality of life has changed since you last filled in this questionnaire? □Yes □No

At Week 12, Month 6, Month 9, Month 12 the additional question will be asked:
Thinking about the questions you have just answered do you think your health and quality of life has changed since you started the study? □Not at all □ A little □ Somewhat □ A lot

EORTC QLQ-C30 Questionnaire (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____

	Not at all	**A little**	**Quite a bit**	**Very much**
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

EORTC QLQ-C30 Questionnaire (version 3) (continued)

During the past week:

16 Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

At Screening #2 the additional question will be asked

Thinking about the questions you have just answered do you think your health and quality of life has changed since you last filled in this questionnaire? ☐Yes ☐No

At Week 12, Month 6, Month 9, Month 12 the additional question will be asked
Thinking about the questions you have just answered do you think your health and quality of life has changed since you started the study? ☐Not at all ☐ A little ☐ Somewhat ☐ A lot

APPENDIX V
LISTING OF ANALGESICS, PAIN AND ANTIHYPERTENSIVE MEDICATIONS

The following lists represent examples of medications for narcotic analgesic agents and antihypertensive medications, these lists are not exhaustive.

Examples of Medications for Narcotic Analgesic Agents

High Potency (Schedule II) Single analgesic agents
- Morphine sulfate 12 hr ER
- Morphine sulfate IR
- Codeine
- Fentanyl
- Hydromorphone
- Levorphanol
- Merperidine
- Methadone
- Morphine products
- Opium tincture
- Opium
- Oxycodone
- Oxymorphone

High potency (Schedule II) combos
- Oxycodone/APAP
- Oxycodone/ASA

Lower potency single analgesic agents
- Tramadol IR or ER
- Buprenorphine injection
- Butorphanol
- Pentazocine/Naloxone
- Propoxyphene
- Nalbuphine

Lower potency combos
- Hydrocodone/APAP
- Codeine/APAP
- Codeine/APAP elixir
- Codeine/ASA
- Codeine/ASA/carisoprodol
- Codeine/caffeine/ butalbital/APAP or ASA
- Dihydrocodeine/caffeine/APA or ASA
- Pentazocine/APAP
- Propoxyphene/APAP
- Propoxyphene/ASA/ caffeine
- Tramadol/APAP

Examples of Antihypertensive Medications[30]

Class	Drug (Trade Name)	Usual Dose Range, mg/d	Usual Daily Frequency*
Thiazide diuretics			
	Chlorothiazide (Diuril)	125–500	1–2
	Chlorthalidone (generic)	12.5–25	1
	Hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5–50	1
	Polythiazide (Renese)	2–4	1
	Indapamide (Lozol†)	1.25–2.5	1
	Metolazone (Mykrox)	0.5–1.0	1
	Metolazone (Zaroxolyn)	2.5–5	1
Loop diuretics			
	Bumetanide (Bumex†)	0.5–2	2
	Furosemide (Lasix†)	20–80	2
	Torsemide (Demadex†)	2.5–10	1
Potassium-sparing diuretics			
	Amiloride (Midamor†)	5–10	1–2
	Triamterene (Dyrenium)	50–100	1–2
Aldosterone receptor blockers			
	Eplerenone (Inspra)	50–100	1
	Spironolactone (Aldactone†)	25–50	1
BBs			
	Atenolol (Tenormin†)	25–100	1
	Betaxolol (Kerlone†)	5–20	1
	Bisoprolol (Zebeta†)	2.5–10	1
	Metoprolol (Lopressor†)	50–100	1–2
	Metoprolol extended release (Toprol XL)	50–100	1
	Nadolol (Corgard†)	40–120	1
	Propranolol (Inderal†)	40–160	2
	Propranolol long-acting (Inderal LA†)	60–180	1
	Timolol (Blocadren†)	20–40	2
BBs with intrinsic sympathomimetic activity			
	Acebutolol (Sectral†)	200–800	2
	Penbutolol (Levatol)	10–40	1
	Pindolol (generic)	10–40	2
Combined α-blockers and BBs			
	Carvedilol (Coreg)	12.5–50	2
	Labetalol (Normodyne, Trandate†)	200–800	2
ACEIs			
	Benazepril (Lotensin†)	10–40	1
	Captopril (Capoten†)	25–100	2
	Enalapril (Vasotec†)	5–40	1–2
	Fosinopril (Monopril)	10–40	1
	Lisinopril (Prinivil, Zestril†)	10–40	1
	Moexipril (Univasc)	7.5–30	1
	Perindopril (Aceon)	4–8	1
	Quinapril (Accupril)	10–80	1
	Ramipril (Altace)	2.5–20	1
	Trandolapril (Mavik)	1–4	1
Angiotensin II antagonists			
	Candesartan (Atacand)	8–32	1
	Eprosartan (Teveten)	400–800	1–2
	Irbesartan (Avapro)	150–300	1
	Losartan (Cozaar)	25–100	1–2
	Olmesartan (Benicar)	20–40	1
	Telmisartan (Micardis)	20–80	1
	Valsartan (Diovan)	80–320	1–2

