**Clinical Study Protocol No. IRP101-301 (NANT 2020-01*)**

**IND No. 146379**

**Clinicaltrials.gov NCT: 04724369**

# A Prospective Phase 3 Multi-center Study to Assess the Efficacy and Safety of $^{18}$F-*m*FBG PET Imaging in Subjects with Neuroblastoma

**(*Developed with the Cooperation of the New Approaches to Neuroblastoma Therapy (NANT) Consortium)**

| | |
|---|---|
| Phase: | 3 |
| Investigational Product: | IRP101 [$^{18}$F-*m*FBG (meta-fluorobenzylguanidine)] |
| Sponsor: | Innervate Radiopharmaceuticals LLC |
| Medical Monitor: | Arnold F Jacobson, MD, PhD<br>c/o 175 Elm Road, Englewood NJ 07631<br>808-856-1406 |
| Principal Investigator: | Neeta Pandit-Taskar, MD |
| IRP Protocol Version No. | 4.0 Revised to incorporate Amendment 03<br>3.0 Revised to incorporate Amendment 02<br>2.0 Revised to incorporate Amendment 01 |

Effective Date v4.0: 05 April 2023

Pharmacovigilance and Clinical CRO: Avance Clinical LLC

113 Cherry St. #77114

Seattle, WA 98104

safety@avancecro.com

Fax: +1-206-299-9118

**Confidential**

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the express written consent of Innervate

Radiopharmaceuticals. The Study will be conducted according to the International Council on Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice (ICH GCP).

**PROTOCOL SIGNATURE PAGE**

**Protocol Number:** **IRP101-301 (NANT 2020-01)**
**Version 4.0, Amendment 03**

**Protocol Title:** **A Prospective Phase 3 Multi-center Study to Assess the Efficacy and Safety of $^{18}$F-*m*FBG PET Imaging in Subjects with Neuroblastoma**

**Approving Officers:**

Arnold F Jacobson, MD, PhD
Chief Medical Officer

DocuSigned by Arnold Jacobson MD, PhD
Arnold F Jacobson
I approve this documen
4/5/2023 | 3:57:00 PM P
150DD1B58020486D89F0369549FB8481

Thomas Tulip, PhD
Chief Scientific Officer

DocuSigned by Thomas Tulip PhD
I approve this doc
4/5/2023 | 6:36:11
5344B4BF319D421FB0E2828E952A009E

# INVESTIGATOR DECLARATION

**Protocol Title: A Prospective Phase 3 Multi-center Study to Assess the Efficacy and Safety of $^{18}$F-*m*FBG PET Imaging in Subjects with Neuroblastoma**

| DECLARATION |
| --- |
| By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, *Institutional Review Board* (*IRB*) procedures, instructions from Innervate Radiopharmaceuticals LLC. representatives, the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and local regulations governing the conduct of clinical studies. |

_____ _____

**Investigator Signature** **Date**

_____

***Printed Name of Investigator***

_____

**Institution name**

## Table of Contents

**TABLE OF CONTENTS** ..... 4
**LIST OF TABLES** ..... 8
**LIST OF FIGURES** ..... 8
**LIST OF ABBREVIATIONS** ..... 9
**1 PROTOCOL SUMMARY** ..... 11
**1.1 Synopsis** ..... 11
**1.2 Figure 1: Schema** ..... 17
**1.3 Schedule of Activities (SoA)** ..... 18
**2 INTRODUCTION** ..... 20
**2.1 Study Rationale** ..... 20
**2.2 Background** ..... 21
**2.3 Risk/Benefit Assessment** ..... 23
**2.3.1 Known Potential Risks** ..... 23
2.3.1.1 Possible Risks and Side Effects: $^{123}$I-*m*IBG ..... 24
**2.3.2 Known Potential Benefits** ..... 24
**2.3.3 Assessment of Potential Risks and Benefits** ..... 25
**3 OBJECTIVES AND ENDPOINTS** ..... 26
**3.1 Primary Objective and Endpoints** ..... 26
**3.2 Secondary Objectives and Endpoints** ..... 26
**3.3 Tertiary / Exploratory Objectives and Endpoints** ..... 26
**4 STUDY DESIGN** ..... 27
**4.1 Overall Design** ..... 27
**4.2 Scientific Rationale for Study Design** ..... 27
**4.3 Justification for Dose** ..... 28
**4.4 End of Study Definition** ..... 28
**5 STUDY POPULATION** ..... 29
**5.1 Inclusion Criteria** ..... 29
**5.2 Exclusion Criteria** ..... 29
**6 STUDY INTERVENTION** ..... 31
**6.1 Study Intervention(s) Administration** ..... 31
**6.1.1 Study Intervention Description** ..... 31
6.1.1.1 Imaging Procedures ..... 31
6.1.1.2 Image Handling and Data Transfer ..... 31
**6.1.2 Dosing and Administration** ..... 33
**6.1.3 Clinical Follow-up** ..... 34
**6.2 Preparation / Handling / Storage / Accountability** ..... 34
**6.2.1 Acquisition and Accountability** ..... 34
**6.2.2 Formulation, Appearance, Packaging and Labelling** ..... 35

**6.2.3 Product Storage and Stability....35**
**6.2.4 Preparation....35**
**6.3 Measures to Minimize Bias: Randomization and Blinding....35**
**6.3.1 Method of Assigning Subjects Numbers....36**
**6.3.2 Expert Panel....36**
**6.3.3 Independent Image Review....36**
**6.4 Study Intervention Compliance....37**
**6.5 Concomitant Therapy....37**
**6.5.1 Rescue Medications....37**
**6.5.2 Prohibited Medications....37**
**7 STUDY INTERVENTION, DISCONTINUATION, AND PARTICIPATION....39**
**7.1 Discontinuation of Study Intervention....39**
**7.2 Participant Discontinuation / Withdrawal from Study / Rescreening....39**
**7.3 Lost to Follow-up....40**
**8 STUDY ASSESSMENTS AND PROCEDURES....41**
**8.1 Efficacy Assessments....41**
**8.1.1 Onsite assessment of imaging data....41**
8.1.1.1 Exploratory Assessment of Potential Impact of $^{18}$F-*m*FBG Image Findings....43
**8.1.2 Offsite assessment of imaging data....43**
**8.1.3 Standard of Reference (SoR)....44**
**8.2 Safety and Other Assessments....45**
**8.2.1 Clinical Laboratory Evaluation....47**
**8.2.2 Vital signs....48**
**8.2.3 Electrocardiograms (ECGs)....49**
8.2.3.1 ECG core laboratory responsibilities....49
**8.2.4 Physical examination....49**
**8.2.5 Discharge Procedures....50**
**8.3 Adverse Events and Serious Adverse Events....50**
**8.3.1 Definitions of Adverse Events....50**
**8.3.2 Definition of Serious Adverse Events (SAEs)....50**
**8.3.3 Classification of an Adverse Event....51**
8.3.3.1 Intensity of an Adverse Event....51
8.3.3.2 Relationship to Study Intervention....51
8.3.3.3 Expectedness....52
**8.3.4 Time Period and Frequency for Event Assessment and Follow-up....52**
**8.3.5 Adverse Event Reporting....52**
**8.3.6 Serious Adverse Event Reporting....53**
**8.3.7 Reporting Events to Investigators....54**
**8.3.8 Events of Special Interest....54**

8.3.8.1 Injection site monitoring ..... 54
8.3.8.2 Clinical Laboratory Abnormalities as AEs ..... 55
8.3.8.3 Vital Sign Abnormalities as AEs ..... 56
8.3.8.4 ECG Abnormalities as AEs ..... 56
8.3.8.5 Physical Examination Abnormalities as AEs ..... 57
**8.3.9 Reporting of Pregnancy ..... 57**
**8.4 Unanticipated Problems ..... 57**
**8.4.1 Definition of Unanticipated Problems (UPs) ..... 57**
**8.4.2 Unanticipated Problem Reporting ..... 57**
**8.4.3 Reporting Unanticipated Problems to Participants ..... 58**
**9 STATISTICAL CONSIDERATIONS ..... 59**
**9.1 Statistical Hypotheses ..... 59**
**9.2 Sample Size Determination ..... 59**
**9.3 Populations for Analyses ..... 60**
**9.4 Statistical Analyses ..... 61**
**9.4.1 General Approach ..... 61**
**9.4.2 Analysis of Primary Efficacy Endpoint(s) ..... 62**
**9.4.3 Analysis of Key Secondary Efficacy Endpoint ..... 63**
9.4.3.1 Additional efficacy analyses and summaries ..... 63
**9.4.4 Other Analyses ..... 63**
9.4.4.1 Inter-reader variability ..... 63
9.4.4.2 Intra-reader variability ..... 64
**9.4.5 Safety Analyses ..... 64**
9.4.5.1 Clinical laboratory evaluation ..... 65
9.4.5.2 Vital signs ..... 65
9.4.5.3 Electrocardiograms (ECGs) ..... 65
*9.4.5.3.1 QTc-specific analyses:* ..... *66*
9.4.5.4 Physical examination ..... 66
9.4.5.5 Injection site reactions ..... 66
9.4.5.6 Adverse events ..... 66
**9.4.6 Baseline Descriptive Statistics ..... 67**
**9.4.7 Planned Interim Analyses ..... 67**
**9.4.8 Subgroup Analyses ..... 67**
**9.4.9 Tabulation of Individual Participant Data ..... 67**
**9.4.10 Exploratory Analyses ..... 67**
**10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ..... 69**
**10.1 Regulatory, Ethical and Study Oversight Considerations ..... 69**
**10.1.1 Informed Consent Process ..... 69**
10.1.1.1 Consent Procedures and Documentation ..... 69

**10.1.2 Study Discontinuation and Closure ..... 69**
**10.1.3 Confidentiality and Privacy ..... 70**
**10.1.4 Future Use of Data ..... 70**
**10.1.5 Key Roles and Study Governance ..... 71**
**10.1.6 Safety Oversight ..... 71**
**10.1.7 Clinical Monitoring ..... 71**
**10.1.8 Quality Assurance and Quality Control ..... 72**
**10.1.9 Data Handling and Record Keeping ..... 72**
10.1.9.1 Data Collection and Management Responsibilities ..... 72
10.1.9.2 Study Records Retention ..... 73
**10.1.10 Protocol Deviations ..... 73**
**10.1.11 Publication and Data Sharing Policy ..... 73**
**10.1.12 Conflict of Interest Policy ..... 73**
**10.2 Additional Considerations ..... 74**
**10.2.1 Insurance ..... 74**
**10.2.2 BIE Manual ..... 74**
**10.2.3 Charter for the Expert Panel ..... 74**
10.2.3.1 Membership ..... 74
10.2.3.2 Committee Process ..... 75
10.2.3.3 Meeting Format ..... 75
10.2.3.4 Reports ..... 76
10.2.3.5 Sponsor Responsibilities ..... 76
10.2.3.6 Confidentiality ..... 76
**10.3 Revision History ..... 76**
**11 REFERENCES ..... 84**
**12 ACTIVITY ADMINISTRATION GUIDELINES FOR PEDIATRIC SUBJECTS ..... 87**

## List of Tables

Table 1: Study Schedule of Events ..... 18
Table 2: Anatomic Grid Location for Observed Abnormalities ..... 41
Table 3: Organ/Organ System Listing ..... 42
Table 4: Study Procedures by Period ..... 46
Table 5: Laboratory Parameters ..... 48
Table 6: Sample Size Calculation ..... 59
Table 7: Formulas for Calculating Endpoints ..... 61

## List of Figures

1.2 Figure 1: Schema ..... 17
Figure 2: Interpretation of Injection Site Findings in Conjunction with the Clinical Situation of the Subject ..... 55
Figure 3: Interpretation of Safety Monitoring Results in Conjunction with the Clinical Situation of the Subject ..... 56

