**Statistical Analysis Plan**

**MIP-IB12B**

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

**SAP Version 5.0**
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Author: [redacted]

Progenics Pharmaceuticals, Inc.
One World Trade Center

Reviewed by [redacted]

Progenics Pharmaceuticals, Inc.
One World Trade Center
New York, NY 10007

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event/Experience |
| AESI | Adverse Events of Special Interest |
| ALT/SGPT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST/SGOT | Aspartate Aminotransferase |
| bpm | Beats per Minute |
| BSA | Body Surface Area |
| C | Celsius |
| CR | Complete Response |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | Electrocardiogram |
| EORTC | European Organisation for Research and Treatment of Cancer |
| F | Fahrenheit |
| FDG | Fluorodeoxyglucose |
| h | Height |
| Hg | Mercury |
| HGB | Hemoglobin |
| I | Iodine |
| ICH | International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| kg | Kilogram |
| LLN | Lower Limit of Normal |
| ln | Natural Logarithm |
| mCi | Millicurie |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIBG | Metaiodobenzylguanidine |
| MIP | Molecular Insight Pharmaceuticals, Inc. |
| mL | Milliliter |
| mm | Millimeter |
| MR | Magnetic Resonance or Moderate Response (per context) |
| MRI | Magnetic Resonance Imaging |
| msec | Millisecond |
| N | Sample Size |
| NE | Not Evaluable |
| ng | Nanogram |
| NIH | National Institutes of Health |
| PD | Progressive Disease |
| PR | Partial Response |
| QoL | Quality of Life |
| RECIST | Response Evaluation Criteria in Solid Tumors |

| | |
|---|---|
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation or Stable Disease (per context) |
| SLD | Sum of Longest Diameters |
| SOP | Standard Operating Procedure |
| SSKI | Potassium Iodide |
| TEAE | Treatment-Emergent Adverse Event |
| ULN | Upper Limit of Normal |
| w | Weight |
| WBC | White Blood Cells |
| WHO | World Health Organization |

# 2. INTRODUCTION

This study is designed to study the efficacy of AZEDRA® iobenguane I 131 (or iobenguane I 131) for the treatment of relapsed/refractory malignant pheochromocytoma and paraganglioma. The purpose of this statistical analysis plan (SAP) is to specify how the data collected in this trial will be summarized and analyzed. The descriptive summaries and inferential analyses described in this SAP will provide the foundation for drawing conclusions about the outcome of the study. This SAP follows the principles set forth in E9 Statistical Principles for Clinical Trials.[1]

# 3. SCOPE

This SAP specifies the analyses that are planned prospectively for data collected in the study clinical database and provided in clinical datasets by Data Management at Molecular Insight Pharmaceuticals Inc., a wholly-owned subsidiary of Progenics Pharmaceuticals, Inc. This includes data captured on the Case Report Form (CRF), data from the clinical safety database, clinical laboratory and electrocardiogram (ECG) data provided by central labs, and image evaluation data provided by the central reviewer.

Radiation dose estimates to some normal organs (i.e., results of the pre-treatment dosimetry study) are not captured in the clinical database. Analysis of these data is the subject of a separate report.

Additional analyses of study data not pre-specified in this SAP may be performed on an ad hoc basis. If the decision is made to include additional analyses, the details will be provided in a SAP addendum prior to their conduct.

# 4. STUDY OBJECTIVES AND ENDPOINTS

## 4.1. Overview of Study

This is a multi-center, open-label, single arm study. This study was initiated in June 2009 and patient enrollment was completed in December 2015. Fifty-eight subjects were planned to be given two Therapeutic Doses each at 500 mCi (or 8 mCi/kg for subjects weighing 62.5 kg or less) of iobenguane I 131. Prior to administration of the first Therapeutic Dose, subjects will be given an Imaging Dose (3 mCi – 6 mCi) ofiobenguane 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. The Therapeutic Dose for a subject will be appropriately decreased 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 baseline, and if bone lesions are found or suspected, additional bone scans will be performed as appropriate. Overall tumor response at 3, 6, 9 and 12 months per RECIST criteria will be assessed centrally by independent, blinded readers. To assess viable tumor tissue, fluorodeoxyglucose (FDG) scans may be performed (optional, if available at study site). Tumor markers (such as serum chromogranin A [CgA]) will be evaluated by a central laboratory at intervals described in the protocol. Use and dose of antihypertensive, pain and other medication required for tumor associated signs and symptoms will be recorded on an on-going basis. Subject-reported Quality of Life (QoL) 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 in the Study Protocol. Subjects 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 (TEAEs), as well as baseline and pre- and post-infusion ECGs, physical examinations, vital signs measurements, and laboratory measurements (including clinical chemistry, hematology and urinalysis). Serious adverse events (SAEs) and non-SAEs will be collected and reported until 16 weeks following the last administration of iobenguane I 131. Adverse events of special interest (AESIs), including radiation toxicity, reported beyond 16 weeks after the last therapeutic dose of study drug will be collected during the 12 month assessment period and until completion of the follow up period.

After the 12-month assessment, subjects enter long-term follow-up and remain in follow-up for a total of 5 years following the first therapeutic dose. Subjects will be followed for AESIs and overall survival for 5 years post-treatment. 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 (to month18 only) will be collected through assessments provided by institutional standard of care.

## 4.2. Trial Objectives: Primary

The primary objective of this trial is 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 up to two Therapeutic Doses each at 500 mCi (or 8 mCi/kg, for subjects weighing

62.5 kg or less) of iobenguane I 131 administered approximately three months apart. A cycle is considered a three-month dosing interval.

## 4.3. Trial Objectives: Secondary

The secondary objectives of this trial are as follows:

- To evaluate the safety of 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 progressive disease [PD] in non-target lesions) per RECIST criteria.
- To assess status of bone lesions using the Soloway Scale.
- To assess tumor marker response in 24 hr urine and other serum tumor markers associated with pheochromocytoma/paraganglioma.
- To describe changes from baseline in the overall QoL 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.

# 5. ANALYSIS SETS

Figure 1 is a flow diagram of the protocol-defined analysis sets.

## 5.1. Enrolled Set

The Enrolled Set includes all subjects who have provided informed consent/assent. If a subject enrolled more than once in the study because of failure to meet inclusion/exclusion criteria at first entry, but met criteria at re-enrollment, the subject will only be counted once. The subject ID number and data associated with therapeutic dosing will be included within the analysis datasets. One subject (PH0408/PH0410) received an imaging dose during the first (screen failure) enrollment; that dosing will be included in the exposure data for the subject. If treatment-emergent adverse events were reported during the screen failure period for this subject, the events will also be included in both summaries and listings of adverse events.

## 5.2. Dosimetry Set/Safety Set

The Dosimetry Set/Safety Set includes all subjects who received the Imaging Dose.