Examples of Antihypertensive Medications (Continued)

Class	Drug (Trade Name)	Usual Dose Range, mg/d	Usual Daily Frequency*
CCBs—Nondihydropyridines			
	Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac†)	180–420	1
	Diltiazem extended release (Cardizem LA)	120–540	1
	Verapamil immediate release (Calan, Isoptin†)	80–320	2
	Verapamil long acting (Calan SR, Isoptin SR†)	120–480	1–2
	Verapamil (Coer, Covera HS, Verelan PM)	120–360	1
CCBs—Dihydropyridines			
	Amlodipine (Norvasc)	2.5–10	1
	Felodipine (Plendil)	2.5–20	1
	Isradipine (Dynacirc CR)	2.5–10	2
	Nicardipine sustained release (Cardene SR)	60–120	2
	Nifedipine long-acting (Adalat CC, Procardia XL)	30–60	1
	Nisoldipine (Sular)	10–40	1
α_1 blockers			
	Doxazosin (Cardura)	1–16	1
	Prazosin (Minipress†)	2–20	2–3
	Terazosin (Hytrin)	1–20	1–2
Central α_2 agonists and other centrally acting drugs			
	Clonidine (Catapres†)	0.1–0.8	2
	Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly
	Methyldopa (Aldomet†)	250–1 000	2
	Reserpine (generic)	0.1–0.25	1
	Guanfacine (Tenex†)	0.5–2	1
Direct vasodilators			
	Hydralazine (Apresoline†)	25–100	2
	Minoxidil (Loniten†)	2.5–80	1–2

Examples of Antihypertensive Medications (Continued)

Combination Type	Fixed-Dose Combination, mg*	Trade Name
ACEIs and CCBs		
	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
	Enalapril-felodipine (5/5)	Lexxel
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
ACEIs and diuretics		
	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
ARBs and diuretics		
	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teveten-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Olmesartan medoxomil-hydrochlorothiazide (20/12.5, 40/12.5, 40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis-HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5, 160/25)	Diovan-HCT
BBs and diuretics		
	Atenolol-chlorthalidone (50/25, 100/25)	Tenoretic
	Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
	Metoprolol-hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
	Nadolol-bendroflumethiazide (40/5, 80/5)	Corzide
	Propranolol LA-hydrochlorothiazide (40/25, 80/25)	Inderide LA
	Timolol-hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic		
	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
	Reserpine-chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton
	Reserpine-chlorothiazide (0.125/250, 0.25/500)	Diupres
	Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic		
	Amiloride-hydrochlorothiazide (5/50)	Moduretic
	Spironolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide

APPENDIX VI
ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

System Organ Class	Event Term
Central Nervous system	Cerebral cortical atrophy
	Coma
	Demyelination
	Headaches
	Myelopathy
	Neuropsychological impairment (e.g. intellectual changes, dementia)
	Paralysis
	Symptomatic (e.g. neurological changes, seizures)
	White matter changes
	White matter necrosis
Cardiac/vascular	Angina
	Cardiac ischemia
	Cardiomyopathy
	Cor pulmonale
	Coronary artery disease
	Conduction abnormality
	Heart failure
	Hypertension
	Increased capillary permeability
	Myocarditis
	Neovascular formation
	Pericardial effusion
	Pericarditis
	Valvular heart disease
	Vascular congestion
	Vascular endothelial changes (e.g. subintimal fibrosis, lumen narrowing, etc)
	Vascular obstruction (e.g. pulmonary capillary obstruction, intracranial vascuopathy, etc)
Endocrine toxicity	Calcitonin deficiency
	Delay or failure to complete puberty
	Growth hormone deficiency
	Hypothalamic pituitary axis dysfunction
	Increased obesity (children)
	Increased prolactinemia
	Precocious puberty
	Premature menopause
	Thyroid abnormalities (hypothyroid,

	thyroiditis, etc)
Eyes and Ears	Blindness
	Cataracts
	Glaucoma
	Hearing loss
	Panophthalmitis
	Retinopathy
Gastrointestinal	Abdominal pain
	Bowel perforation
	Bowel obstruction
	Chronic atrophic gastritis
	Chronic diarrhea
	Dyspepsia
	Dysphagia
	Malabsorption
	Proctitis
	Rectal bleeding
	Rectal or anal stricture
	Separation of bowel loops (fibrosis, strictures and narrowing)
	Ulcers (e.g. peptic, duodenal, etc)
Genitourinary	Albuminuria
	Altered growth of reproductive organs
	Bladder contracture
	Cystitis
	Diminished erectile potency
	Elevated creatinine
	Elevated urea
	Hematuria
	Hypertension
	Impotency
	Renal dysfunction
	Renal failure
	Trigonal ulcer
	Urethral stricture
Head and Neck	Arytenoid edema
	Chondritis
	Fibrosis/atrophy in muscles
	Tracheal aspiration
	Voice change
	Xerostomia (permanent)
Hepatic	Abnormal liver functions tests
	Ascites
	Hepatic insufficiency

Malignancies	Bone sarcomas
	Esophageal cancer
	Leukemias
	Mesothelioma
	Myelodysplastic syndrome
	Skin cancer
	Thyroid cancer
	Other cancers
Peripheral nervous system	Numbness
	Peripheral nerve deficits
	Shock like paresthesias
Pulmonary	Bronchiolitis
	Pleural fibrosis
	Pneumonitis
	Pneumothorax
	Pulmonary failure
	Pulmonary fibrosis
	Respiratory insufficiency
Skin	Skin lesions
	Skin necrosis
Soft Tissue and bone	Atrophy
	Bone pain or tenderness
	Bone sclerosis
	Contracture
	Fibrosis or induration
	Impaired growth
	Joint stiffness
	Loss of subcutaneous tissue
	Secondary fractures