## List of Abbreviations

| | |
|---|---|
| AE | Adverse event |
| BIE | Blinded Image Evaluation |
| BPM | Beats per minute |
| C | Celsius |
| CI | Confidence intervals |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case report form |
| CT | Computed tomography |
| d | Day |
| DBP | Diastolic blood pressure |
| DICOM | Digital Imaging and Communication in Medicine |
| dL | Deciliter |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| F | Fahrenheit |
| FDA | Food and Drug Administration |
| FDG | Fluorodeoxyglucose |
| FN | False negative |
| FP | False positive |
| FTP | File transfer protocol |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GFP | Ground Fluor Pharmaceuticals |
| hr | Hour |
| ICH | International Conference on Harmonisation |
| ICL | Imaging Core Laboratory |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug application |
| IRB | Institutional/Independent Review Board |
| IRP | Innervate Radiopharmaceuticals |
| $^{18}$F-*m*FBG | meta-fluorobenzylguanidine ($^{18}$F) |
| $^{123}$I-*m*IBG | meta-iodobenzylguanidine ($^{123}$I) |
| keV | kiloelectron volt |

| | |
|---|---|
| kg | Kilogram |
| MBq | Megabecquerel |
| mCi | Millicurie |
| MedDRA | Medical Dictionary of Regulatory Activities |
| mg | Milligram |
| m | Minutes |
| mmHg | Millimeters of Mercury |
| MR or MRI | Magnetic resonance imaging |
| msec | Milliseconds |
| MSKCC | Memorial Sloan Kettering Cancer Center |
| NDA | New Drug Application |
| NE | Norepinephrine |
| NIH | National Institutes of Health |
| NPA | Negative Predictive Agreement |
| PET | Positron Emission Tomography |
| PPA | Positive Predictive Agreement |
| RR | Respiration rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SoA | Schedule of Activities |
| SOPs | Standard operating procedures |
| SoR | Standard of Reference |
| SPECT | Single photon emission computed tomography |
| SUV | Standardized Uptake Value |
| TBR | Target-to-Background Ratio |
| TN | True negative |
| TP | True positive |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

| | |
|---|---|
| **Study Title:** A Prospective Phase 3 Multi-center Study to Assess the Efficacy and Safety of $^{18}$F-*m*FBG PET Imaging in Subjects with Neuroblastoma | |
| **Name of Product:** $^{18}$F-*m*FBG | |
| **Study Number:** IRP-301 | **Study Phase:** 3 |
| **Clinical Sites:** Multi-center | |
| **Primary Objective:**<br>The primary objective of this study is to demonstrate that $^{18}$F-*m*FBG PET scintigraphy (PET/CT or PET/MR) is sensitive and specific (in terms of positive and negative percent agreement (PPA and NPA) with the Standard of Reference (SoR)) on a subject-level in confirming or excluding the presence of neuroblastoma. | |
| **Secondary Objectives:**<br>The secondary objectives of this study include:<br>• To compare the performance of $^{18}$F-*m*FBG and $^{123}$I-*m*IBG imaging on a subject-level with regard to disease presence or absence (PPA/NPA with the SoR).<br>• To collect safety data on $^{18}$F-*m*FBG. | |
| **Study Design:**<br>This is a prospective, Phase 3, multi-center, open-label study designed to assess the use of $^{18}$F-*m*FBG PET imaging in subjects with known or presumed neuroblastoma. Eligible participants will have either histopathologically established diagnosis of neuroblastoma or a presumed diagnosis based on signs, symptoms, physical examination, imaging findings, and laboratory and genetic test results.<br>Subjects with neuroblastoma treatment within the previous 36 months will only be administered $^{18}$F-*m*FBG if they have undergone a $^{123}$I-*m*IBG or $^{18}$F-FDG scan within 30 days of the date of the $^{18}$F-*m*FBG scan. Such subjects should not have received any chemotherapy, immunotherapy or radiotherapy between the clinical and $^{18}$F-*m*FBG imaging studies. Subjects in durable remission (no objective evidence of disease) for at least 3 years will only be administered $^{18}$F-*m*FBG if they have undergone imaging evaluation(s) for neuroblastoma surveillance within 12 months of the date of $^{18}$F-*m*FBG imaging.<br>Additional details on timing of study procedures are provided in the Schedule of Events (Table 1).<br>All $^{18}$F-*m*FBG PET studies will be examined on-site by a board-certified nuclear medicine physician or a board-certified radiologist experienced in reading $^{123}$I-*m*IBG and PET scans to ensure technical image quality and information content.<br>$^{18}$F-*m*FBG PET studies and clinical $^{123}$I-*m*IBG scans will be evaluated off-site by 3 independent radiologists and/or nuclear medicine physicians who are blinded to all subject information and the SoR. Blinded readers | |

will record whether findings on $^{18}$F-*m*FBG and $^{123}$I-*m*IBG scans are consistent with presence of neuroblastoma (Disease +) or absence of disease (Disease -).

Subject-level diagnostic performance will be assessed on the basis of positive and negative percent agreement between the blinded $^{18}$F-*m*FBG scan interpretations and disease status (SoR + or – for neuroblastoma) as independently assessed by an Expert Panel of pediatric oncologists.

The secondary efficacy analyses will compare PPA and NPA between $^{18}$F-*m*FBG and $^{123}$I-*m*IBG interpretations provided by the blinded readers.

**Study Population**

The planned population will consist of subjects with known or presumed diagnosis of neuroblastoma.

**Inclusion Criteria:**

Subjects will be eligible for participation in the study only if they meet ALL of the following criteria:

1. a) An established diagnosis of neuroblastoma based on unequivocal histopathology from tissue obtained at any time prior to enrolment in the trial;

   OR

   b) A presumed diagnosis of neuroblastoma based on signs, symptoms, physical examination, imaging findings, and laboratory and genetic test results, including individuals in whom therapy has already been empirically initiated.
2. a) The subject received neuroblastoma therapy within the previous 36 months and has undergone or is scheduled to undergo evaluation of neuroblastoma disease status, including at least one functional imaging study ($^{123}$I-*m*IBG or $^{18}$F-FDG), within 30 days of the date of $^{18}$F-*m*FBG imaging, with no interval therapy between such evaluation and investigational drug administration.

   OR

   b) The subject has been in remission (no evidence of disease on surveillance evaluations) for at least 3 years, is receiving no therapy for neuroblastoma, and has undergone imaging evaluation(s) for neuroblastoma surveillance within 12 months of the date of $^{18}$F-*m*FBG imaging.
3. Ability of subject or subject's legal guardian to understand and sign a written informed consent document, including, for subjects age 7-17, an assent form.

**Exclusion Criteria:**

Subjects will <u>not</u> be eligible for participation in the study if they meet ANY of the following criteria:

1. The subject was previously entered into this study.
2. The subject is pregnant, breast feeding, or menarchal and unwilling to use effective contraception during the study.
3. The subject has a history or suspicion of significant allergic reaction or anaphylaxis to any components of the $^{18}$F-*m*FBG imaging agent.
4. The subject is unable to lie flat or remain still for approximately 30 minutes to allow performance of a PET scan.
5. The subject uses medications that are known to interfere with uptake of NET-dependent agents and

these medications cannot be safely withheld 24 hours before study procedures.

**Planned Number of Subjects: 35**

**Test Product; Dose; and Mode of Administration:**
Subjects weighing <70 kg will receive an activity of $^{18}$F-*m*FBG calculated on the basis of an adult reference activity of 296 MBq (8 mCi), scaled to body weight. Subjects weighing ≥70 kg will receive an activity of 296 MBq (8 mCi) $^{18}$F-*m*FBG.

The $^{18}$F-*m*FBG dose will be administered intravenously by study site personnel.

**Standard of Reference (SOR)**

Presence or absence of neuroblastoma tumor as of the date of $^{18}$F-*m*FBG imaging study will be based on the consensus of the Expert Panel of pediatric oncologists following review of all clinically relevant histopathology and clinical imaging results, including $^{123}$I-*m*IBG. The panel will be blinded to the study $^{18}$F-*m*FBG imaging findings.

**Duration of Treatment:**

$^{18}$F-*m*FBG is provided through a slow bolus IV administration. The $^{18}$F-*m*FBG scan will begin at 60 minutes (±15 min) post-injection. Safety will be monitored over a 24-hour period after the $^{18}$F-*m*FBG injection.

**Duration of Study Participation:**

The minimum duration for study participation is from consent through 24 hours following $^{18}$F-*m*FBG imaging. Maximum duration of study participation is anticipated to be 3 months (+1 month at investigator discretion) to allow completion of data collection for adjudication of disease status.

**Efficacy Assessments:**
Primary Endpoint:

- Focal increased $^{18}$F-*m*FBG uptake (presence or absence) when imaging at 60 minutes with PET/CT or PET/MR, reported as PPA and NPA with the Standard of Reference (SoR).

Secondary Endpoint:

- Focal increased $^{123}$I-*m*IBG uptake (presence or absence), reported as PPA and NPA with the SoR.

Exploratory Endpoints:

- To assess intra- and inter-reader variability
- To determine if additional disease detected on $^{18}$F-*m*FBG PET (specifically $^{18}$F-*m*FBG+/$^{123}$I-*m*IBG- findings) could potentially have an impact on therapeutic strategy.
- To evaluate the contribution of quantitation (absolute and in relation to lesion dimensions) in determining the presence or absence of active tumor
- If sufficient PET/MR exams are included, to compare subject-level PPA and NPA of PET/CT and PET/MR.

**Safety Assessments:** Safety assessments will include pre- and post-administration physical examinations,

measurements of vital signs, laboratory tests, and electrocardiograms (ECGs). Adverse events (AEs) will be recorded through 24 hours after the $^{18}$F-*m*FBG injection and will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

**Statistical Methods:**

Sample Size Determination:

Predicted positive percent agreement (PPA) is 85%. Predicted negative percent agreement (NPA) is 80%. For a power of 80% and null hypotheses of $H_0$: positive percent agreement = 50% and $H_0$: negative percent agreement = 50%, the required numbers of positive and negative SOR diagnoses are 15 and 20 respectively. The minimum sample size is therefore 35.

Subject enrollment will continue until the required subject numbers for both positive and negative SOR have been confirmed. It is estimated that a total sample size up to 52 subjects might be required to achieve this.

*Datasets:*

The following analysis sets will be evaluated during the course of this study:

- The Intent-to-Image Population (IIP) will include all subjects who received one administration of $^{18}$F-*m*FBG.
- The Diagnostic Efficacy Population (DEP) will consist of all subjects who underwent an $^{18}$F-*m*FBG scan at baseline and completed the study.

The IIP will be the primary population for assessment of the primary and secondary efficacy endpoints, as well as safety endpoints. The primary and secondary efficacy endpoints will also be assessed in a sensitivity analysis based on the DEP.

*Primary Efficacy Objective:*

The primary efficacy analysis will test the positive and negative percent agreement at a subject-level between $^{18}$F-*m*FBG scan interpretations by each independent reader and Standard of Reference for neuroblastoma. Positive and negative percent agreement will be calculated as:

$$positive\ percent\ agreement = 100\% \times a/(a+c)$$

$$negative\ percent\ agreement = 100\% \times d/(b+d)$$

Where a, b, c and d are defined as:

| | **Standard of Reference Positive** | **Standard of Reference Negative** |
|---|---|---|
| **$^{18}$F-*m*FBG Read Positive** | **a(TP)** | **b(FP)** |
| **$^{18}$F-*m*FBG Read Negative** | **c(FN)** | **d(TN)** |

The point estimates (expressed as percentages) and the two-sided 95% exact confidence intervals (CI) will be calculated.