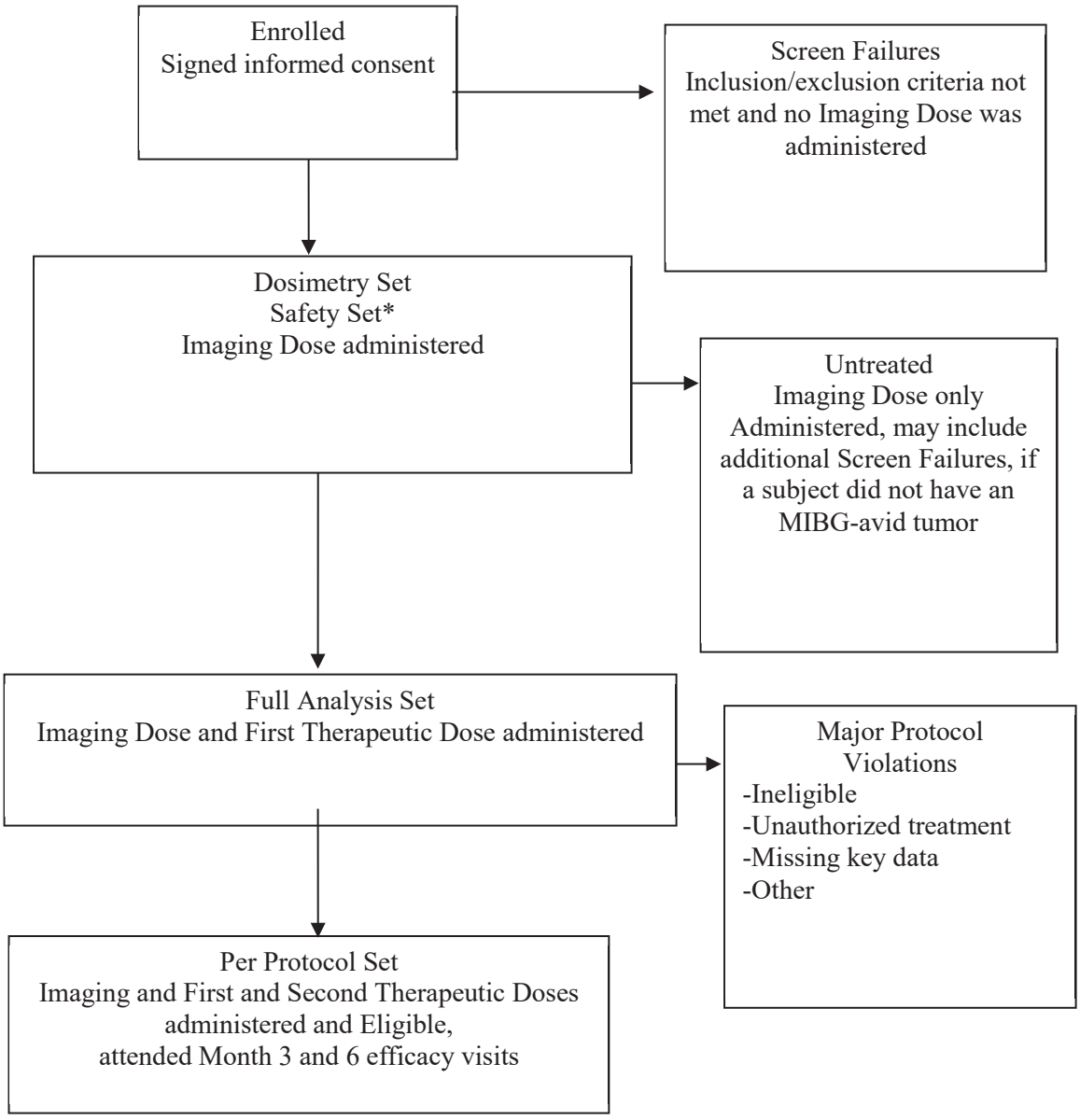
## 5.3. Full Analysis Set

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.

## 5.4. Per Protocol Set

The Per Protocol Set includes a subset of the Full Analysis Set, excluding subjects who received only one Therapeutic Dose, who did not attend the Month 3 and Month 6 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 endpoint data, received an unauthorized treatment, etc. A review of the protocol deviations will be performed prior to database lock and the listing of all major violations will be identified and included as an addendum to the Analysis Plan.

**Figure 1: Schematic of Protocol-Defined Analysis Sets**




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

# 6. DETERMINATION OF SAMPLE SIZE

The planned sample size for this study is 58 subjects, 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 a reduction (including discontinuation) of all antihypertensive medications 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 was based on a one-sided significance level of $\alpha = 0.025$ and power of 0.90 (90%).

# 7. STATISTICAL METHODS

Standard descriptive statistics will be presented for data collected. For continuous measures, the mean, standard deviation (SD), median, range and sample size (N) will be presented; for categorical measures, frequency distributions including the number of subjects and percentages in each category will be presented. Correlations between outcomes will be computed and presented as appropriate (e.g., between levels of different tumor markers). Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated two-sided 95% confidence intervals, as well as percentage of censored observations.

Numbering for tables and listings will follow the following convention: tables will be numbered 14.x.x.x and listings will be numbered 16.2.x.x.x.

Additional descriptive or inferential analyses not described in this document will be performed on an ad hoc basis.

For the purpose of calculation of the primary endpoint and tumor marker reporting, a month is defined as 28 days to be consistent with the visit schedule. For the purposes of defining the 12-month efficacy period in which the primary endpoint benefit could begin, this period is 12 calendar months. For the calculation of overall survival using Kaplan-Meier methods, a month will be defined as a calendar month or 30.25 days to approximate calendar time.

For each study variable of interest, the subsections that follow provide: when and how it is to be measured; whether it will be summarized in a table, included in listings or displayed in figures; what additional statistical analyses, if any, will be performed using the variable.

## 7.1. Visit Windows and Relative Days

The complete list of visit windows used throughout the study is provided in Appendix 1.

For efficacy summary tabulations, the visit windows will be used as they apply to the evaluation schedule for each endpoint. In the case of multiple visits per reporting window, the visit closest to the midpoint of the interval will be used for summary assessments. If there are multiple visits equally distant from the midpoint of a window, then the earlier visit will be used. These windows apply to, tumor response, bone scans, site assessment of disease, and Karnofsky performance status tumor markers.

For safety tabulations, day of measurement is computed relative to date of each dose until the next dose occurs, for example prior to the first therapeutic infusion until the second therapeutic infusion occurs, then relative to the second therapeutic infusion. These windows apply to ECGs, vital signs and labs. The visit windows for each assessment (vital signs, ECGs, laboratory tests) are specified in Appendix 1 as the scheduled evaluations vary by assessment.

ECGs will be obtained and summarized for readings within 15 minutes prior to the second and third imaging scans as well as those obtained within seven days following each therapeutic dose.

Vital signs will be summarized for readings 4 hours prior and 4 hours post each dose.

Laboratory results taken within 24 hours post imaging and first therapeutic dose and 48 hours post second therapeutic dose will be summarized in addition to those visits where the assessment are scheduled.

Relative days:

The following relative days will be computed for subjects:

For all subjects and visit dates, compute SDAY (Study day) as assessment date minus informed consent date + 1.

For subjects with at least one dose and visit dates:

- TDAYDOS1 (Treatment day from 1st dosimetry) as assessment date minus date of first dosimetry dose + 1.
- TDAYDOS2 (Treatment day from 2nd dosimetry) as assessment date minus date of second dosimetry dose + 1 for any subjects who received a second dosimetry dose.
- TDAYTX1 (Treatment day from therapeutic dose 1) as assessment date minus date of first therapeutic dose + 1; missing for subjects with only a dosimetry dose.
- TDAYTX2 (Treatment day from therapeutic dose 2) as assessment date minus date of second therapeutic dose + 1; missing for subjects with only 1 therapeutic dose and also for subjects with only a dosimetry dose.

## 7.2. Subject Disposition and Characteristics

### 7.2.1. Subject Disposition

The summary of disposition of subjects includes the number and percentage of subjects in each analysis population, subjects who completed the efficacy phase, completed long-term follow-up, and subjects discontinued from study, as well as the reason for study discontinuation and the last follow-up status (Alive, Dead). The Enrolled Set will be used for this summary (this is the only table based on the full Enrolled Set). The disposition data will be listed as well, including reasons for those subjects who did not receive a therapeutic dose of study medication.

### 7.2.2. Inclusion and Exclusion Criteria

Listings will present inclusion and exclusion criteria for each subject in the Enrolled Set.

### 7.2.3. Summary of Subject Characteristics

The following subject characteristics will be summarized in a table: demographics, baseline characteristics, medical history, cancer diagnosis, sites of metastases as identified from pre-treatment CT/MR and bone scans (lung, liver, abdomen other than lung, pelvis, bone, other) and the number and percentage of subjects receiving different types of prior cancer treatment (radiation, drug or biologic, surgical). Previous exposure to I 131 MIBG, identified in the subject's cancer history, whether by participation in an earlier study of iobenguane I 131 or other I 131 MIBG preparations will be summarized and presented in a listing. The Safety Set will be used for this summary.

#### 7.2.3.1. Demographics and Baseline Characteristics

Demographics (sex, race and ethnicity) and baseline characteristics (age at enrollment [defined as age=floor((intck('month', birthdate, consentdate) – (day(consentdate) < day(birthdate)))/12) ]), height at screening, weight at screening and body surface area) will be summarized and listed.

#### 7.2.3.2. Cancer Diagnosis, Medical History and Prior Cancer Treatment

Cancer diagnosis and sites of metastases will be summarized by the number and percent of subjects reporting the preferred term using Medical Dictionary for Regulatory Activities® (MedDRA) version 19.0 and listed. Medical history data and prior cancer treatments will be tabulated and provided in listings. This information will be summarized for the Safety Set.

## 7.3. Subject Medications and Study Drug Administration

### 7.3.1. Study Drug Administration/Exposure

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 each 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/m2) using the DuBois formula:

$$BSA = w^{0.425} \times h^{0.725} \times 0.007184,$$

where w is body weight in kilograms and h is height in centimeters. The amount of the Imaging Dose will be presented as absolute amount of radioactivity (mCi). The total exposure for each subject (defined as the sum of all therapeutic and imaging doses) will be summarized. For subjects who received more than one imaging dose, all doses of study drug will be included in that subject's total exposure.

The injection volume (mL) will be summarized for each dose and for the sum of the two therapeutic doses.

Dosing will be tabulated by the number of doses received (imaging and therapeutic doses), the time in days from the imaging to the first therapeutic dose, and the time in months from the first to the second therapeutic dose.

### 7.3.2. Concomitant and Prior Medications, other than Antihypertensives

Concomitant medications and prior medications will be coded according to the World Health Organization (WHO) Drug Dictionary v. March 2016 and summarized in tables by ATC4 code as well as in listings.