APPENDIX VII: SCHEDULE OF PROCEDURES

Procedure/Test	Screening/ Baseline	Imaging Dose/ Scans	Therapeutic Doses	Ultratrace I 131 Scan	Post Therapy I	Post Each Therapy	Post Therapy I		Long Term Follow Up* Every 6 mo
	Week -4 to Imaging Dose	Imaging Dose within 30 days of therapeutic dose	Day 0 and Month 3	Within 7 days after each therapeutic dose	Weekly through 24 Weeks	6 weeks after each therapy	Monthly post 1st Therapy	3, 6, 9 ,12 Months post 1st Therapy	Years 2 through 5 after 1st Therapy
Medical History	X								
Physical Exam/Month 12 Dry Mouth[1]	X	X	X			X (±10 days)		X	
Weight	X	X	X						
Karnofsky Performance	X		X			X (±10 days)		X	
Vital Signs[2]	X	X	X						
Blood Pressure & Heart Rate by professional staff[3]	X			X	1x a week (at weeks when not collected twice weekly through Week 24)	2X a week in the first six weeks after each dose	1x month (Months 7-12)		
Patient Self-taken Blood Pressure	Subjects will measure their blood pressure at least 1-2 times per week (preferably no more than 7 days between measurements) at the same time of day from the Screening/Baseline period through Month 12.								
Antihypertensive Status & Meds	Use of antihypertensive medication will be measured through standard, ongoing reporting of concomitant medications throughout the study								
Adverse Events[4]	AEs collected until last day of Week 15 after last dose/CM throughout the study until completion of follow-up/ AEs of Special Interest after 16 weeks after the last therapeutic dose until completion of follow-up								
Concomitant Medications	Concomitant medications taken throughout the study will be recorded								
Hematology, Chem, UA[5]	X	X	X		Week 2-Week 24	X	1x month (Months 7-12)		
TSH, T3, T4	X							X (Month 12 ONLY)	

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Procedure/Test	Screening/ Baseline	Imaging Dose/ Scans	Therapeutic Doses	Ultratrace I 131 Scan	Post Therapy I	Post Each Therapy	Post Therapy I		Long Term Follow Up* Every 6 mo
	Week -4 to Imaging Dose	Imaging Dose within 30 days of therapeutic dose	Day 0 and Month 3*	Within 7 days after each therapeutic dose	Weekly through 24 Weeks	6 weeks after each therapy	Monthly post 1st Therapy	3, 6, 9 ,12 Months post 1st Therapy	Years 2 through 5 after 1st Therapy
Renal function (GFR or 24 hr CC)[6]	X							Month 6 & 12	
Renal Volume	X								
Tumor Markers	X				Every 2 weeks during weeks 2-24		1x month (Months 7-12)		X
Pregnancy Test, serum or urine(if applicable)	X (serum)	X (urine, within 48hrs prior to dose)	X (urine, within 48 prior to dose)						
CT or MR Scan of chest, pelvis and abdomen[7]	X							X	X
Optional FDG scan	X							X	
Bone Scan[8]	X							X[8]	
ECG[9]		X		X					
Holter Monitor (24 hours)[10]			X						
SSKI Administration[11]		X (Day -2 to Day 0)	X						
Imaging Dose 3 to 6 mCi Ultratrace I 131		X							
Imaging Scans Ultratrace I 131[12] (scintigraphic)		X (3)		X					
Dosimetry Calculation for Therapy Dose		X (Day -2 to Day 0)							
Therapeutic Dose Ultratrace I 131			X(dose 1 on day 0 and dose 2 on Month 3)						
EORTC QLQ-C30[13]/NIH Pheo Clinical Questionnaire[13]	X (2)				Week 3,6,10,12,15, 18,22		Monthly Months 6-12		

*Long term follow up procedures will be performed as institutional standard of care approximately every 6 months.

[1] Physical examination will be performed during the screening period, prior to the administration of the first Imaging Dose, prior to each Therapeutic Dose, at the 6 week safety visit following each therapeutic infusion and at Months 3 (prior to the second Therapeutic Dose, if administered), 6, 9 and 12. The Physical Exam performed 6 weeks after each Therapeutic Dose administration may occur within ±10 days of the Week 6 window to accommodate potential blood count nadir or travel restrictions. Clinical evaluation for possible dry mouth will be performed at the Month 12 Efficacy Visit ONLY.

[2] Vital signs will be taken at Screening, within 4 hours prior to and within 4 hours after each Ultratrace iobenguane I 131 administration

[3] Blood pressure and heart rate should be measured every time antihypertensive therapy is changed. The professional staff (site staff or visiting nurses) will measure blood pressure and heart rate at Screening/Baseline, twice weekly in the first 6 weeks following each therapeutic dose, weekly through Week 24 (at weeks when not collected twice weekly), and monthly at Months 7 through 12. If the second therapeutic dose is delayed, the twice weekly or weekly blood measurements may occur past Week 24. The twice weekly measurements will occur for at least 6 weeks after the second therapeutic dose and the weekly measurements will continue until at least 12 weeks past the second therapeutic dose.