*Secondary Efficacy Objectives:*

The secondary endpoint, focal increased uptake (presence or absence) on $^{123}$I-*m*IBG scintigraphy consistent

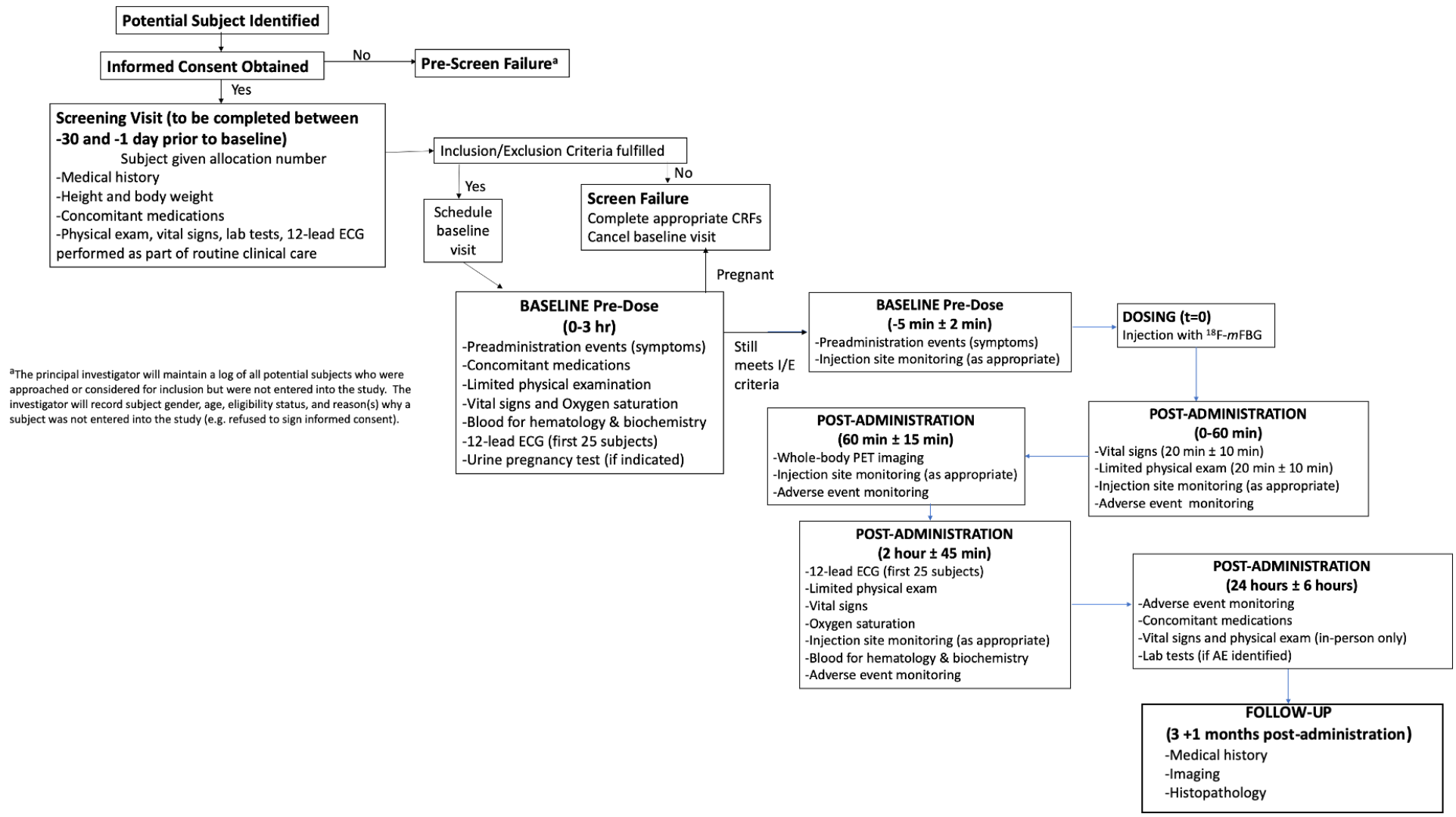
with active tumor, will be used to compare $^{18}$F-*m*FBG PET and $^{123}$I-*m*IBG imaging. For each reader and each SoR category, McNemar's test will be used to test the null hypothesis that the marginal probabilities of a correct reading are equal for $^{18}$F-*m*FBG and $^{123}$I-*m*IBG, that is, pr(a+b) is equal to pr(a+c) in the table below. The two-sided alternative hypothesis is that the marginal probabilities of a correct reading are not equal. For SoR positive, correct means the image interpretation is positive for tumor, while for SoR negative, it means the image interpretation is negative for tumor.

| | **$^{123}$I-*m*IBG Read Correct** | **$^{123}$I-*m*IBG Read Incorrect** |
|---|---|---|
| **$^{18}$F-*m*FBG Read Correct** | **a** | **b** |
| **$^{18}$F-*m*FBG Read Incorrect** | **c** | **d** |

Statistical tests for secondary endpoints will be conducted at the alpha = 0.05 level of significance, with no adjustments for multiplicity. Where such tests are not appropriate, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for each quantitative variable for both $^{18}$F-*m*FBG and $^{123}$I-*m*IBG scan results. Frequencies and percentages will be reported for categorical data.

**Interim Analysis:** None

## 1.2 Figure 1: Schema




[a]The principal investigator will maintain a log of all potential subjects who were approached or considered for inclusion but were not entered into the study. The investigator will record subject gender, age, eligibility status, and reason(s) why a subject was not entered into the study (e.g. refused to sign informed consent).

## 1.3 Schedule of Activities (SoA)

**Table 1: Study Schedule of Events**

| | **Subject Enrollment** | **Screen Pre-Dose[15]** | **Baseline Pre-Dose** | | **Dose** | **Post-Dose (Baseline Day)** | | | **Safety Follow-up** | **Clinical Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | | **To be completed between -30 and -1d** | **1hr +2 to -1hr** | **5m ±2m** | **t = 0** | **20m ±10m** | **60m ±15m** | **120m ±45m** | **24hr ±6hr[1]** | **3 months (+1 month)[2]** |
| Informed Consent | X | | | | | | | | | |
| Inclusion/Exclusion | | x | x | | | | | | | |
| Urine pregnancy test[3] | | | x | | | | | | | |
| Medical History | | x | x | | | | | | | x |
| Concomitant Medications | | x | x | x[4] | | x[4] | | x[4] | x[4] | |
| Histopathology | | x[5, 6] | | | | | | | | x[7] |
| Anatomical Imaging (CT/MRI) | | x[6] | | | | | | | | x[7] |
| Functional Imaging ($^{123}$I-*m*IBG/$^{18}$F-FDG) | | x[6, 8] | | | | | | | | x[7] |
| Physical Exam | | x | x | | | x | | x | x[9] | |
| Lab Tests | | x[10] | x[11] | | | | | x[12] | x[13] | |
| 12-Lead ECG (first 25 subjects) | | | x | | | | | x | | |
| Vital Signs | | x | x | | | x | | x | x[9] | |
| O2 Saturation | | | x | | | x | | x | | |
| Schedule dosing | | x | | | | | | | | |
| $^{18}$F-*m*FBG Injection[8] | | | | | x | | | | | |
| PET Imaging | | | | | | | x | | | |
| Injection Site Monitoring (as appropriate) | | | | x | x | x | x | x | x[9] | |
| Adverse Events | | | | | → | | | x[14] | x | |

**Abbreviations:**

AE = adverse event; CT = computed tomography; I/E = inclusion/exclusion; MRI = magnetic resonance imaging

Footnotes:

---

[1] Telephone contact unless unresolved AE post-dose or interval occurrence of AE post-discharge. In that case, in-person visit is required.

[2] Follow-up period after $^{18}$F-*m*FBG scan, to capture additional clinical or imaging results to support Expert Panel adjudication. Standard 3-month follow-up period may be extended by an additional month to capture further planned evaluations, at discretion of investigator.

[3] Females of childbearing potential

[4] To document medication administered in the radiology/nuclear medicine clinic or prescribed post-discharge only.

[5] Histopathology of primary tumor at time of original diagnosis of neuroblastoma will be recorded in CRF. A summary of relevant subsequent histology reports will be prepared and recorded in CRF.

[6] Results of CT/MRI anatomical imaging, $^{123}$I-*m*IBG scan, $^{18}$F-FDG scan, or other PET scan (functional imaging), and bone marrow histology/cytology performed as part of clinical care within 1 year prior to baseline date should be recorded during the screening period. For subjects in durable remission, if most recent functional imaging was >1 year prior to the baseline date, results for that scan should be recorded. Dosing of $^{123}$I-*m*IBG on day -1 (scan on Baseline Day) is acceptable in accordance with specifications in footnote 8.

[7] Information collected during the follow-up interval as part of clinical care.

[8] For subject with neuroblastoma therapy within previous 36 months: $^{123}$I-*m*IBG (or $^{18}$F-FDG) and $^{18}$F-*m*FBG scans should be obtained within 7 days of each other if possible. A qualifying $^{123}$I-*m*IBG (or $^{18}$F-FDG) study is required within 30 days of the baseline date. $^{18}$F-*m*FBG scan prior to a scheduled $^{123}$I-*m*IBG (or $^{18}$F-FDG) study is acceptable. If a repeat $^{123}$I-*m*IBG exam is scheduled after $^{18}$F-*m*FBG imaging, the repeat $^{123}$I-*m*IBG imaging must be performed at least 1 day later. $^{18}$F-*m*FBG can be performed on the same day after $^{123}$I-*m*IBG imaging as long as image quality using the site PET scanner will not be affected by high energy $^{123}$I photons. Otherwise, $^{18}$F-*m*FBG scan should be performed at least 1 day after $^{123}$I-*m*IBG imaging.

[9] In-person visit only

[10] Performed as part of the subject's routine clinical care. The laboratory tests may include hematology and biochemistry parameters, urine catecholamine metabolites (eg, vanillylmandelic acid, homovanillic acid).

[11] Hematology and biochemistry blood samples unless performed as part of clinical care within 3 days of baseline visit.

[12] Pre-discharge laboratory tests.

[13] If new changes in subject status (eg, vital signs and/or ECG) and/or a new AE were observed between discharge and 24-hour follow-up, hematology and biochemistry blood tests will be performed.

[14] Adverse event monitoring is continuous from time of $^{18}$F-*m*FBG administration until discharge. Results of that monitoring are recorded at discharge. Adverse event monitoring is completed as of the 24-hour telephone or in-person (if necessary) contact. Results of this further monitoring are recorded following the contact.

[15] The 30 days prior to the baseline visit is the screening interval. If baseline visit is scheduled and then must be rescheduled, results of screening evaluations from within the new screening interval should be recorded. For subject with neuroblastoma therapy within previous 36 months, a new clinically-indicated $^{123}$I-*m*IBG or $^{18}$F-FDG scan must be available, per Inclusion criterion 2a. If all Inclusion and no Exclusion criteria are still met, reconsenting is not required. However, reconsenting may be performed as required by institutional policy or the IRB of record.

# 2 INTRODUCTION

## 2.1 Study Rationale

Nuclear imaging is widely used to support diagnosis and treatment assessment of pediatric patients with the neural crest tumor neuroblastoma. The most commonly used radiopharmaceutical imaging agent is meta-iodobenzylguanidine labeled with $^{123}$I ($^{123}$I-*m*IBG) based upon its analogy with the neurotransmitter norepinephrine (NE), which is produced and released by most neuroblastoma tumors. $^{123}$I-*m*IBG was developed more than 40 years ago and has been a staple in diagnostic evaluations of neuroblastoma patients for 30 years. $^{123}$I-*m*IBG gamma camera imaging was originally performed exclusively with planar techniques, but single-photon emission computed tomography (SPECT) is now routinely used as well. While SPECT and SPECT/CT have provided improved disease localization in conventional nuclear studies, the field of radionuclide imaging has advanced in the past 20 years with widespread availability of positron-emission tomography (PET) systems which provide superior resolution and increased sensitivity for disease detection. As such, most current oncology nuclear imaging is performed using PET. A suitable PET radiopharmaceutical to replace $^{123}$I-*m*IBG would therefore be desirable.