Medications will be assigned to one or more study periods (prior medications or concomitant medications) based on the medication start and stop dates relative to the study drug dosing. For example, medications that were started and stopped before the date of the imaging dose will be classified as prior medications only, while medications started before the imaging dose and either stopped after the imaging dose or indicated as "ongoing" will be assigned as both prior and concomitant medications. Medications started on or after the date of the imaging dose will be

classified as concomitant medications. A given medication can therefore be assigned to one or more study periods in the tabular summaries, depending on its start and end dates.

Because antihypertensive medications are a measure of efficacy in this study, they will be tabulated and listed separately. Medications that could be used to treat hypertension, but were being used to treat other non-hypertensive indications, will be listed under the concomitant and prior medications listing rather than the hypertensive medication listing. Analgesic medications reported for treatment of tumor pain will also be tabulated and listed separately.

### 7.3.3. SSKI Administration

In addition to being included in the listing of concomitant medications, administration of potassium iodide (SSKI) administered corresponding with each dose of iobenguane I131 will be presented in a separate listing.

## 7.4. Efficacy

The primary efficacy endpoint in this study is the proportion of subjects with a reduction (including discontinuation) of all antihypertensive medications by at least 50% for at least six months or two cycles of iobenguane I131.

The Full Analysis Set will be used in the primary analysis and the Per Protocol Set will be used in the secondary analysis of the primary endpoint.

### 7.4.1. Primary Analysis: Reduction in Use of Antihypertensive Medication

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 of iobenguane I 131. The 50% reduction is determined separately for each baseline medication, based on the total daily dose of the antihypertensive medication(s) on the day of the first therapeutic dose.

A benefit duration period is measured by maximum duration as follows. The benefit duration period commences when the subject's medication is reduced to a level below 50% of baseline, and continues until the subject's medication rises above 50% of baseline, until the onset of a new antihypertensive medication of >14 days' duration, or to the last subject date as described in section 7.4.2, Primary Endpoint Calculation. A benefit duration period must begin during the 12-Month Efficacy Phase but may end during the Long-term Follow-up Phase. If the subject discontinues participation in the study before the Month 12 efficacy evaluation, the last date for calculation of the duration of benefit is the date of termination in the study.

For purposes of illustration, the following examples are provided (Month refers to the number of 28-day months after the first Therapeutic Dose).

- Example 1: A subject 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 subject 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. Even though the subject 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 subject experiences the benefit from the beginning of Month 2 to the beginning of Month 9. At Month 10, the subject receives another anticancer treatment and is discontinued from the study. Since the maximum duration of the benefit was 7 months, prior to discontinuation, the subject is considered a success on the primary endpoint.

For the primary analysis of the primary endpoint, a point estimate (with a 95% confidence interval, calculated using the Agresti-Coull method) for the proportion of subjects in the Full Analysis Set with a reduction (including discontinuation) of all antihypertensive medications 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 this two-sided 95% confidence interval exceeds 0.10 (10%).

A listing of response to treatment (yes/no) with supporting information (antihypertensive medications with their dates of use, doses and relative change from baseline) will be presented.

Use of antihypertensive medication over time will be presented graphically by subject. These figures will include the mean systolic and diastolic blood pressure measurements from healthcare providers (either at site visits or at the subject's home) for each visit window. This information will also be presented in a data listing.

### 7.4.2. Calculation of the Primary Endpoint

Criteria for Meeting the Primary Endpoint

Subjects must:

1. Receive an Imaging Dose
2. Receive at least one Therapeutic Dose
3. Have a reduction of each pre-therapeutic dosing (baseline) antihypertensive medication ≥50% for a minimum of six consecutive months beginning during the 12-Month Efficacy Phase of the study, during which no new, long-term antihypertensive medication is introduced and maintained for longer than 14 days.

Considerations

1. The introduction of a new, transient (i.e., duration ≤ 14 days) antihypertensive medication regimen at any point during the study will not disqualify a subject from being able to achieve the primary efficacy endpoint. Short duration therapy may be instituted to address an acute increase in blood pressure that might be associated with a transient increase in catecholamine release secondary to a variety of factors including tumor cell death. On the contrary, the primary outcome measures chronic control of hypertension necessitated by long term catecholamine secretion by the active tumor.
2. A transient (i.e., duration ≤ 14 days) dose increase over the baseline dose of an existing antihypertensive medication regimen at any point during the study will not disqualify a subject from being able to achieve the primary endpoint. Existing antihypertensive therapy may be increased for a short duration to address an acute increase in blood pressure that might be

associated with a transient increase in catecholamine secretion secondary to a variety of factors including tumor cell death.

3. The introduction of a new, long-term (i.e., duration > 14 days) antihypertensive medication regimen after receiving a therapeutic dose will disqualify a subject from being able to achieve the primary endpoint while the subject is still taking any dose of the new medication. If the new long-term antihypertensive medication is discontinued, the start date for assessment of the primary endpoint is the date when both the new medication is discontinued and the baseline antihypertensive medications are reduced ≥50%.
4. New long-term antihypertensive medications introduced before Therapeutic Dose #1 is administered are considered part of the baseline antihypertensive medication regimen that must be reduced by at least 50% for achieving primary endpoint.
5. A long-term (i.e., duration > 14 days) increase in dose over the baseline dose of an existing antihypertensive medication regimen after receiving a therapeutic dose will not disqualify a subject from being able to achieve the primary endpoint if all antihypertensive medications are reduced to a level of 50% or below the baseline dose for at least six consecutive months in duration, since the increase may have been made before a tumor response was obtained. The introduction of a new antihypertensive medication with a duration of >14 days will be considered as the end of a benefit duration period. The start date for the duration of response is the date that the last antihypertensive medication is reduced to the level of 50% or below the baseline dose.
6. The introduction of an antihypertensive medication regimen or increase in existing antihypertensive medication regimen that occurs after the subject has already met the primary endpoint (i.e., had a ≥50% reduction of all antihypertensive medications for at least six consecutive months) will not disqualify the subject from achieving the primary endpoint.

Calculation of Duration of Response

The six-month duration of the primary endpoint response begins on the date during the 12-Month Efficacy Phase when all baseline antihypertensive medications have been reduced by at least 50% and any new medications are discontinued (the date post- therapeutic dosing when the reduction of the last antihypertensive medication reduced by at least 50% or the new medication is discontinued) and ends once six consecutive months (i.e., 168 days) duration of sustained ≥ 50% reduction has been achieved, regardless of the phase of the study during which the end date of the response occurs (i.e., 12-Month Efficacy Phase vs. Long-Term Follow-Up Phase).

The end date for which the duration of the ≥50% reduction of all antihypertensive medications is determined as the earlier of:

a. the date that the subject no longer meets the criteria of having a ≥50% reduction of all baseline antihypertensive medications (i.e., the starting date of a new long-term continuing antihypertensive medication or a dose change in an existing regimen of antihypertensive medication that exceeds the ≥50% reduction of the baseline dose that is greater than 14 days in duration and continues without a reduction to the ≥50% level)

   OR

b. the date of the subject's last applicable recorded study-related disposition date. If the subject has discontinued the study prior to the end of the 12-Month Efficacy Phase due to any of the following reasons:

- Withdrew consent
- Was lost to follow-up
- Death
- Withdrew due to progressive disease
- Received other anticancer therapy
- Experienced an adverse event resulting in study discontinuation

The last participation date is the corresponding disposition date within the 12-Month Efficacy Phase (i.e., date that the subject withdrew consent, was lost to follow-up, died, withdrew due to disease progression, received other anticancer therapy, or experienced an adverse event resulting in study discontinuation).

If the subject has completed the 12-Month Efficacy Phase but continues to meet the criteria of having a ≥50% reduction of all antihypertensive medications, the last applicable disposition date would be the long-term follow-up completion/discontinuation date.

### 7.4.3. Reduction in Use of Antihypertensive Medications for the Per Protocol Set

The primary analysis will be repeated, using only those subjects in the Per Protocol Set.

### 7.4.4. Other Analyses of Reduction in Use of Antihypertensive Medications

Other analyses of use of antihypertensive medications will include descriptions of the maximum duration of benefit (reduction by at least 50%) beginning during the 12-Month Efficacy Phase, and the proportion of subjects discontinuing all antihypertensive medications completely for at least 6 months beginning during the 12-Month Efficacy Phase. Additional correlations between relative changes in antihypertensive medications and other endpoints may be performed as exploratory analyses. The Spearman correlation coefficient will be reported for any exploratory analyses.

### 7.4.5. Objective Radiologic Tumor Response

Objective tumor response and overall tumor response will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0)[2], with the additional category of moderate response, defined below. The RECIST system is described in full in the paper by Therasse et al.[2], an abbreviated description is provided below.