[4] Adverse events for non-serious AEs and SAEs will be captured from signing of ICF through the last day of Week 15 weeks after the last therapeutic dose. AEs of Special Interest will be captured 16 weeks after the administration of the last therapeutic dose until completion of the follow up period. A Safety call will be conducted 16 weeks after the last dose. If the timepoint of the 16 week Safety Call after the last therapeutic dose falls within 2 weeks of a scheduled visit, this assessment can be performed at that visit instead of through a phone call.

[5] Blood and urine samples will be collected for hematology, clinical chemistry and urinalysis within 24 hours prior to the imaging and first therapeutic Ultratrace iobenguane I 131 infusion, within 48 hours prior to the second therapeutic Ultratrace iobenguane I 131 infusion and it should be done weekly starting with Week 2 until 24 weeks following administration of the first Therapeutic Dose of Ultratrace iobenguane I 131 and continued for at least 12 weeks following administration of the second Therapeutic Dose. See Section 11.5.4 for further details.

[6] A 24 hour urine specimen creatinine clearance or GFR will be assessed for any subject who has not had a creatinine clearance or GFR within 4 weeks of screening/baseline and for all subjects at the 6 and 12 month Efficacy Visits.

[7] A CT or MR scan of chest, abdomen, and pelvis with IV contrast (unless medical condition or allergy prevents its use) will be collected at screening/baseline and should be performed within 4 weeks prior to the first Ultratrace iobenguane I 131 administration. Additionally, scans will be acquired at 3, 6, 9, and 12 months following the first Therapeutic Dose and at all follow-up visits

[8] Bone scan will be performed at screening/baseline and if probable metastatic disease is observed at Screening/Baseline these scans should be repeated at Month 3, 6, 9, 12 (see Section 11.5.11)

[9] Obtain 3 12-lead ECGs at least 5 minutes apart within 2 hours prior to the Imaging Dose, then up to 2 minutes post Imaging Dose, and at 10± 2 minutes, 15± 2 minutes, and 20 ± 2 minutes post Imaging Dose, and then within 15 minutes prior to the second and third Imaging I 131 Scans. A 12-lead ECG will be performed within 7 days post each Therapeutic Dose.

[10] Holter Monitor: A Holter monitor will be initiated between 100 minutes before to 45 minutes before each therapeutic dose administration and will be continued for approximately 23 hours after each therapeutic dose administration.

[11] SSKI: Before administration of Ultratrace iobenguane I 131, the subject's thyroidal and gastric uptake should be blocked with inorganic iodine. A representative schedule for potassium iodide (SSKI, 1 g/mL) administration can be found in Protocol Section 10.7 and represents the suggested minimum requirement. Alternatively, sites may use institutionally approved thyroid blocking protocols.

[12] Imaging Scans: Prior to the first Therapeutic Dose of Ultratrace iobenguane I 131, subjects will be given an Imaging Dose of Ultratrace iobenguane I 131, followed by three scans. Within seven days after each Therapeutic Dose of Ultratrace iobenguane I 131 subjects will have an additional Ultratrace iobenguane I 131 scan to further assess biodistribution.

[13] EORTC QLQ-C30 and NIH Pheo/Paraganglioma Questionnaire will be administered at Screening/Baseline (twice) before the first therapeutic dose, Week 3, Week 6, Week 10, Week 12, Week 15, Week 18, Week 22, and monthly from 6-12 months following the first Therapeutic Dose.

Appendix VIII

Contact Information for SAE Reporting and Adverse Events of Special Interest Reporting

[redacted]	
Address	[redacted]
Safety Email	[redacted]
Worldwide Safety Fax	[redacted]
Worldwide Safety Hotline	[redacted]
Specific country information will be provide if needed	