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) have performed a National Institutes of Health (NIH)-supported study of neuroblastoma patients comparing $^{123}$I-*m*IBG with the PET analog meta-fluorobenzylguanidine labeled with $^{18}$F ($^{18}$F-*m*FBG). This study consisted of two phases. The first phase (10 patients) involved acquisition of images at multiple time points to determine biodistribution for radiation dosimetry and the optimal imaging time post-radiopharmaceutical administration for tumor detection. Incorporating the results of this first phase, the second phase consisted of $^{18}$F-*m*FBG imaging studies of an additional 16 neuroblastoma patients at a single time point. In aggregate, the combined study data showed that PET imaging consistently identified more neuroblastoma lesions than planar and SPECT $^{123}$I-*m*IBG studies.

The rationale for the present study is that, given the established clinical utility of $^{123}$I-*m*IBG and the strongly positive results of the MSKCC trial of $^{18}$F-*m*FBG in neuroblastoma, a pivotal Phase 3 trial of the diagnostic performance of $^{18}$F-*m*FBG is justified. Specifically, this study will enroll a broad population of subjects who currently might be referred for $^{123}$I-*m*IBG imaging for known or presumed neuroblastoma, irrespective of previous evidence of *m*IBG disease avidity. By comparison, the MSKCC studies only enrolled patients with known *m*IBG-avid disease.

At the completion of this study, there will be sufficient data to support a New Drug Application (NDA) to Food and Drug Administration (FDA) for approval of $^{18}$F-*m*FBG as a diagnostic imaging agent.

In this protocol, unless otherwise stated, the term “tumor” refers to neuroblastoma.

## 2.2 Background

The unique embryology and pathophysiology of neural crest tumors has provided a number of targets for development of scintigraphic agents capable of imaging these rare malignancies (1-3). In particular, the capability of the neural crest tumor neuroblastoma to synthesize, release, and reaccumulate catecholamine neurohormones such as norepinephrine and epinephrine has been exploited by a number of nuclear agents developed in the past 40 years (4-7). The most successful such compound has been meta-iodobenzylguanidine (*m*IBG or Iobenguane). This agent, labeled with $^{123}$I and $^{131}$I, has been used for more than 30 years in clinical imaging of patients with known or suspected neuroblastoma (4,8-12). Presence of tumor is reflected by increased uptake of *m*IBG compared with surrounding normal or uninvolved tissue. A 2010 meta-analysis estimated $^{123}$I-*m*IBG sensitivity of 97% [95% confidence interval (CI), 95 to 99%], but specificity could not be estimated because of insufficient published data (13). Sensitivity and specificity estimates from a prospective trial of $^{123}$I-*m*IBG imaging were 88% and 83% respectively (14). General acceptance of *m*IBG imaging in clinical practice is reflected by its inclusion in pediatric oncology guidelines (15). In the United States, $^{131}$I-*m*IBG was approved in 1994 (16) and $^{123}$I-*m*IBG was approved in 2008 (17) for the diagnostic localization of neuroblastoma.

Because of its superior imaging characteristics, $^{123}$I-*m*IBG is the preferred labeled *m*IBG compound for diagnostic use (12). Nevertheless, $^{123}$I-*m*IBG has well-defined technical and procedural limitations as a gamma-camera imaging agent. Image quality of $^{123}$I-labeled radiopharmaceuticals is degraded by presence of high-energy (>500 keV) photons, which result in septal penetration and increased scatter when low-energy collimators are used. If medium energy collimators are used to reduce these effects, image count density is reduced, with resultant loss in image quality for comparable acquisition durations. In addition, although single-photon emission computed tomography (SPECT) can be used to provide 3-dimensional image data with $^{123}$I-*m*IBG, primary efficacy validation of the method was based on planar images. Other limitations of $^{123}$I-*m*IBG include the need to wait 24 hours post-administration for performance of imaging and lack of adequate objective methods for quantitation of individual lesion severity and total disease burden, important considerations in judging response to therapy and patient prognosis (15). Improved imaging techniques for evaluating patients with neuroblastoma are still needed.

In the past 20 years, PET has become the dominant nuclear imaging technique for evaluating oncology patients (18,19). PET provides better image resolution than SPECT and in most cases higher sensitivity and specificity for detection of active tumor than equivalent imaging using conventional gamma-emitting nuclear agents (20-22). PET has the potential to provide absolute quantitation of tracer uptake in malignant and benign tissues, which cannot be done reliably with current SPECT agents and imaging systems. In addition, virtually all modern PET systems include either computed tomography (CT) or magnetic resonance imaging (MRI) for attenuation correction and provision of cross-sectional images for correlation with the functional information provided by the positron-emitting radiopharmaceutical. Nuclear imaging specialists regard PET as a superior technology for clinical patient evaluation compared to SPECT (22,23).

$^{18}$F-meta-fluorobenzylguanidine ($^{18}$F-*m*FBG) is structurally equivalent to $^{123}$I-*m*IBG, with the $^{123}$I atom in the latter replaced by a $^{18}$F atom. $^{18}$F-*m*FBG was first synthesized more than 20 years ago, and its biodistribution is very similar to *m*IBG (24-26). However, animal and limited human experience suggest that clearance of $^{18}$F-*m*FBG from blood and certain target organs is more rapid than $^{123}$I-*m*IBG, enhancing the performance characteristics of same-day imaging of norepinephrine transporter (NET)-dependent tumor uptake with $^{18}$F-*m*FBG (25,26). As noted earlier, the advantages of $^{18}$F as a positron emitter over the single-photon emitter $^{123}$I also should result in better imaging performance for $^{18}$F-*m*FBG. Direct comparisons between $^{123}$I-*m*IBG and $^{18}$F-*m*FBG suggest that diagnostic results using the latter are superior (26).

Investigators at MSKCC have completed a Phase 1 study of $^{18}$F-*m*FBG in neuroblastoma and pheochromocytoma/paraganglioma patients and published results from the first 10 (5 neuroblastoma, 5 pheochromocytoma/paraganglioma) (27). This study was designed to obtain biodistribution data for dosimetry and determination of the optimal imaging time post- radiopharmaceutical administration for tumor detection. Based upon visual and quantitative examination of whole-body images at 30-60 minutes, 1-2 hours, and 3-4 hours post- administration, MSKCC researchers determined an imaging time of 60-90 minutes post- administration provided an optimal balance between the competing considerations of photon count density, lesion conspicuity and contrast, and patient tolerability. Analysis of $^{18}$F-*m*FBG images at a lesion-level also demonstrated that more lesions were detected in every patient compared to previously acquired $^{123}$I-*m*IBG images (27).

Based upon the success of the Phase 1 program, MSKCC investigators initiated a Phase 2 trial of additional neuroblastoma patients (clintrials.gov number NCT02348749). In this study, whole-body imaging was only performed at 60-90 minutes. A total of 16 patients underwent $^{18}$F-*m*FBG in this study (Pandit-Taskar, private communication).

The MSKCC studies were facilitated by radiofluorination technology obtained from Ground Fluor Pharmaceuticals (GFP) that provides improved yields in synthesis of $^{18}$F-*m*FBG (28). Innervate Radiopharmaceuticals (IRP) (formerly Illumina Radiopharmaceuticals) has licensed this technology from GFP, which will be used to produce the radiopharmaceutical drug product for the present study.

As noted previously, there are limitations to the generalizability of the MSKCC trial data. As not all neuroblastoma tumors are *m*IBG-avid (10-20% are non-avid either based upon genetic characteristics or previous therapy) (14,29), use of documented *m*IBG tumor avidity as a primary inclusion criterion in the trials introduces an element of bias into the results. By studying a more heterogeneous group of subjects, IRP intends to expand on the results of the work from MSKCC and demonstrate the performance characteristics of $^{18}$F-*m*FBG in a population representative of individuals who might be referred for clinical examinations.

The primary objective of the present Phase 3 study is to document that $^{18}$F-*m*FBG is effective for imaging subjects who are or might be evaluated for known or presumed neuroblastoma. This includes subjects who are judged to be in durable remission, defined as having no objective evidence of disease for at least 3 years. Effectiveness will be judged on a subject-level in terms of the identification of abnormal uptake of the

radioactive compound in one or more anatomic locations where tumor is or has been identified at surgery, biopsy (bone marrow or tissue), CT/MRI, or functional imaging ($^{123}$I-*m*IBG or $^{18}$F-FDG), or detection of no abnormal uptake in subjects whose clinical evaluation demonstrates no objective evidence of tumor. The study design and population to be examined will be representative of those patients currently referred for $^{123}$I-*m*IBG or in selected cases $^{18}$F-FDG imaging. The null hypothesis is that the positive and negative percent agreements (PPA and NPA) of $^{18}$F-*m*FBG imaging compared to the accepted standard methods will each be greater than 50%.

Safety data will be collected using conditions and standards for data collection, review and analysis that are appropriately defined at the outset of the study (e.g., adverse event [AE] collection and serious adverse event [SAE] notification) as well as using suitable preset thresholds (e.g., criteria for changes in vital signs, ECG, and clinical laboratory parameters) at the start of the study in order to flag any potential safety concerns.

## 2.3 Risk/Benefit Assessment

### 2.3.1 Known Potential Risks

There have been no reported side effects associated with administration of $^{18}$F-*m*FBG.

Exposure to ionizing radiation has the theoretical potential for cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations, the likelihood of such occurrences is very low because of the low radiation doses incurred. The expected effective dose from the $^{18}$F-*m*FBG PET procedure (1-6 mSv depending on weight of subject) is comparable to that received from $^{123}$I-*m*IBG and $^{18}$F-FDG studies. Radiation dose from the CT component of a PET/CT exam is also equivalent to that from the CT used for $^{123}$I-*m*IBG SPECT/CT and $^{18}$F-FDG PET/CT.

Aseptic conditions must be observed during any manipulation of the subject dose. For investigational medicinal product (IMP) in a vial, microbial decontamination of the rubber stopper with a suitable disinfectant should be performed prior to withdrawal of a subject dose. This product is not preserved and must be used on the day of calibration. Storage should take place in accordance with national regulations for radioactive materials. Do not store the preparation above 25°C (77°F). Do not freeze.

The administration of radiopharmaceuticals creates risks to other persons, from external radiation or contamination from spills of urine, vomiting, etc. Waste must be disposed of according to national regulations for radioactive material.

Radiation protection precautions in accordance with national regulations for diagnostic radionuclide procedures must be taken.

Similar to $^{123}$I-*m*IBG, $^{18}$F-*m*FBG is excreted primarily via the kidneys. Therefore, subjects are encouraged to remain well-hydrated and void frequently during the 24 hours post-administration in order to minimize the radiation dose to the bladder.

Due to the potential for certain categories of therapeutic pharmaceuticals (such as antidepressants, neuropsychiatric medications, antihypertensive, and sympathomimetic agents) to interfere with NET-dependent uptake, it is recommended that these drugs be withheld for a minimum of 24 hours before administration of $^{18}$F-*m*FBG. See Section 6.5.2 for further details.

Regarding adverse effects of the product, previous human exposure is limited, but no significant adverse events have been documented to date. However, there have been minimal such events during the long and extensive experience with the related compound *m*IBG. For reference, those rare undesirable effects are described in Section 2.3.1.1.

#### 2.3.1.1 Possible Risks and Side Effects: $^{123}$I-*m*IBG

Due to the structural and physiological similarity of *m*FBG and *m*IBG, it is expected that rare adverse effects associated with the 2 agents might be similar. However, as the mass quantity of *m*FBG in $^{18}$F-*m*FBG injection is approximately 2 orders of magnitude less than the mass quantity of *m*IBG in the diagnostic radiopharmaceutical, the likelihood of any such effects is substantially reduced. Nevertheless, the following information is provided as general guidance.