At baseline, a maximum of 5 lesions per organ and 10 lesions in total are identified on CT/MRI scans as target lesions and recorded and measured. The 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 objective tumor response. 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. All bone lesions are considered to be non-target lesions.

Objective tumor response criteria for target lesions are as follows:

| Response | Criteria for Response |
|---|---|
| Complete Response (CR)* | Disappearance of all target lesions |
| Partial Response (PR)* | Decrease of at least 30% in the SLD, taking as reference the baseline SLD |
| Moderate Response (MR)* | Decrease of at least 15% but at most 29% in the SLD, taking as reference the baseline SLD |
| Stable Disease (SD) | Changes do not meet the criteria for CR, PR, MR or PD |
| Progressive Disease (PD) | Increase of at least 20% in SLD, taking as reference the smallest SLD recorded since treatment started |

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

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

| Response | Criteria for Response |
|---|---|
| Complete Response (CR)* | 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 |

* To be assigned a status of CR changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than four weeks after the criteria for response are first met.
† For bone lesions, at least two new lesions will be required for a finding of disease progression.

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 PR, CR or MR changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than four weeks after the criteria for response are first met.
† For bone lesions, at least two new lesions will be required for a finding of disease progression.

Radiologic assessments will be listed by target, non-target, and bone (also considered non-target) lesions, for each reviewer, and the case selected by the adjudicator if there was a discrepant result for the overall tumor response. A frequency distribution table will be provided showing, by visit, target, non-target and overall response. This summary will exclude the MR category above (patients with Stable Disease (SD) with a reduction of sum of LD of at least 15% but <30%) as these patients will be classified as SD. A separate summary will be based on the modified RECIST criteria, and will include the MR category. The best overall tumor response using RECIST criteria and best overall tumor response using modified RECIST criteria will also be presented by primary endpoint response status.

The results of the imaging scans including lesion status (e.g., measurable) and tumor size by longest diameter will be listed. A waterfall plot of the greatest decline in the sum of the longest diameters of the target lesions will be presented.

### 7.4.6. Bone Lesions

Findings of bone scans will be assessed using the Soloway Scale (0 = No lesions, 1 = 1-5 lesions, 2 = 6-20 lesions, 3 = ≥21 lesions but not a superscan, 4 = superscan). The Soloway Scores by visit will be summarized using descriptive statistics. The number of subjects with bone lesions only (no measurable soft tissue lesions) will also be summarized as frequency distributions at each visit. A shift table of Soloway Scores by study visit against the baseline scores for Months 3, 6, 9, and 12 will be prepared. Soloway Scores for each subject will also be listed.

### 7.4.7. Tumor Markers

Tumor markers (e.g., serum chromogranin A) will be assessed as stated in the Schedule of Procedures. For each individual tumor marker, results will be categorized per the response criteria in the following table. If the tumor marker value prior to dosing is less than 1.5 times the upper limit of normal for the respective marker, it will not be included in this analysis.

| **Response** | **Criteria for Response** |
|---|---|
| Complete Response (CR)* | Normalized, at or below upper limit of normal (ULN) |
| Partial Response (PR)* | ≥50% decrease in baseline value but above the ULN |
| Stable Disease (SD) | Any response other than CR, PR or PD |
| Progressive Disease (PD) | ≥50% increase in baseline value |
| Not Evaluable (NE) | Below 1.5 X ULN at baseline, or baseline missing |

* To be assigned a status of CR or PR changes in tumor marker measurements must be confirmed by repeat assessments

For the Full Analysis Set, summary tables for confirmed tumor marker response, for each marker, will be prepared by visit window and all measurements of tumor markers will be listed. A confirmed response will require that the subsequent tumor marker assessment be identical or better compared with the previous response assessment.

Subjects will be evaluated to determine the best confirmed response for each tumor marker that is ≥ 1.5 x ULN at baseline. A listing of the best confirmed response for each tumor marker, at what time it becomes apparent, and the duration of any positive response (CR or PR) will be generated. The response is considered to be ended when the tumor marker response becomes confirmed at SD or PD.

Each subject will also be evaluated to determine if that subject is an overall tumor marker responder. An overall responder will be a subject who achieves a best confirmed response of either CR or PR at some time point, on each of the plasma and urine tumor markers that were abnormal at baseline, with the exception of urine VMA.

An additional analysis will be performed where the tumor marker response will be summarized for the dominant tumor marker for each subject. The dominant tumor marker will be identified prior to database lock by the Medical Monitor.

Analysis will determine if there is an association between achieving an overall best tumor marker response of CR or PR with achieving primary endpoint responder status based on the reduction in antihypertensive medications.

Additional correlations between tumor marker responses and other endpoints may be performed as exploratory analyses.

Correlations using the tumor marker response for each tumor marker will be performed at the 3, 6, 9, and 12 month visit windows. These correlations are listed below.

- Tumor marker responses among the different tumor markers.
- Tumor marker response and overall unmodified RECIST response will also be performed: tumor response will be coded as 1 (CR), 2 (PR), 3 (SD), and 4 (PD).
- An additional analysis, tabulating the best overall confirmed tumor marker response and best overall RECIST response through 12 months post first therapeutic dose, will also be performed. For this analysis, the best overall confirmed tumor marker response and the best overall RECIST tumor response will be treated as binary variables, with responses of CR and PR combined as a positive response and SD and PD combined as a negative response.

Spearman correlation coefficients will be reported for all correlations, and Fisher's exact test will be used for binary response comparisons.

For the purposes of tabulations, tumor marker evaluations where there is a comment that the value is above or below the clinical reportable range will be set to the upper or lower limit of normal as applicable.

### 7.4.8. Symptom Response/Quality of Life

A symptom response instrument will be used to evaluate symptoms specific to NIH Quality of Life and Symptoms Questionnaire for Pheochromocytoma and Paraganglioma. The questionnaire is administered twice during the baseline period prior to the first therapeutic dose. The results of the two responses will be averaged by item and will be treated as the baseline values. Results by item will be summarized for the Full Analysis Set, and questionnaire data will be listed.

The EORTC QLQ-C30 v.3[3] will be used to evaluate QoL. The questionnaire is administered twice during the baseline period prior to the first therapeutic dose. The last non-missing values obtained closest to dosing will be treated as the baseline values. The results of QoL and changes from baseline will be summarized by visit and domain across the Full Analysis Set and will be listed. This data will be summarized as follows: Global Health Status/Quality of Life, Functional Scales, and Symptom Scales. The best response within 12 months after first therapeutic dose will also be reported.

### 7.4.9. Tumor Pain Medicine

Pain medication used to relieve tumor pain will be defined as medication identified in the case report form to relieve tumor pain.

A shift table for tumor pain medication usage by subject will be presented by visit, with pain medication usage categorized into three intensity levels: any opioid use, other pain medication use, and no pain medication use. This categorization will be made based on usage at 3 months (91 days), 6 months (182 days), 9 months (273 days), and 12 months (365 days) post first therapeutic dose. Analgesics identified for other uses will not be included in this summary.

A separate listing of analgesic medications other than those used for tumor pain reduction will be provided.

### 7.4.10. Karnofsky Performance Status

Karnofsky Performance Status (KPS) score will be summarized using descriptive statistics and listed at each time point assessed. A stacked bar chart illustrating the distribution of KPS scores at baseline, 3 months, 6 months, 9 months, and 12 months post first therapeutic dose will be provided for the Full Analysis Set.

### 7.4.11. Overall Survival

Overall survival (OS) is defined as the time from the date of first therapeutic dose to the date of death from any cause. OS time will be censored at the last date the subject is known to be alive. The Kaplan-Meier predicted survival rates at Years 1-5 will be reported. Overall survival will be listed and Kaplan-Meier curves will be prepared. The last date that the patient was confirmed to be alive will be obtained from information reported by the clinical site: if this information is collected outside of the CRF the last date the subject is known to be alive or date of death reported from the site will be provided in a spreadsheet and integrated into analysis datasets.

Overall survival will also be presented by primary endpoint status.

### 7.4.12. Site Assessment of Disease

A clinical assessment of subject status is performed during office visits. This information will be provided in a data listing.

### 7.4.13. Viable Tumor Tissue (exploratory)

Results of FDG PET assessments will be listed for those subjects who underwent the scans.

## 7.5. Safety

Safety analyses will include TEAEs, clinical laboratory measurements, vital signs measurements, ECGs, and physical examination findings. The Safety Set will be used in all analyses of safety. However, those in the Safety Set who are lacking follow-up for safety will not be included when computing incidence of AEs, because their inclusion would dilute the percentages of subjects with AEs or laboratory toxicities.