In the pivotal trial of $^{123}$I-*m*IBG in neuroblastoma and pheochromocytoma subjects (n = 251), the following reactions were reported in a maximum of 2 subjects each: dizziness, rash, pruritus, flushing or injection site hemorrhage. In earlier trials of $^{131}$I-*m*IBG, transient episodes of marked hypertension were reported. Other reported adverse reactions included nausea, vomiting, sleepiness, fever, chills, and hypotension. When the drug is administered rapidly, palpitations, dyspnea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration and disappear within 1 hour. It is therefore recommended that as a precaution, *m*IBG should be administered as a slow intravenous injection (15 seconds to 2 minutes). This latter precaution is much less likely to be necessary for use of $^{18}$F-*m*FBG.

### 2.3.2 Known Potential Benefits

Benefits of $^{18}$F-*m*FBG have not been established. The following represent possibilities based on experience with other PET radiopharmaceuticals and procedural details for $^{123}$I-*m*IBG.

An expected potential benefit from use of $^{18}$F-*m*FBG PET is more accurate identification of anatomic sites of active tumor for neuroblastoma disease status evaluation. Quantitative analysis of individual lesions using measures such as standardized uptake value (SUV) and target-to-background ratio (TBR) could also enhance assessment of disease severity and improve precision of quantitation of disease extent and severity.

Expected procedural benefits include completion of the imaging procedure within 2 hours of drug administration (rather than 24 hours as required for $^{123}$I-*m*IBG) and reduced total imaging time compared with that required for planar plus SPECT $^{123}$I-*m*IBG acquisitions. Another benefit of $^{18}$F-*m*FBG is absence of radioiodine, eliminating the need for pretreatment with thyroid-blocking medication.

### 2.3.3 Assessment of Potential Risks and Benefits

Study participants will incur a small increase in risk based on ionizing radiation dose and potential for adverse reaction to components of the drug product, including the microdose quantity of *m*FBG (≤4 μg). The improved information from the investigational scan will not provide immediate benefit to the subject but will be of value to future neuroblastoma patients undergoing diagnostic evaluations.

The risk to benefit ratio for $^{18}$F-*m*FBG is acceptable given the low risks based on historical experience with PET imaging agents and the substantial potential benefits to future patients from clinical availability of a high-performance PET radiopharmaceutical for assessment of neuroblastoma.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Primary Objective and Endpoints

The primary objective of the study is to demonstrate that $^{18}$F-*m*FBG PET scintigraphy (PET/CT or PET/MR) is sensitive and specific on a subject level in confirming or excluding the presence of neuroblastoma. These pivotal data will be used to support an NDA submission.

The primary endpoint is focal increased uptake (presence or absence) on PET/CT or PET/MR imaging at 60 minutes post-$^{18}$F-*m*FBG administration, reported as PPA and NPA with the Standard of Reference (SoR). The primary efficacy endpoint also will be used for secondary analyses of PPA and NPA.

## 3.2 Secondary Objectives and Endpoints

The key secondary objective of the study is:

a. To compare the performance of $^{18}$F-*m*FBG and $^{123}$I-*m*IBG imaging on a subject-level in terms of PPA/NPA with the SoR.

This objective will be assessed using the secondary endpoint of focal increased $^{123}$I-*m*IBG uptake (presence or absence), reported as PPA and NPA with the SoR. The independent blinded reader assessments of $^{18}$F-*m*FBG and $^{123}$I-*m*IBG images will be used.

An additional secondary objective is:

b. To collect safety data on $^{18}$F-*m*FBG.

This objective will be assessed by examining changes in vital signs, laboratory results, ECG findings, and clinical condition between pre- and post-administration assessments, as well as occurrence of adverse events (AE) and serious adverse events (SAE), following administration of $^{18}$F-*m*FBG.

## 3.3 Tertiary / Exploratory Objectives and Endpoints

Exploratory objectives of the study are:

a. To assess intra- and inter-reader variability.

b. To determine if additional disease detected on $^{18}$F-*m*FBG PET (specifically $^{18}$F-*m*FBG+/$^{123}$I-*m*IBG- findings) could potentially have an impact on therapeutic strategy.

c. To evaluate the contribution of quantitation in determining the presence or absence of active tumor.

d. If sufficient PET/MR exams are included, to compare subject-level PPA and NPA of PET/CT and PET/MR.

# 4 STUDY DESIGN

## 4.1 Overall Design

This is an open-label, multicenter study assessing $^{18}$F-*m*FBG PET scintigraphic imaging in subjects being evaluated for neuroblastoma. The study is designed as a pivotal Phase 3, powered on PPA and NPA.

Each eligible subject will receive an injection of $^{18}$F-*m*FBG between 1 and 8 mCi (37-296 MBq). Children <18 years of age (with a weight of <70 kg) will receive a dose of $^{18}$F-*m*FBG calculated on the basis of a reference activity of 8 mCi (296 MBq) scaled to body weight. Adults and children with weight ≥70 kg will receive an 8 mCi (296 MBq) injection of $^{18}$F-*m*FBG. See Section 6.1.2 for additional details.

Participants will be imaged at 60 minutes (± 15 minutes) post-administration.

Safety parameters will be monitored prior to administration of $^{18}$F-*m*FBG and after administration.

## 4.2 Scientific Rationale for Study Design

Effectiveness will be judged in terms of:

1. Identification of abnormal uptake of $^{18}$F-*m*FBG in subjects in whom tumor has been confirmed by accepted methods including histology, CT, MRI, and functional imaging results, and catecholamine and metabolite bioassays.

AND

2. Detection of no abnormal uptake of $^{18}$F-*m*FBG in subjects whose histological, imaging, and biochemical evaluations and clinical follow-up demonstrate no objective evidence of tumor.

This study's safety monitoring plan is justifiable and adequate as:

1. The design of the safety plan permits a comparison of the condition of the subject at baseline and post-administration with $^{18}$F-*m*FBG.

2. Considering the extremely small mass quantity of investigational drug and the short half-life of the radioactive component (10 half-lives in <20 hours), safety monitoring period on the day of administration and for a maximum of 24 hours thereafter including the performance of vital sign monitoring, permits the evaluation of late-appearing AEs that may emerge or progress post-administration of $^{18}$F-*m*FBG.

3. The measures used to assess safety are well defined and reliable, and the proposed safety analyses are adequate to assess the effects of administration with $^{18}$F-*m*FBG. No control subjects will be evaluated as part of the study.

## 4.3 Justification for Dose

An adult activity of 10 mCi (370 MBq) is in common clinical use for several $^{18}$F-labeled PET agents, including the most widely used such drug, $^{18}$F-FDG (30). While it is well established that this activity provides satisfactory PET images as late as 1-2 hours post-administration, a number of recently approved PET radiopharmaceuticals have lower recommended maximum administered activities, including gallium Ga 68 dotatate (5.4 mCi) and FluoroDOPA F 18 (5 mCi). In addition, although the MSKCC Phase I study of $^{18}$F-*m*FBG used a maximum activity of 12 mCi, an adult neuroblastoma patient in that study was successfully imaged following administration of 4.4 mCi (27). Use of a lower maximum activity in this Phase 3 study is justified because: a) it will result in a lower subject radiation dose than for $^{123}$I-*m*IBG administered as per the approved label (reference activity 10 mCi) (17); b) the 20% reduction from the 10 mCi reference activity is less than the $^{18}$F decay between 1 and 2-hour post-injection images commonly obtained with $^{18}$F-FDG, the latter of which provide acceptable image quality (31); and c) if pre-imaging detected count rate is less than the desired minimum for clinical procedures (e.g. for administered activity of 10% below the nominal amount (reference section 6.1.2) and acquisition start time of 75 minutes post-administration (reference section 6.1.1.1)), acquisition time can be increased (e.g. from 3 to 4 minutes/bed position) to assure that images meet quality standards (as detailed in study Imaging Manual) and are consistent across studies and investigational sites.

## 4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed the 3-month clinical follow-up period shown in the Schedule of Activities (SoA) (Section 1.3), or prematurely discontinued from the study. The end of the study is defined as either when all subjects administered $^{18}$F-*m*FBG have completed the study or the Sponsor has terminated the study early (see Section 10.1.2).

# 5 STUDY POPULATION

## 5.1 Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1) The subject has:

   a) An established diagnosis of neuroblastoma based on unequivocal histopathology from tissue obtained at any time prior to enrolment in the trial;

OR

   b) A presumed diagnosis of neuroblastoma based on signs, symptoms, physical examination, imaging findings, and laboratory and genetic test results, including individuals in whom therapy has already been empirically initiated.

2) a) The subject has received neuroblastoma therapy within the previous 36 months and has undergone or is scheduled to undergo evaluation of neuroblastoma disease status, including at least one functional imaging study ($^{123}$I-*m*IBG or $^{18}$F-FDG), within 30 days of the date of $^{18}$F-*m*FBG imaging, with no interval therapy between such evaluation and investigational drug administration.

   OR

   b) The subject has been in remission (no evidence of disease on surveillance evaluations) for at least 3 years, is receiving no therapy for neuroblastoma, and has undergone imaging evaluation(s) for neuroblastoma surveillance within 12 months of the date of $^{18}$F-*m*FBG imaging.

3) The subject is able and willing to comply with study procedures and a signed and dated informed consent (supplemented by signed and dated assent from subjects age 7-17) is obtained from the subject and/or parent/guardian

## 5.2 Exclusion Criteria

Subjects must be excluded from participating in the study if they meet any of the following criteria:

1) The subject was previously entered into this study.

2) The subject is pregnant, breast feeding, or menarchal and unwilling to use effective contraception during the study.

3) The subject has a history or suspicion of significant allergic reaction or anaphylaxis to any components of the $^{18}$F-*m*FBG imaging agent.

4) The subject is unable to lie flat or remain still for up to 30 minutes to allow performance of a PET scan.

5) The subject uses medications that are known to interfere with uptake of NET-dependent agents and these medications cannot be safely withheld 24 hours before $^{18}$F-*m*FBG administration.

# 6 STUDY INTERVENTION

## 6.1 Study Intervention(s) Administration

Each investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with regulatory guidelines (e.g., International Conference on Harmonisation [ICH] E6-Good Clinical Practice [GCP] and the Code of Federal Regulations), and used in accordance with this protocol.

### 6.1.1 Study Intervention Description

Subjects will be monitored for safety in various parameters. Imaging procedures will be performed as per on-site practice for clinical PET/CT (or PET/MR).

#### 6.1.1.1 Imaging Procedures

All $^{18}$F-*m*FBG imaging will be performed on clinical PET/CT or PET/MR systems using standard technical parameters used at the investigational site. Whole-body imaging will be performed from the vertex to the feet. Images will be reconstructed using manufacturer-provided iterative reconstruction algorithms and attenuation, deadtime, randoms, and scatter corrections similar to $^{18}$F-FDG imaging. This will yield whole-body tomographic images that can be viewed in standard axial, coronal, or sagittal projections, or as rotating maximum intensity projection (MIP) displays.

On-site image assessments will be performed per standard practice for PET imaging at the investigational site. Data for the on-site interpretations will be collected.

Imaging will commence at 60 minutes (±15 minutes) post-administration of $^{18}$F-*m*FBG.

#### 6.1.1.2 Image Handling and Data Transfer

To ensure the logistics of image data transfer and the feasibility of data transcription for various computer storage media, the following requirements must be met.

##### 6.1.1.2.1 $^{18}$F-*m*FBG

- Each center must send unprocessed and reconstructed PET image files to the designated imaging core laboratory (ICL).
- The digital files must be of acceptable quality, as judged by imagers at the investigational site, with regard to:
  - Complete coverage of all anatomical regions from vertex to feet.
  - Adequate image counts.
  - No or minimal subject motion.