### 7.5.1. Adverse Events

TEAEs are defined as AEs whose onset dates are on or after the first administration of any amount of study drug to the end of 15 weeks after the administration of the last therapeutic dose of iobenguane I 131. If the onset date is incomplete, then assessment will be made based on available information (i.e., comparing available onset month and year). If the onset date is incomplete and assessment could not be made based on the available information (for example, year is missing) then the AE will be considered as TEAE. Events that resolve prior to date of the first dose of study drug will not be considered as TEAEs regardless of completeness of the onset date. In all table summaries, only TEAEs will be presented. All AEs will be presented in listings, regardless of whether they are treatment-emergent.

All adverse events that are neither serious adverse events nor adverse events of special interest reported with start dates on or after the first day of week 16 following the last therapeutic dose will be presented in a summary table and will be included in the listing of all adverse events.

For subjects who discontinue participation in the study due to receiving another anticancer therapy, all adverse events reported with start dates after the initiation date of the new therapy but prior to the last day of week 15 after the last therapeutic dose will be summarized separately. These events will also be included in the overall adverse event summaries. These events will be flagged in the listings of adverse events.

AEs were originally coded according to system organ class and preferred term using MedDRA version 12, and were recoded to MedDRA version 19.1 for analysis. The AE terms were graded for severity according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3).

### 7.5.2. Relationship of Adverse Events to Study Drug

TEAEs will be summarized by relationship to study drug (related/not related). If a subject experienced more than one TEAE within a preferred term or system organ class, the more related TEAE will be presented at each level of summarization. If the relationship is missing, then 'Related' will be used for the summary table, and the relationship in the listing will be presented as missing.

### 7.5.3. Severity of Adverse Event

The number of subjects with AEs and number of subjects under each system organ class and preferred term will be summarized by severity (grade 1 = mild AE, grade 2 = moderate AE, grade 3 = severe AE, grade 4 = life-threatening or disabling AE, grade 5 = death related to AE). If a subject experienced more than one TEAE within a preferred term or system organ class, the TEAE with the most extreme severity will be presented at each level of summarization. If the severity is missing, then 'grade 3' will be used for the summary table, and the severity in the listing will be presented as missing. The summary table will also include a row indicating the number of missing severity ratings.

Separate from the listing of all AEs, additional summary tabulations will present all grade 3/4 TEAEs, and all grade 3/4 TEAEs where the relationship to drug is related (or is missing).

A horizontal bar chart will be created using most frequent AEs (≥20%) experienced by subjects by incidence rate. The bars for AEs will be sorted in descending sequence of the incidence rate, e.g., an AE with the highest incidence rate will appear at the top; an AE with the second highest incidence rate will appear next and so on. This chart will be limited to TEAEs.

### 7.5.4. Serious Adverse Events

SAEs are any untoward medical occurrences that meet any of the criteria for SAEs as described in the protocol. The number of subjects with at least one Treatment Emergent SAE and the number of subjects under each body system and preferred term will be tabulated by relation to study drug for the Safety Set. All SAEs will be included in the listing of AEs. Two additional listings will be provided: one including all SAEs, and one including all SAEs where the relationship to drug is Related (or is missing).

### 7.5.5. Hematologic Adverse Events

AEs of a hematologic nature are of particular interest in this study. However, similar hematologic AEs are often coded under different preferred terms (e.g., 'leukopenia' and 'white blood cell count decreased'). An additional summary of hematologic events categorized as either grade 3, grade 4, or as SAEs, combining such similar preferred terms, will be presented. The following preferred terms are classified as hematologic AEs. This list may be updated prior to database lock and analysis if additional preferred terms are reported.

- 'Anaemia'
- 'Anaemia macrocytic'
- 'Febrile neutropenia'
- 'Haemolytic anaemia'
- 'Haematocrit decreased'
- 'Haemoglobin decreased'
- 'International Normalised Ratio Increased'
- 'Leukopenia'
- 'Leukocytosis'
- 'Lymphopenia'
- 'Lymphocyte count decreased'
- 'Lymphocyte percentage decreased'
- 'Monocyte count decreased'
- 'Monocyte count increased'
- 'Eosinophil count decreased'
- 'Neutropenia'
- 'Neutrophil count increased'
- 'Neutrophil percentage increased'
- 'Pancytopenia'
- 'Red blood cell count decreased'
- 'Thrombocytopenia'
- 'Platelet count decreased'
- 'Platelet count increased'
- 'Mean platelet volume decreased'
- 'Neutrophil count decreased'

- 'Neutrophil percentage decreased'
- 'White blood cell count decreased'
- 'Prothrombin time prolonged'

### 7.5.6. All Deaths during the Study

All deaths reported during the study will be reported in a separate listing. This listing will include the period of death (during the efficacy phase or during the follow-up phase), date of death, relative day of death relative to the first therapeutic dose, and the cause of death.

### 7.5.7. Adverse Events Resulting in a Discontinuation in Study Treatment

Adverse events where the action taken is a discontinuation of study treatment will be reported in a separate listing.

### 7.5.8. Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are defined in the protocol as being any serious or nonserious event of scientific or medical concern specific to iobenguane I 131 reported beyond 16 weeks after the last therapeutic dose of study drug, and have been associated with long term radiation toxicity. This list will be updated prior to database lock and analysis if additional preferred terms are reported. AESIs are to be captured in the safety database along with SAEs. A separate analysis will be performed for AESIs outside of the analyses already defined for SAEs. Each AESI is to be written up in the Clinical Study Report (CSR) (Section 10.3.3: Narratives of Deaths and Other Serious and Certain Other Adverse Events).

The events of special interest indicated in Protocol Section 12.1.2.1 with an onset beyond 16 weeks after the last therapeutic dose of study drug will be summarized and reported in a separate listing.

### 7.5.9. Clinical Laboratory Evaluations

Blood and urine samples will be collected for hematology, clinical chemistry and urinalysis as described in the protocol, at time points described in the protocol.

Numeric hematology and clinical chemistry laboratory results will be presented using SI units.

All individual laboratory values will be listed with occurrence of values above and below the normal reference range.

Pregnancy test results will be reported in a separate listing.

Hematology and clinical chemistry laboratory values and change from Screening values will be summarized by study visit window.

For those parameters that have CTCAEv3 criteria, shift tables showing changes in CTCAEv3 grade from baseline to the worst grade post Screening will be presented. Parameters with CTCAEv3 criteria defined bi-directionally will have low value abnormalities represented by a negative sign so that they may be differentiated from high value abnormalities. If the CTCAEv3 criteria are unidirectional the negative sign will not be used even if the criteria were defined to flag low value abnormalities.

An additional indicator of drug-induced liver injury will be presented. A listing will be prepared of all subjects who received a dose of study drug and met Hy's Law following dosing. The criteria for Hy's Law are either AST or ALT > 3X the upper limit of normal (ULN) coincident with ALP < 2XULN and total bilirubin > 2XULN.[4]

The number of subjects with post-Screening CTC grade 3/4 labs will be summarized.

Additional listings will be provided for four hematological parameters: WBC, HGB, absolute neutrophils, and platelets. These listings will provide, by therapeutic dose, screening values, nadir values/grade, time to nadir value, and time to recovery (grade ≤1) post nadir value. Figures will be produced by subject for absolute neutrophils and platelets.

Renal function testing was performed for the subjects. For most subjects either glomerular filtration rate (GFR) or serum creatinine clearance was reported. For some subjects, only 24-hour urine creatinine was reported and will be used to evaluate renal function if either GFR or serum creatinine clearance was not reported. If the urine creatinine clearance values were reported in units other than mL/min or cannot be converted into units of volume/time, then those records will be treated as unevaluable (missing).

An estimated creatinine clearance may be calculated based on serum creatinine, urine creatinine and urine volume. Serum creatinine values within 7 days prior to urine collection may be combined with the urinalysis parameters. Renal function based on estimated creatinine clearance values will be categorized as normal (≥90 ml/min), mild decrease in GFR (60-89 ml/min), moderate decrease in GFR (30-59 ml/min), severe decrease in GFR (15-29 ml/min) and end stage renal disease (<15 ml/min not on dialysis or requiring dialysis). A shift table of creatinine clearance from Baseline to the 12-month endpoint will be provided.

### 7.5.10. Vital Signs Measurements

Vital signs (blood pressure, pulse, temperature and respiration) will be collected at the time points listed in the protocol. All vital signs measurements will be provided in listings. The listing will include all measurements recorded during the study, with a column included for origin (e.g., health care provider vs. subject measurement).

Summary statistics of vital signs and the changes from Screening will be presented in the table by visit according to its respective visit window. Pre-dose to post-dose changes for each administration of iobenguane I 131 will also be summarized.

Heart rate and blood pressure measurements are recorded both by healthcare providers and by the subjects, as indicated in the protocol. The results from the healthcare providers at site visits or at the subjects' homes will be combined for each subject for sitting and supine positions and respective visit window as indicated in Appendix 1. This table will exclude blood pressure readings by subjects themselves. The recordings done by the subjects themselves were used to help guide the investigators in management of anti-hypertensive medications, but were not intended to be included in the vital sign data set. The mean values for each subject and time point will be used as the basis of the summaries. Summary statistics for heart rate and blood pressure results and their respective changes from baseline will be prepared.