Prior to the start of the study, each Principal Investigator (PI) must provide the ICL suitable test images on each PET system that might be used, as specified in the Study Imaging Manual. Information concerning the specific equipment used in the test acquisitions should be provided, including:

- PET camera manufacturer and model.
- Specifications for associated CT or MR equipment.
- Computer system, and software, and reconstruction modes available.
- Format of submitted digital images (DICOM 3.0 or higher).
- Data transfer capabilities: (Electronic Data Capture (EDC) portal, file transfer protocol (FTP) or physical)
- Acquisition parameters.
- Technical contact person.
- Study center information.

Every subject image set file sent to the ICL must be accompanied by an image data transmittal form for tracking and processing purposes. The following guidelines should be followed:

- Identify the PET/CT or PET/MR system used (if site has qualified multiple systems)
- Submit only original digital files, including attenuation-, randoms-, deadtime-, decay-, and scatter-corrected PET images.
- Submit corresponding anatomical data: CT or MRI.
- Submit daily quality control data.
- If physical media are used, the outside of the storage medium must be labeled with the center and subject number and study acquisition date.

#### 6.1.1.2.2 $^{123}$I-*m*IBG

Image data files from clinical $^{123}$I-*m*IBG studies performed during subject participation in the trial will also be transferred to the ICL for blinding, randomization, image processing, evaluation, and data analysis.

Prior to the start of the study, each Principal Investigator (PI) will provide the ICL the following information about the investigational site gamma camera systems on which clinical $^{123}$I-*m*IBG studies might be performed.

- Camera manufacturer and model.
- Specifications for associated CT on SPECT/CT systems.
- Computer system, software, and reconstruction modes available.
- Format of submitted digital images (DICOM 3.0 or higher).

Every subject image set file sent to the ICL must be accompanied by an image data transmittal form for tracking and processing purposes. The following guidelines should be followed:

- Identify the gamma camera system used (if site has qualified multiple systems).
- Submit planar $^{123}$I-*m*IBG files in DICOM format as unfiltered data.
- Submit SPECT $^{123}$I-*m*IBG files in DICOM format as either raw rotating projections or tomographic reconstructions.
- Submit corresponding anatomical data: CT.
- If physical media are used, the outside of the storage medium must be labeled with the center and subject number and study acquisition date.

If $^{123}$I-*m*IBG files from a center other than the investigational site are submitted, include the above information about the gamma camera system used as accompanying documentation. Refer to the Imaging Manual or contact the sponsor for additional guidance.

#### 6.1.1.2.3 General Guidelines for Image Submissions

The investigational site is responsible for maintaining a back-up copy of each imaging study and data transmittal form in case the Quality Assurance group of the ICL requires a resubmission.

Investigators will be required to convert images into DICOM 3.0 or higher format and submit imaging data through a digital portal (EDC) or through physical transfer on digital media. In case of digital submission, the investigator will be supplied an account identification number, address, and password. If data cannot be converted to DICOM 3.0 or higher format, the investigator must obtain approval from the sponsor prior to submitting imaging data via a proprietary format on digital media.

All image data must be anonymous, with no reference to the subject's identity. The data must only be labelled with subject's 5-digit study number, the study number, and the exam date.

### 6.1.2 Dosing and Administration

The IMP, $^{18}$F-*m*FBG, is to be administered intravenously and may be administered undiluted. $^{18}$F-*m*FBG should be injected slowly through a cannula (or indwelling catheter) in the vein, with the subject lying in a supine position. After the injection of $^{18}$F-*m*FBG is complete, the cannula or indwelling catheter must then be immediately flushed through with at least 5 mL of 0.9% sodium chloride solution.

All subjects ≥18 years of age and children with a weight of ≥70 kg will receive an intravenous injection of 8 mCi ±10% (7.2-8.8 mCi) (266-326 MBq) of $^{18}$F-*m*FBG.

Children <18 years of age (with a weight of 8-70 kg) will receive an activity of $^{18}$F-*m*FBG calculated on the basis of a reference adult activity of 8 mCi ±10% (7.2-8.8 mCi) (266-326 MBq) scaled to body weight according to the formula recommended by the 2010 North American Consensus Guidelines:

(Body mass (kg) * adult dose)/70 kg (32,33).

For children ≤7 kg, a fixed minimum activity of 1 mCi ±10% (0.9-1.1 mCi) (33 to 41 MBq)), the minimum activity recommended for $^{18}$F-FDG, will be used (32). Refer to Section 12 for tabular listing of activity scaling in pediatric subjects.

Subjects will be asked to void prior to the first $^{18}$F-*m*FBG imaging session and every few hours after completion of imaging in order to minimize radiation dose to the bladder.

### 6.1.3 Clinical Follow-up

Safety follow-up for the imaging portion of the study is 24 hours following investigational agent administration.

The follow-up period for data collection in support of SoR determination is 3 months. The investigator may request sponsor approval to extend follow-up for 1 additional month to capture further information from planned diagnostic evaluations. Results of all diagnostic testing and clinical assessments performed during follow-up will be collected and recorded in the CRF. Activities during the 3-month (or 4-month with sponsor approval) follow-up period will be guided exclusively by the clinical judgment of the managing physicians.

## 6.2 Preparation / Handling / Storage / Accountability

### 6.2.1 Acquisition and Accountability

Each investigator is responsible for ensuring that deliveries of IMP and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with regulatory guidelines (e.g., International Conference on Harmonisation [ICH] E6-Good Clinical Practice [GCP] and the Code of Federal Regulations [CFR]), and used in accordance with this protocol.

$^{18}$F-*m*FBG will be provided by Innervate Radiopharmaceuticals as a single dose in a syringe or vial. Refer to the Investigator's Brochure for details concerning the physical and chemical characteristics of $^{18}$F-*m*FBG. Refer to the Radiopharmacy Manual for additional information on IMP ordering, handling and accountability.

All investigational medicinal product containers (opened, unopened, or empty) will be destroyed on site after the study and overall drug accountability have been completed by the sponsor or designee. A list of investigational medicinal product and other materials that were destroyed must be prepared and signed by the principal investigator. If there are any discrepancies, an explanation for these should also be provided.

### 6.2.2 Formulation, Appearance, Packaging and Labelling

A packing list to confirm the information on the IMP label is provided with each delivery requested by the investigator. The IMP should appear as a colorless, particle-free solution. The label of the IMP container will conform to the applicable FDA and NRC labeling requirements for radioactive products and will include:

- Product name
- Lot number
- Calibration date/time
- Expiration date/time
- Activity at calibration
- Container volume
- Concentration at calibration

### 6.2.3 Product Storage and Stability

$^{18}$F-*m*FBG storage should take place in accordance with national regulations for radioactive materials. The preparation should be stored at 20-25ºC.

The administration of radiopharmaceuticals may create risks to other persons, from external radiation or contamination from spills of urine, vomiting, etc. Waste must be disposed according to national regulations for radioactive material.

### 6.2.4 Preparation

The activity in the container with the IMP should be measured in a dose calibrator within 1 hour ± 15 minutes of the scheduled administration time and the measurement time and activity recorded in the CRF. If the product is supplied in a ready-to-use syringe and it is calculated that the activity at the scheduled administration time will be too high, an appropriate amount of IMP should be withdrawn under aseptic conditions and the remaining activity measured using the same dose calibrator. The date, time, and quantity of each activity measurement will be recorded in the CRF.

If IMP is supplied in a vial, aseptic conditions must be observed during withdrawal of a dose, including microbial decontamination of the rubber stopper with a suitable disinfectant before removal of a dose.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-labeled study; therefore, the subjects and study staff performing safety assessments will not be blinded. The study design also does not require randomization; all enrolled subjects who meet all inclusion and no exclusion criteria will receive the IMP.

The potential for bias in this study is considered minimal since the presence or absence of tumor will be established by accepted medical methods and will not influence enrollment.

### 6.3.1 Method of Assigning Subjects Numbers

A unique allocation number will be assigned to each subject in successive order of entering the study after signing the informed consent document. No subject may be entered or screened (after failing to meet inclusion/exclusion criteria) into the study more than once.

The allocation number will be unique for each subject in the study and will consist of an identification of 5 digits at the center (e.g., 02001: first subject in center No. 2). No subject can be administered $^{18}$F-*m*FBG before it has been determined that the subject meets the study's inclusion/exclusion criteria and a signed and dated informed consent has been obtained.

Once an allocation number is assigned, it cannot be reassigned even if the subject is deemed ineligible or withdraws consent. Allocation numbers will be assigned sequentially within center.

### 6.3.2 Expert Panel

An Expert Panel will be used to adjudicate the SoR for all subjects. The panel will be provided with all available clinical information, with the exception of $^{18}$F-*m*FBG imaging data. Details of the SoR and the format of the Expert Panel are presented in more detail in Sections 8.1.3 and 10.2.3 respectively.

### 6.3.3 Independent Image Review

All image data files and processed/reconstructed PET images will be transferred to the ICL for blinding, randomization, image processing, evaluation, and data analysis as described in Sections 6.1.1.2.1 and 6.1.1.2.3. $^{18}$F-*m*FBG images will be qualitatively examined by 3 independent readers with no knowledge of the clinical status of the subjects but with access to anatomic cross-sectional images (CT or MRI) acquired as part of the PET exam.

Image data files from clinical $^{123}$I-*m*IBG studies performed during subject participation in the trial will also be transferred to the ICL for blinding, randomization, image processing, evaluation, and data analysis as described in Sections 6.1.1.2.2 and 6.1.1.2.3. $^{123}$I-*m*IBG images will be qualitatively examined by the same 3 independent readers with no knowledge of the clinical status of the subjects but with access to anatomic cross-sectional images (CT) acquired as part of SPECT exams. $^{123}$I-*m*IBG image interpretation will be performed independently of $^{18}$F-*m*FBG study reviews and with sufficient time between readings to minimize possible memory of unusual or atypical findings.

Readers will be aware that the trial involves neuroblastoma subjects but will be blinded to all other clinical information, including results from the Expert Panel.

All activities of each reader will be overseen by ICL personnel in accordance with the Blinded Image Evaluation (BIE) Manual supporting this protocol.

## 6.4 Study Intervention Compliance

Subjects will receive $^{18}$F-*m*FBG under direct supervision of study personnel including the investigator or designated physician. Appropriate resuscitation equipment will be available within the radiology/nuclear medicine clinic when $^{18}$F-*m*FBG is administered and where the subject is monitored until discharge. Subjects will be under direct supervision by a physician until discharge from the hospital or clinic. The information concerning each administration of $^{18}$F-*m*FBG (i.e. date, time, activity, and volume administered) will be checked and the container lot number and pre- and post-administration activity (measured in the dose calibrator) and volume of the administration will be recorded in the subject's CRF.

A confidential list of study subjects will be completed and will include each subject's study number and initials. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided signed and dated informed consent. The principal investigator must also maintain a separate screening log of all the subjects screened for participation in the study, the reasons for their exclusion or non-participation if applicable, gender, age, eligibility status, reason for ineligibility if applicable and study allocated subject number and initials if applicable.

## 6.5 Concomitant Therapy

Any prior and concurrent medication, including over-the-counter and prescription drugs, vitamins, minerals, and dietary supplements disclosed by the subject at any time period from 14 days before investigational drug administration through completion of the study procedures must be documented on the Medication CRF page. Generic or trade names, indication for use, and date of last dose prior to the administration of $^{18}$F-*m*FBG, will be recorded on these CRF pages.

### 6.5.1 Rescue Medications

The AE profile of $^{18}$F-*m*FBG has been established in a limited number of humans. Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available from the time of dosing to the time of discharge at the conclusion of imaging. Treatment of SAEs should be primarily supportive of vital functions.