Subjects who develop changes from Screening or values of potential clinical importance will be tabulated by study visit and overall, and will be flagged in the subject data listings. Criteria will be as follows:

- Systolic BP increase or decrease >20 mmHg
- Diastolic BP increase or decrease >10 mmHg
- Pulse rate increase or decrease >20 bpm
- Temperature >38.0ºC or >100.4ºF

Vital signs obtained within 24 hours of administration of the study drug will also be flagged if the change in BP or pulse rate specified above occurred compared to the vital signs obtained 30 minutes pre-administration.

By-subject figures for systolic and diastolic BP measurements for sitting and supine positions combined relative to days post first therapeutic infusion, along with antihypertensive medication dose, will be provided as indicated in Section 7.4.2. Two set of figures will be provided: one set will exclude measurements obtained by the subject. The other set will present the measurements obtained by the subjects.

### 7.5.11. 12-Lead Electrocardiograms

Quantitative parameters of ECGs (heart rate and length of RR-, PR-, QT-, QTcB, QTcF- and QRS-intervals) will be presented. The average of the three 12-lead ECGs acquired pre-Imaging injection will be used as Baseline. Post Baseline quantitative parameters and changes from Baseline will be summarized by study visits and time points:

- Following the Imaging dose at 10± 2 minutes, 15±2 minutes, and 20 ± 2 minutes, and within 15 minutes prior to the second and third Imaging I 131 Scans.
- Within 7 days following each Therapeutic Dose.

Changes from baseline of potential clinical importance will be tabulated by study visit window and will be flagged in the subject data listings. Criteria will be as follows:

- Heart Rate: Increase >20 bpm
  Decrease >20 bpm
- PR Interval: Increase >30 msec
  Decrease >30 msec
- QRS Width: Increase >16 msec
  Decrease >16 msec
- QT, QTcB, QTcF Interval: Increase 31–60 msec
  Increase > 60 msec
  Decrease 31–60 msec
  Decrease >60 msec
  > 450 msec - 480 msec
  > 480 msec - 500 msec
  > 500 msec

Qualitative findings, including evaluation of ST-segments and all abnormalities indicated on the assessments following dosing that were not noted at baseline will be listed.

### 7.5.12. 24-hour Electrocardiogram Monitoring at Therapeutic Dosing

At the time of therapeutic dosing, 24-hour Holter ECG monitoring is performed. The data from these assessments will be summarized for each dosing period.

ECGs will be summarized including changes from the respective predose baseline values. The baseline values are defined as the average of the two readings obtained prior to dosing for results. The following time points are assessed following each therapeutic dose:

- 2 minutes post dosing
- 10 minutes post dosing
- 1 hour post dosing
- 22 hours post dosing

All analyses listed above in Section 7.5.11 for 12-lead ECG data will be performed for the 24-hour Holter monitoring data at these time points.

### 7.5.13. Pregnancy Test

Results of pregnancy tests will be presented in the listing of laboratory results.

### 7.5.14. Physical Examinations

Physical examination findings will be presented in the listings.

### 7.5.15. Dosimetry

Analysis of dosimetry data will be the subject of a separate report.

## 7.6. 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 the primary analysis.

Subjects who receive the study agent but have no follow-up for safety will not be included when computing incidence of AEs 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.

Incomplete medication start and end dates are handled as follows: a missing start month is imputed as June and a missing end month is imputed as December. A missing start and end date are imputed as the last day of the month. If only the year is provided, the start date would be imputed as June 30 and the end date would be imputed as December 31. If the assignment of a missing start or end date conflicts with the available reported data, then the assigned dates will be modified. All modifications will be identified in data listings.

For anti-hypertensive medications, if the start year cannot be determined, this medication should be considered a baseline medication unless the end year is present and prior to the first therapeutic dose of iobenguane I 131.

## 7.7. Procedures for Handling Dose and Dosing Frequency (Anti-hypertensive and Pain Medications)

In order to standardize the reporting of doses and dose frequency, all unique values of these fields from the raw concomitant medication dataset will be exported to an Excel spreadsheet where the total daily dose will be added to create a coded dataset. The Excel sheet will be prepared by the Sponsor and used in the creation of analysis datasets. This standardization will be applied to medications identified as anti-hypertensive medications on the CRF and, separately, to medications identified as analgesics with indications for pain relief

## 7.8. Subgroup Analyses

The following subgroups will be used for selected analysis including primary and additional efficacy analyses, overall survival and treatment-emergent adverse events:

- Number of therapeutic doses (0, 1 or 2).
- Baseline factors, such as location of metastases (lung and/or liver vs no lung or liver metastases).
- Any prior MIBG/Azedra treatment (yes or no) as recorded in the cancer history case report form.

## 7.9. Sensitivity Analysis

A sensitivity analysis will be performed on the primary endpoint where at least six months of the duration of clinical benefit is required to be completed within the 12-month efficacy period. An additional sensitivity analysis will treat subjects who begin a new antihypertensive medication following therapeutic dosing that continues for at least 14 days as non-responders.

## 7.10. Statistical Software Used in Data Analysis

All data listings, tables, and figures described in this SAP will be produced using SAS®, Version 9.3 or higher. All statistical analyses described in this SAP (not including those for dosimetry) will be produced using SAS®, Version 9.3 or higher. Informal or ancillary analyses may be performed with alternate software (such as R).

# 8. CONCLUSION

This SAP includes a description of the pre-specified plans for key analyses of the data collected in clinical trial MIP-IB12B. Additional data analyses not described in this document will be performed on an ad hoc basis.

# 9. CHANGES FROM VERSION 1.0 OF SAP

The following are a summary of changes from those specified in Version 1.0 of the SAP (16 November 2009). Additional changes from Version 3.0 to 4.0 of this SAP are indicted at the end of this table.

| Section | Version | Change |
|---|---|---|
| 5.1 | 5.0 | Clarification of handling of subjects with multiple enrollments |
| 6 | 5.0 | Removal of identification of per-protocol population |
| 7.0 | 2.0 | Time to event analyses added to statistical methods section. |
| 7.0 | 5.0 | Clarification of period definitions |
| 7.2.4 | 2.0 | New section added to reference imaging listings. |
| 7.1 | 4.0 | Addition of visit windows for summaries |
| 7.3.1 | 2.0 | Clarifications and additional details added to define algorithms for primary endpoint duration and for 50% reduction in antihypertensive medication use. |
| 7.2.3.2 | 5.0 | Update in MedDRA dictionary version |
| 7.3.2 | 5.0 | Update in WHO Drug Dictionary version |
| 7.3.4 | 2.0 | Listing of tumor response, clinical benefit status, and % change in CgA added. |
| 7.3.6 | 2.0 | Correlations between tumor change from baseline and tumor response, and among tumor markers added. |
| 7.3.7 | 3.0 | Section for tumor marker trend analysis deleted, all subsequent sections renumbered. |
| 7.3.8 | 3.0 | NIH Questionnaire reporting limited to reporting by item by visit. |
| 7.3.9 | 2.0 | Shift tables of pain medication use added. Comparisons of changes in potency using narcotic to NSAID conversions deleted. |
| 7.3.11 | 2.0 | Overall survival algorithm changed to reference date of first therapeutic dose as opposed to informed consent date. |
| 7.3.12 | 2.0 | New section added for site assessment of disease. |
| 7.4.1 | 5.0 | Definition of end of assessment period for subjects who terminate the study early, clarification of blood pressure measurements to be presented in figures by subject, clarification of clinical benefit period. |
| 7.4.2 | 5.0 | Added section with calculation of the primary endpoint, which was Appendix 1. |
| 7.4.4 | 3.0 | Threshold for reporting most frequent adverse events increased to 20% from 5%. |
| 7.4.5 | 5.0 | Clarification of objective tumor response criteria |
| 7.4.7 | 5.0 | Clarification of tumor marker analyses, change in correlation measures from percent change from baseline to tumor marker response, addition of a binary response comparison |
| 7.4.8 | 5.0 | Change in definition of baseline values |
| 7.4.9 | 2.0 | Added reporting for estimated creatinine clearance, including classification of values into estimates of renal function added. |
| 7.4.9 | 2.0 | Added by subject listings of nadir values by therapeutic dose for WBC, HGB, absolute neutrophils, and platelets. |
| 7.4.9 | 2.0 | Plots of ALT and AST deleted. |
| 7.5.10 | 5.0 | Clarification of summaries blood pressure results |
| 7.5.1 | 5.0 | Clarification of adverse event dictionary coding |
| 7.5.5 | 4.0 | Updated listing of hematologic adverse events |
| 7.5.8 | 5.0 | Clarification that final list of events may be updated |
| 7.5.9 | 5.0 | Addition of analysis to detect drug-induced liver injury; clarification of assessments of renal function |

| | | |
|---|---|---|
| 7.5.10 | 5.0 | Clarification of summaries of blood pressure results and presentations of the results |
| 7.5.11 | 5.0 | Clarification of ECG changes of clinical importance |
| 7.6 | 5.0 | Clarification on date imputations |
| 7.8 | 4.0, 5.0 | Updated subgroup analyses |
| 7.9 | 4.0, 5.0 | Added sensitivity analyses |
| 10 | 5.0 | Added a reference |
| Appendix 1 | 5.0 | Removed Appendix 1, moved to section 7.4.2 |
| Appendix 1 | 5.0 | Revised Appendix 1, was Appendix 2 |
| Appendix 2 | 5.0 | Added Appendix 2, was Appendix 3, updated with terms to be included for analysis |