### 6.5.2 Prohibited Medications

Based upon pharmaceutical mechanisms of action and extensive human experience with radiolabeled *m*IBG, there is demonstrated potential for certain antihypertensive, neuropsychiatric, and sympathomimetic drugs to interfere with NET-dependent cellular uptake. The most commonly used of these medications are as follows (34,35).

a. Antihypertensive: Reserpine; labetalol

b. Neuropsychiatric: amitryptiline; bupropion; clomipramine; dothiepin; duloxetine; imipramine; nortriptyline; venlafaxine

c. Sympathomimetic: Pseudoephedrine; phenylephrine

In particular, neuropsychiatric medications that affect NET function (e.g., tricyclic and serotonin-norepinephrine reuptake inhibitor antidepressants), whether or not included on the above list, should be withdrawn for at least 1 day and longer (4 biological half-lives if clinically feasible) to prevent potential false-negative $^{18}$F-*m*FBG imaging studies.

# 7 STUDY INTERVENTION, DISCONTINUATION, AND PARTICIPATION

## 7.1 Discontinuation of Study Intervention

There are no formal withdrawal or termination criteria for the study. The sponsor reserves the right to stop the study if: a) safety signals suggest unexpected or potentially unacceptable risk for subjects; b) the enrollment rate is too slow to complete the study within 2 years of first subject inclusion; or c) other factors develop that would prevent the sponsor from completing the study as planned.

During the conduct of the study, the Safety Officer will review the safety data for trends and signals that would indicate the need for withdrawal of a subject or termination of the trial.

## 7.2 Participant Discontinuation / Withdrawal from Study / Rescreening

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant is unable to schedule baseline (imaging) visit within 1 month of signing informed consent and is no longer judged a suitable candidate for the study.
- Subject lack of co-operation or inability to remain still for imaging procedures
- Any other concern for the subject's health or wellbeing

Should a subject decide to withdraw following baseline assessments but prior to administration of the IMP, the investigator will record the reason for withdrawal on the CRF. Should a subject decide to withdraw after administration of the IMP, or should the investigators decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

If the reason for subject withdrawal is an AE or abnormal laboratory test result(s), monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the CRF.

Subjects who sign the informed consent form but do not receive the study intervention ($^{18}$F-*m*FBG administration) will be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be included in the safety but not the diagnostic efficacy population. These latter subjects will be replaced as necessary to meet the study statistical requirements.

A subject whose baseline date must be rescheduled due to unforeseen circumstances (e.g. subject illness, logistical issues with drug product availability) can continue in the study as long as all Inclusion and no Exclusion criteria continue to be met. If the rescheduled baseline date is >30 days after the most recent $^{123}$I-*m*IBG or $^{18}$F-*m*FBG scan, a new $^{123}$I-*m*IBG or $^{18}$F-*m*FBG scan, performed as a clinical care procedure during the new screening interval, is required. Results of the new functional imaging study, as well as other clinical evaluations performed within 30 days prior to the new baseline date (new screening interval), should be recorded. In this circumstance, the subject does not need to be reconsented unless this is required by the IRB or institutional guidelines.

## 7.3 Lost to Follow-up

All subjects will continue in the follow-up arm of the study after their 24 hr post-dose visits or telephone contacts. All relevant clinical and imaging data collected during the 3 months following $^{18}$F-*m*FBG imaging will be summarized in the CRF.

Subjects without current histology information at the time of $^{18}$F-*m*FBG imaging and no scheduled follow-up in the next 3 months should be contacted via telephone at least every 6 weeks. After 3 failed attempts, subjects should be contacted via certified mail.

Subjects without a definitive histological diagnosis at the time of $^{18}$F-*m*FBG imaging who cannot be reached after 4 months post-study will be identified as Lost to Follow-up.

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 Efficacy Assessments

### 8.1.1 Onsite assessment of imaging data

Onsite assessment of imaging data is required to ensure that all quality control requirements have been met. An onsite experienced nuclear medicine technologist will review the $^{18}$F-*m*FBG whole body images according to standard local procedures to verify appropriate subject positioning, PET scanner and computer function. Any findings suggestive of technical or system malfunction should be immediately reported to the PI or his/her designee. The investigator or an appropriately trained designee will also review all images for diagnostic quality. Any images judged to be of poor quality should be repeated, if possible, before discharge of the subject from the imaging site and reason for poor quality should be recorded in the CRF. All images obtained, including poor quality and repeated acquisitions, should be saved for submission to the ICL.

The radiology/nuclear medicine investigator will record in the CRF a diagnostic evaluation of the PET images with respect to sites of abnormal $^{18}$F-*m*FBG uptake. All images will be reviewed, and the following will be recorded:

1. Presence or absence of abnormalities.

2. Anatomical location of all abnormalities (refer to Table 2), unless lesions are too numerous to catalog (e.g., >3 lesions in a single rib or liver segment). In this circumstance, the image review CRF will be completed in accordance with the instructions for CRF completion.

3. Affected organ or organ systems (refer to Table 3)

4. Classification of abnormalities as either equivocal (mild degree of uptake, possibly physiological or an anatomic variant) or definite (distinctly abnormal uptake).

**Table 2: Anatomic Grid Location for Observed Abnormalities**

| Region | Modifier 1 | Modifier 2 | Modifier 3 | Modifier 4 | Modifier 5 | Modifier 6 | Modifier 7 | Modifier 8 |
|---|---|---|---|---|---|---|---|---|
| **Head** | Right | Left | Anterior | Posterior | | | | |
| **Neck** | Right | Left | Anterior | Posterior | | | | |
| **Thorax** | Right Upper | Midline Upper | Left Upper | Right Lower | Midline Lower | Left Lower | Anterior | Posterior |
| **Abdomen** | Right Upper | Midline Upper | Left Upper | Right Lower | Midline Lower | Left Lower | Anterior | Posterior |
| **Pelvis** | Right | Midline | Left | Anterior | Posterior | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Extremities** | Proximal Right Upper | Distal Right Upper | Proximal Left Upper | Distal Left Upper | Proximal Right Lower | Proximal Left Lower | Distal Right Lower | Distal Left Lower |

**Table 3: Organ/Organ System Listing**

| Organ | Organ System |
|---|---|
| **Head** | Brain<br>Bone<br>Salivary Glands<br>Soft tissue component<br>Other |
| **Neck** | Lymph nodes<br>Bone/bone marrow<br>Thyroid<br>Other |
| **Thorax** | Lung<br>Heart<br>Lymph nodes<br>Bone/bone marrow<br>Paravertebral soft tissue<br>Other |
| **Abdomen** | Liver<br>Spleen<br>Adrenal<br>Kidney<br>Lymph nodes<br>Bone/bone marrow<br>Paravertebral soft tissue<br>Other |
| **Pelvis** | Bladder<br>Genitalia<br>Lymph nodes<br>Bone/bone marrow<br>Other |
| **Extremities** | Bone/bone marrow<br>Other soft tissue |

The investigator will also record if the imaging findings are consistent with neuroblastoma when disease has been identified and describe the disease as follows:

- Primary tumor (in neurogenic tissue), no metastases.
- Primary tumor with metastases.

- No primary tumor, but metastases.

Sites of metastases will also be subcategorized as: soft tissue only; osteomedullary only; soft tissue and osteomedullary.

All responses to the image assessments will be recorded in the CRF.

#### 8.1.1.1 Exploratory Assessment of Potential Impact of $^{18}$F-*m*FBG Image Findings

Prior to performance of $^{18}$F-*m*FBG imaging, the treating oncologist will record the current management plan, based on current clinical and diagnostic imaging information, including *m*IBG/FDG results, in the CRF. After study imaging procedures, the oncologist will review the $^{18}$F-*m*FBG imaging results with the on-site nuclear medicine/radiology investigator. Thereafter, the oncologist will record a new assessment of disease status in the CRF using one of the following categories:

a) Less severe (fewer lesions on $^{18}$F-*m*FBG than *m*IBG/FDG);

b) Unchanged (No new sites of disease);

c) Possibly worse (1-2 more sites of disease);

d) Moderately worse (3-5 more sites of disease);

e) Much worse (>5 more sites of disease).

The oncologist will then record in the CRF whether any additional investigations (e.g. diagnostic imaging, targeted biopsy) would be indicated to confirm $^{18}$F-*m*FBG findings. Finally, assuming findings on $^{18}$F-*m*FBG imaging were confirmed, the oncologist will indicate whether a change in management plan would be warranted (Yes or No). If "Yes", details of the new plan will be recorded in the CRF.

The above assessments are for exploratory purposes only. The treating oncologist will not make changes in the current management plan for the subject based on the $^{18}$F-*m*FBG imaging findings.

### 8.1.2 Offsite assessment of imaging data

Digital unprocessed image data files and all processed/reconstructed PET images will be transferred to the ICL for image processing, blinding and randomization. ICL personnel will oversee the qualitative examination of $^{18}$F-*m*FBG PET images by 3 independent readers with no knowledge of the clinical status of the subjects or the SoR. Each reader will assess the image quality on a 4-point scale (1-poor; 2-fair; 3-good; 4-excellent) and identify the presence of abnormal increased uptake consistent with tumor. Readers will have access to cross-sectional anatomic images (CT or MR) acquired as part of the PET imaging study to aid in anatomic localization of sites of abnormal increased $^{18}$F-*m*FBG uptake.

Digital unprocessed image data files for clinical $^{123}$I-*m*IBG studies performed within 30 days prior to $^{18}$F-*m*FBG administration and during the 3-month follow-up period will also be transferred to the ICL for

image processing, blinding and randomization. These will include planar images (whole-body and spot) and SPECT acquisitions.

The complete set of $^{123}$I-*m*IBG images will be qualitatively examined by the same 3 independent readers as interpreted the $^{18}$F-*m*FBG studies, with oversight by ICL personnel as for $^{18}$F-*m*FBG images. The independent readers will have no knowledge of the clinical status of the subject (including the SoR) and there will be no association with the $^{18}$F-*m*FBG images for that subject. Each reader will assess the image quality of all images submitted (as diagnostic-optimal/suboptimal or non-diagnostic) and identify the presence of abnormal uptake consistent with tumor. Readers will have access to any CT images acquired as part of the SPECT exams to aid in anatomic localization of sites of abnormal increased $^{123}$I-*m*IBG uptake.

Blinded image evaluation procedures for both $^{123}$I-*m*IBG and $^{18}$F-*m*FBG are described in detail in the Blinded Image Evaluation (BIE) Manual supporting this protocol. $^{123}$I-*m*IBG and $^{18}$F-*m*FBG images will be read in separate review sessions.

For exploratory purposes, image core laboratory technologists will perform quantitative analyses of all $^{18}$F-*m*FBG lesions identified by the independent readers. Standard methods will be used to determine SUV and TBR for each site of abnormal uptake. These results will be recorded on a technologist CRF.

Readers will record all sites of abnormal $^{18}$F-*m*FBG and $^{123}$I-*m*IBG uptake unless lesions are too numerous to catalog (e.g. >3 lesions in a single rib or liver segment). In this circumstance, the image review CRF will be completed in accordance with rules presented in the BIE Manual for documenting more than a specified number of abnormalities in a particular anatomic region. With the exception of "too-numerous to report" findings, all sites of abnormal uptake will be recorded in terms of anatomic location and intensity. Readers will also record an overall disease extent score based on the 10-segment model (9 osteomedullary regions, 1 soft tissue) routinely employed with $^{123}$I-*m*IBG image assessments (15). Further details are presented in the BIE Manual.

For each image set, the reader will indicate whether the total study is consistent with presence or absence of active tumor on a subject-level. The term "active tumor" means tissue that would be identified as neuroblastoma on histological examination.

### 8.1.3 Standard of Reference (SoR)

Presence or absence of tumor will be determined by the Expert Panel of 2 pediatric oncologists. The standard of reference (SoR) will be a consensus binary decision based on all evidence presented to the Panel. Histopathology results from biopsy or surgical specimens will be considered current if the tissue was obtained within 30 days of study imaging procedures, with no interval therapy between the dates of $^{18}$F-*m*FBG imaging and tissue sampling. SoR determinations will be based on the aggregate of available information, including current histopathology, imaging (including $^{123}$I-*m*IBG), biochemistry, and clinical data.