# 10. REFERENCES

1. Guidance of Industry E9 Statistical Principles for Clinical Trials, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) September 1998 ICH.
2. Therasse P, Arbuck S, Eisenhauer E, Wanders J, Kaplan R, Rubinstein L, Verwiej J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New Guidelines to Evaluate the Response to Treatment in Solid Tumors, *Journal of the National Cancer Institute* (2000); 92, 205-16.
3. Aaronson NK, Ahmedzai S, Bergman B, Bulinger M, Cull A, Duez NJ, Filberti A, Fletchner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-30: a quality-of-life instrument for use in international clinical trials in oncology, *Journal of the National Cancer Institute* (1999); 85, 365-76.
4. Guidance for Industry Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009)

# 11. LIST OF PLANNED TABLES, LISTINGS AND FIGURES

The tables, listings and figures listed below will be prepared in accordance with the descriptions provided in this SAP.

**Tables:**

| | |
|---|---|
| Table 14.1.1 | Disposition (Population: Enrolled) |
| Table 14.1.2 | Subject Characteristics (Population: Safety) |
| Table 14.1.3 | Medical History (Population: Safety) |
| Table 14.1.4 | Cancer History (Population: Safety) |
| Table 14.15 | Prior Treatment for Cancer (Population: Safety) |
| Table 14.2.1.1A | Primary Endpoint: Decrease in Use of Antihypertensive Medications (Population: Full Analysis Set) |
| Table 14.2.1.1B | Primary Endpoint: Decrease in Use of Antihypertensive Medications (Population: Per Protocol Set) |
| Table 14.2.1.1C | Primary Endpoint: Decrease in Use of Antihypertensive Medications: Sensitivity Analysis (Population: Full Analysis Set) |
| Table 14.2.1.1D | Primary Endpoint: Decrease in Use of Antihypertensive Medications: Sensitivity Analysis (Population: Full Analysis Set) |
| Table 14.2.1.2A | Duration of Clinical Benefit (Population: Full Analysis Set) |
| Table 14.2.1.2B | Duration of Clinical Benefit (Population: Per Protocol Set) |
| Table 14.2.2.1 | Tumor Response Assessment per RECIST Criteria (Population: Full Analysis Set) |
| Table 14.2.2.2 | Tumor Response Assessment per RECIST Criteria Modified to Include Moderate Response (Population: Full Analysis Set) |
| Table 14.2.2.3 | Tumor Response Assessment per RECIST Criteria by Primary Endpoint Status (Population: Full Analysis Set) |
| Table 14.2.2.4 | Tumor Response Assessment per RECIST Criteria Modified to Include Moderate Response by Primary Endpoint Status (Population: Full Analysis Set) |
| Table 14.2.2.3 | Bone Lesions (Population: Full Analysis Set) |
| Table 14.2.2.4 | Bone Lesions: Shift from Baseline by Visit |
| Table 14.2.3.1 | Tumor Marker Response Proportions (Population: Full Analysis Set) |
| Table 14.2.3.2 | Tumor Marker Response Proportions by Dominant Tumor Marker (Population: Full Analysis Set) |
| Table 14.2.3.3 | Spearman Correlation between Tumor Marker Response Proportions and relative change in tumor marker by Tumor Marker (Population: Full Analysis Set) |
| Table 14.2.3.4 | Spearman Correlation between Tumor Marker Response Proportions & Overall Tumor Response (Population: Full Analysis Set) |
| Table 14.2.35 | Spearman Correlation between Response Proportions & Best Overall Tumor Response (Population: Full Analysis Set) |
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# APPENDIX 1. VISIT WINDOWS

These windows are intended for data summaries by time point. When multiple assessments fall within a window, the assessment closest to the nominal time will be used in summaries. If there are multiple visits equally distant from the midpoint of a window, then the earlier visit will be used.

**Efficacy Assessments**

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| 1 | **Overall Tumor Response (CT/MRI Scans)** | Screening / Baseline (Day -28 to Day 0) | Month 3 (Day 81 - Day 101) | |
| | | | Month 6 (Day 173 - Day 193) | |
| | | | Month 9 (Day 264 - Day 284) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | Month 18 (Day 518 - Day 578) | |
| | | | Month 24 (Day 700 - Day 760) | |
| | | | Month 30 (Day 883 - Day 943) | |
| | | | Month 36 (Day 1065 - Day 1125) | |
| | | | Month 42 (Day 1248 - Day 1308) | |
| | | | Month 48 (Day 1430 - Day 1490) | |
| | | | Month 54 (Day 1613 - Day 1673) | |
| | | | Month 60 (Day 1795 - Day 1855) | |
| | | | | |
| 2 | **Tumor Markers** | Screening / Baseline (Day -28 to Day 0) | Week 2 (Day 8 - Day 14) | |
| | | | Week 4 (Day 22 - Day 28) | |
| | | | Week 6 (Day 36 - Day 42) | |
| | | | Week 8 (Day 50 - Day 56) | |
| | | | Week 10 (Day 64 - Day 70) | |
| | | | Week 12 (Day 78 - Day 84) | |
| | | | Week 14 (Day 92 - Day 98) | |
| | | | Week 16 (Day 106 - Day 112) | |
| | | | Week 18 (Day 120 - Day 126) | |
| | | | Week 20 (Day 134 - Day 140) | |
| | | | Week 22 (Day 148 - Day 154) | |
| | | | Week 24 (Day 162 - Day 168) | |
| | | | Month 7 (Day 203 - Day 223) | |

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| | | | 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) | |
| | | | Month 18 (Day 518 - Day 578) | |
| | | | Month 24 (Day 700 - Day 760) | |
| | | | Month 30 (Day 883 - Day 943) | |
| | | | Month 36 (Day 1065 - Day 1125) | |
| | | | Month 42 (Day 1248 - Day 1308) | |
| | | | Month 48 (Day 1430 - Day 1490) | |
| | | | Month 54 (Day 1613 - Day 1673) | |
| | | | Month 60 (Day 1795 - Day 1855) | |
| | | | | |
| **3** | **Soloway Score (Bone Scan) and optional FDG-PET Scan** | Screening / Baseline (Day -28 to Day 0) | Month 3 (Day 81 - Day 101) | |
| | | | Month 6 (Day 173 - Day 193) | |
| | | | Month 9 (Day 264 - Day 284) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | | |
| **4** | **Karnofsky Performance** | Screening / Baseline (Day -28 to Day 0) | Day 1 | Day 1 |
| | | | Week 6 ± 10 days (Day 32 - Day 52) | Week 6 ± 10 days (Day 32 - Day 52) |
| | | | Month 3 (Day 81 - Day 101) | |
| | | | Month 6 (Day 173 - Day 193) | |
| | | | Month 9 (Day 264 - Day 284) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | | |
| **5** | **Symptom Response (NIH Pheochromocytoma Clinical Questionnaire) and EORTC QLQ-30 Questionnaire** | Screening / Baseline (Day -28 to Day 0)<br>Note: two assessments are to be performed prior to the first therapeutic dose within this window | Week 3 (Day 15 - Day 21) | |
| | | | Week 6 (Day 36 - Day 42) | |
| | | | Week 10 (Day 64 - Day 70) | |
| | | | Week 12 (Day 78 - Day 84) | |
| | | | Week 15 (Day 99 - Day 105) | |
| | | | Week 18 (Day 120 - Day 126) | |
| | | | Week 22 (Day 148 - Day 154) | |
| | | | Month 6 (Day 173 - Day 193) | |
| | | | Month 7 (Day 203 - Day 223) | |
| | | | Month 8 (Day 233 - Day 253) | |

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| | | | Month 9 (Day 264 - Day 284) | |
| | | | Month 10 (Day 294 - Day 314) | |
| | | | Month 11 (Day 325 - Day 345) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | | |
| **6** | **Tumor Pain Medication** | | Month 3 (Day 81 - Day 101) | |
| | | | Month 6 (Day 173 - Day 193) | |
| | | | Month 9 (Day 264 - Day 284) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | | |

## Safety Assessments

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| **1** | **Vital Signs (pulse, temperature, respiration)** | Screening / Baseline (Day -28 to Day 0) | | |
| | | Day 1: 4 hours prior | Day 1: 4 hours prior | Day 1: 4 hours prior |
| | | Day 1: 4 hours post | Day 1: 4 hours post | Day 1: 4 hours post |
| | | | | |
| **2** | **Vital Signs (body weight)** | Day 1: prior to dosing | Day 1: prior to dosing | Day 1: prior to dosing |
| **3** | **Vital Signs (BP and heart rate by Health Staff and Subject Readings)** | Screening / Baseline (Day -28 to Day 0) | | |
| | | Day 1: 4 hours prior | Day 1: 4 hours prior | Day 1: 4 hours prior |
| | | Day 1: 4 hours post | Day 1: 4 hours post | Day 1: 4 hours post |
| | | | Week 1 (Day 2 - Day 7) 2x week | Week 1 (Day 2 - Day 7) 2x week |
| | | | Week 2 (Day 8 - Day 14) 2x week | Week 2 (Day 8 - Day 14) 2x week |
| | | | Week 3 (Day 15 - Day 21) 2x week | Week 3 (Day 15 - Day 21) 2x week |
| | | | Week 4 (Day 22 - Day 28) 2x week | Week 4 (Day 22 - Day 28) 2x week |
| | | | Week 5 (Day 29 - Day 35) 2x week | Week 5 (Day 29 - Day 35) 2x week |
| | | | Week 6 (Day 36 - Day 42) 2x week | Week 6 (Day 36 - Day 42) 2x week |
| | | | Week 7 (Day 43 - Day 49) | Week 7 (Day 43 - Day 49) |
| | | | Week 8 (Day 50 - Day 56) | Week 8 (Day 50 - Day 56) |
| | | | Week 9 (Day 57 - Day 63) | Week 9 (Day 57 - Day 63) |
| | | | Week 10 (Day 64 - Day 70) | Week 10 (Day 64 - Day 70) |
| | | | Week 11 (Day 71 - Day 77) | Week 11 (Day 71 - Day 77) |

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| | | | Week 12 (Day 78 - Day 84) | Week 12 (Day 78 - Day 84) |
| | | | Week 13 (Day 85 - Day 91) | Week 13 (Day 85 - Day 91) |
| | | | Week 14 (Day 92 - Day 98) | Week 14 (Day 92 - Day 98) |
| | | | Week 15 (Day 99 - Day 105) | Week 15 (Day 99 - Day 105) |
| | | | Week 16 (Day 106 - Day 112) | Week 16 (Day 106 - Day 112) |
| | | | Week 17 (Day 113 - Day 119) | Week 17 (Day 113 - Day 119) |
| | | | Week 18 (Day 120 - Day 126) | Week 18 (Day 120 - Day 126) |
| | | | Week 19 (Day 127 - Day 133) | Week 19 (Day 127 - Day 133) |
| | | | Week 20 (Day 134 - Day 140) | Week 20 (Day 134 - Day 140) |
| | | | Week 21 (Day 141 - Day 147) | Week 21 (Day 141 - Day 147) |
| | | | Week 22 (Day 148 - Day 154) | Week 22 (Day 148 - Day 154) |
| | | | Week 23 (Day 155 - Day 161) | Week 23 (Day 155 - Day 161) |
| | | | Week 24 (Day 162 - Day 168) | Week 24 (Day 162 - Day 168) |
| | | | 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) | |
| | | | | |
| **4** | **ECG and 24-Hour Holter Monitoring** | Day 1: 2 hours prior (triplicate ECG) | Day 1 (24-hr Holter monitoring to begin between 100 to 45 minutes prior to dosing and to continue for approximately 23 hours following dosing) | Day 1 (24-hr Holter monitoring to begin between 100 to 45 minutes prior to dosing and to continue for approximately 23 hours following dosing) |
| | | up to 2 minutes post | Week 1 (Day 2 - Day 8) | Week 1 (Day 2 - Day 8) |
| | | 10 $\pm$ 2 minutes post | | |
| | | 15 $\pm$ 2 minutes post | | |
| | | 20 + 2 minutes post | | |
| | | within 15 minutes prior to imaging scans 2 and 3 | | |
| | | | | |
| **5** | **Hematology, Chemistry & Urine Analysis** | Screening / Baseline (Day -28 to Day 0) | Day 1 within 24 hr prior | Day 1 within 48 hr prior |
| | | Day 1 within 24 hr prior | Week 2 (Day 8 - Day 14) | Week 2 (Day 8 - Day 14) |
| | | | Week 3 (Day 15 - Day 21) | Week 3 (Day 15 - Day 21) |

| No | End Point | From Imaging Dose 1 | From Therapeutic Dose 1 | From Therapeutic Dose 2 |
|---|---|---|---|---|
| | | | Week 4 (Day 22 - Day 28) | Week 4 (Day 22 - Day 28) |
| | | | Week 5 (Day 29 - Day 35) | Week 5 (Day 29 - Day 35) |
| | | | Week 6 (Day 36 - Day 42) | Week 6 (Day 36 - Day 42) |
| | | | Week 7 (Day 43 - Day 49) | Week 7 (Day 43 - Day 49) |
| | | | Week 8 (Day 50 - Day 56) | Week 8 (Day 50 - Day 56) |
| | | | Week 9 (Day 57 - Day 63) | Week 9 (Day 57 - Day 63) |
| | | | Week 10 (Day 64 - Day 70) | Week 10 (Day 64 - Day 70) |
| | | | Week 11 (Day 71 - Day 77) | Week 11 (Day 71 - Day 77) |
| | | | Week 12 (Day 78 - Day 84) | Week 12 (Day 78 - Day 84) |
| | | | Week 13 (Day 85 - Day 91) | |
| | | | Week 14 (Day 92 - Day 98) | |
| | | | Week 15 (Day 99 - Day 105) | |
| | | | Week 16 (Day 106 - Day 112) | |
| | | | Week 17 (Day 113 - Day 119) | |
| | | | Week 18 (Day 120 - Day 126) | |
| | | | Week 19 (Day 127 - Day 133) | |
| | | | Week 20 (Day 134 - Day 140) | |
| | | | Week 21 (Day 141 - Day 147) | |
| | | | Week 22 (Day 148 - Day 154) | |
| | | | Week 23 (Day 155 - Day 161) | |
| | | | Week 24 (Day 162 - Day 168) | |
| | | | 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) | |
| | | | | |
| **6** | **Renal Function** | Screening / Baseline (Day -28 to Day 0) | Month 6 (Day 173 - Day 193) | |
| | | | Month 12 (Day 355 - Day 375) | |
| | | | | |
| **7** | **TSH, T3. T4** | Screening / Baseline (Day -28 to Day 0) | Month 12 (Day 355 - Day 375) | |
| | | | | |

# APPENDIX 2. ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)

| Body System | Event Term |
|---|---|
| | Demyelination |
| | Myelopathy |
| | Dementia |
| | White matter changes |
| Cardiac/Vascular | Angina |
| | Cardiac ischemia |
| | Cardiomyopathy |
| | Myocarditis |
| Endocrine Toxicity | Gonadal insufficiency |
| | Oligospermia |
| | Amenorrhea |
| | Hypothalamic pituitary dysfunction |
| | Increased follicle stimulating hormone |
| | Increased luteinizing hormone |
| | Graves' disease |
| | Hypothyroidism |
| Gastrointestinal | Bowel obstruction |
| | Chronic gastritis |
| | Chronic diarrhea |
| | Dysphagia |
| | Rectal bleeding |
| Genitourinary | Bladder contracture |
| | Cystitis |
| | Elevated creatinine |
| | Erectile dysfunction |
| | Hematuria |
| | Renal dysfunction (failure) |
| Head and Neck | Dry mouth |
| | Salivary gland dysfunction |
| | Lacrimal gland dysfunction |
| | Xerostomia |
| Hepatic | Abnormal liver functions tests |
| | Acute liver necrosis |
| | Hepatic insufficiency |
| Malignancies | Bone sarcomas |
| | Schwannoma |
| | Leukemias |
| | Angiomatoid fibrous histiocytoma |
| | Myelodysplastic syndrome |
| | Rhabdomyosarcoma |

| **Body System** | **Event Term** |
|---|---|
| | Thyroid cancer |
| | Other cancers |
| Musculoskeletal | Bone pain or tenderness y |
| | Fibrosis |
| | Secondary fractures |
| Peripheral Nervous System | Neuropathy |
| | Paresthesias |
| Pulmonary | Bronchiolitis |
| | Bronchiolitis obliterans organizing pneumonia (BOOP) |
| | Pneumonitis |
| | Respiratory insufficiency |
| Skin | Skin lesions |
| | Alopecia (hair loss) |