For all subjects who completed a $^{18}$F-*m*FBG scan at baseline (including any who were Lost-to-Follow-up), clinical data recorded in the CRFs (and supporting source documents as appropriate) will be presented to the Expert Panel. These data will include information obtained prior to and during a maximum of 4 months following $^{18}$F-*m*FBG imaging, such as results of recent imaging procedures (CT, MRI, scintigraphy), previous tumor therapy (if any), and sites and histopathology from relevant past tissue sampling. The Panel members, who will be blinded to the study $^{18}$F-*m*FBG imaging findings, will render a final consensus decision for each subject of either presence or absence of tumor as of the date of $^{18}$F-*m*FBG imaging.

The Expert Panel will function under the guidance of the Expert Panel Charter (Section 10.2.3).

## 8.2 Safety and Other Assessments

All subjects (or their legal guardians) will sign informed consent prior to conduct of any study procedures. The investigators and study team overseen by the sponsor will review the safety data. The safety data will be collected and evaluated according to the following schedule:

**Table 4: Study Procedures by Period**

| | |
|---|---|
| **Informed Consent** | • Informed Consent signed |
| **Screening Period**<br>**(Day -30 to day -1 before Baseline)** | • Verification of eligibility based on the inclusion and exclusion criteria.<br>• Medical history.<br>• Review of concomitant medications.<br>• Review of imaging and histopathology results from within one year of the expected baseline date for all subjects and earlier functional imaging for subjects in durable remission as appropriate.<br>• Physical examinations, ECGs, vital signs, and laboratory tests that were performed as part of the subject's routine clinical care |
| **Baseline**<br>**(0-3 hr prior to dosing)** | • Limited physical examination.<br>• Pre-administration events (any symptoms occurring before dosing).<br>• Vital signs (heart rate, systolic and diastolic blood pressure, and respiration rate), oxygen saturation, and body temperature.<br>• Review of concomitant medications.<br>• Blood samples for hematology and biochemistry unless obtained as part of clinical care within the previous 3 days<br>• 12-lead ECG (until obtained on 25 subjects)<br>• Urine pregnancy test for all female subjects of childbearing potential, to confirm a negative result.<br>A subject who does not continue to meet the inclusion/exclusion criteria must be withdrawn from the study as a screen failure and must not receive $^{18}$F-*m*FBG. |
| **Baseline**<br>**(5 ± 2 minutes prior to dosing)** | • Injection site monitoring (as appropriate).<br>• Pre-administration events (any symptoms occurring before dosing). |
| **Administration of $^{18}$F-*m*FBG** | • Adverse event monitoring from time of administration to discharge, including injection site monitoring as appropriate<br>• Recording of any medications administered during this time period |
| **Post-administration of $^{18}$F-*m*FBG**<br>**(20 ± 10 minutes)** | • Vital signs (heart rate, systolic and diastolic blood pressure, and respiration rate) and oxygen saturation.<br>• Limited physical examination (visual inspection supplemented by other assessments at discretion of investigator) |

| | |
|---|---|
| **Discharge**<br>**(2 hr ± 45 min post dose)**<br><br>*After completion of the PET imaging session and prior to subject discharge from the clinic* | • Vital signs (heart rate, systolic and diastolic blood pressure, and respiration rate), oxygen saturation, and body temperature.<br>• 12-lead ECG (first 25 subjects)<br>• Recording of AEs.<br>• Limited physical examination.<br>• Blood samples for hematology and biochemistry |
| **Safety follow-up**<br>**(24 hr ± 6 hr post-dose)** | • Telephone contact unless there is an unresolved post-dose AE or interval occurrence of AE post-discharge. In that case, in-person visit is required. In-person visit should include vital signs, limited physical examination, specified laboratory tests, and other assessments appropriate to nature of AE. |

If the same evaluation was performed more than once during a time interval (e.g. physical examination, vital signs measurement), the time and results of each evaluation and the reason for replicate assessments will be recorded.

All subjects will be followed initially for 24 hours following the administration of $^{18}$F-*m*FBG, at which time safety assessments will conclude. Clinical data for potential use in efficacy assessments will be collected for a maximum of 3 months (+1 month at request of participating investigator) post-administration of $^{18}$F-*m*FBG, but these data will not be used for identifying late-occurring adverse effects of the IMP.

Adverse events (AE) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5 (36). Grades 1, 2, and 3 are mild, moderate, and severe or medically significant but not immediately life-threatening AEs respectively. Grades 4 and 5 are serious AEs (SAEs), life-threatening requiring urgent intervention, and death related to AE, respectively.

Interpretation of the clinical situation of the subject should be performed in accordance with the appropriate decision algorithm in Section 8.3. Once AE notification is decided upon, the investigators are required to follow the procedure described for AE notification.

Subjects will be followed up to 24 ± 6 hours post-administration of $^{18}$F-*m*FBG for any occurrence of AEs. All serious and non-serious AEs must be followed until the end of the follow-up period or until a final outcome is known. An outcome of "Not Resolved" is an accepted final outcome for non-serious AEs at the end of a subject's participation in the study, and for SAEs at database lock.

### 8.2.1 Clinical Laboratory Evaluation

Results of blood and urine samples performed as part of the routine clinical care during the screening period will be recorded on the subject's CRF. These may include hematology parameters, serum biochemistry, and plasma and urine catecholamine metabolites (e.g., vanillylmandelic acid (VMA), homovanillic acid (HVA)).

The following bloodwork will be obtained on the baseline date prior to administration of $^{18}$F-*m*FBG unless the same tests were performed as part of clinical care during the preceding 3 days.

**Table 5: Laboratory Parameters**

| Hematology | Biochemistry |
|---|---|
| Hematocrit | Creatinine |
| Hemoglobin | Chloride |
| White blood cell (WBC) count | Urea nitrogen |
| WBC differential | Bicarbonate |
| Platelet count | Sodium |
| | Potassium |
| | Glucose |
| | Alkaline phosphatase |
| | Aspartate transaminase |
| | Alanine transaminase |
| | Bilirubin (Total) |
| | Lactic dehydrogenase |

These same determinations will be made from blood samples drawn at discharge following completion of $^{18}$F-*m*FBG imaging. If changes in blood test results meet the criteria for an AE, the subject will have an in-person visit the following day. At that visit, the blood test(s) that resulted in the AE determination will be repeated. In addition, if new changes in subject status and/or a new AE are observed between discharge and the 24-hour safety contact, the above laboratory tests will be performed as part of the in-person visit on the day following the baseline visit.

Laboratory reports, with appropriate documentation of investigator review, will be retained in the subject's study binder at the site.

It is anticipated that the maximum amount of blood taken will not exceed 30 mL for all the samples taken during the subject's study participation.

For females of childbearing potential, a urine pregnancy test will be performed at baseline (1 hour ± 30 min) pre-administration of $^{18}$F-*m*FBG. Any woman whose pregnancy test is positive at baseline will not be administered the IMP and will be withdrawn from the study.

As part of study site initiation, the investigator will supply the sponsor with the reference ranges as well as all certifications and licenses held by any laboratory that will provide test results for this study.

### 8.2.2 Vital signs

Vital sign parameters include measurements of heart rate, systolic and diastolic blood pressure, respiration rate, and body temperature. Vital signs should be measured with the subject at rest. If $^{18}$F-*m*FBG is administered in a peripheral arm vein, blood pressure should be measured in the contralateral arm if possible.

### 8.2.3 Electrocardiograms (ECGs)

Pre- and post-$^{18}$F-*m*FBG administration ECGs will be obtained on each subject until a total of 25 individuals have undergone those exams. The sponsor will closely monitor enrollment and procedural details and will advise all investigational sites when this number of subjects has been achieved. ECGs will not be required for subsequent subjects but can still be obtained at the discretion of the investigator based on clinical safety considerations.

Each 12-lead ECG will be evaluated at the site by a study investigator or designee. The primary purpose of the on-site review is to determine if an AE has occurred, in accordance with the decision algorithm in Section 8.3. Each 12-lead ECG tracing must be signed and dated by the interpreter and archived with the subject's study records.

Additional review of all ECGs will be performed off-site at an independent ECG core laboratory, as described in Section 8.2.3.1.

#### 8.2.3.1 ECG core laboratory responsibilities

The ECG data obtained specifically for this study will be independently read within 72 hours of the ECG examinations by a board-certified cardiologist at an ECG core laboratory. The ECG core laboratory cardiologist will review, interpret, and provide a written assessment of the ECGs, determining all intervals (eg, PR, QRS, QT, and RR) and wave changes and calculating QTc intervals. Copies of the report for each ECG interpretation will be provided to the sponsor and the investigational site. The investigational site will archive the report in the investigator's study record for the subject.

### 8.2.4 Physical examination

A qualified medical professional will perform a limited physical examination at baseline and discharge that will include recording an assessment for the presence of abnormalities in general appearance, lungs, cardiovascular system, abdomen, skin, and extremities. A visual inspection of the subject will be performed following administration of the IMP as part of adverse event monitoring.

In the event that new or worsening abnormal physical examination findings are encountered during the study, these terms are defined as follows: a new abnormal physical examination finding is defined as one that occurs when a subject's normal baseline physical examination becomes abnormal post baseline, based on clinical grounds. A worsening abnormal physical examination finding is defined as one that occurs when a subject's abnormal baseline physical examination becomes worse post baseline, also based on clinical grounds.

Any abnormal finding observed post-administration that is new or represents a worsening from baseline is an AE. Investigators are required to follow the procedure described for AE notification and document the abnormal physical examination finding in the subject's CRF.

### 8.2.5 Discharge Procedures

At time of discharge, study personnel shall provide to the subject (or parent, legal guardian, or accompanying caregiver) an instruction sheet concerning actions that might be required following departure from the clinic. This sheet will list any untoward reactions or unpleasant feelings that might be noted (e.g., swelling, rash, nausea, dizziness, warmth, localized pain) and provide contact telephone numbers for study personnel. The subject (or legally responsible caregiver) will be instructed to call the listed number(s) to report any reactions or any other concerns that he/she might have and to return to the hospital for any symptoms of more serious concern. The instruction sheet will also provide the subject with the time and location to return on the following day in either of the following circumstances:

a) an AE requiring further follow-up occurred on the baseline day prior to discharge; or

b) the investigator believes that an AE may have occurred subsequent to discharge from the clinic.

Prior to discharging the subject, it is the investigator's responsibility to be certain that the subject or caregiver clearly understands what should be done during the next 24 hours in case any reactions or other problems are noted.

An investigator will contact the subject (or caregiver) by telephone at 24 hours (±6 hours) to determine his/her condition and confirm that no untoward reactions have occurred since discharge. If the investigator receives information that is concerning for a possible new AE, he/she will schedule an in-person follow-up visit with the subject on that day to reassess his/her condition. If an AE is confirmed at that visit, the laboratory tests listed in Table 5 are to be performed.

## 8.3 Adverse Events and Serious Adverse Events

### 8.3.1 Definitions of Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Only events/signs that begin or worsen in severity after administration of $^{18}$F-*m*FBG will be reported as AEs.

### 8.3.2 Definition of Serious Adverse Events (SAEs)

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 8.3.3 Classification of an Adverse Event

#### 8.3.3.1 Intensity of an Adverse Event

All AEs should be recorded using acceptable diagnoses, if possible. AE intensity will be graded in accordance with CTCAE v5.0 (see Section 8.2). Alternatively, intensity of AEs not specifically defined in CTCAE v5.0 can be described using the following definitions:

a. **Mild**: Events that are tolerable and require minimal or no treatment and do not interfere with the subject's daily activities.

b. **Moderate**: Events that result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning or normal activity.

c. **Severe**: Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 Relationship to Study Intervention

All AEs must have their relationship to study intervention assessed by the investigator who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals and follows a clinically reasonable response.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – An event whose temporal relationship to study intervention administration

makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provide plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

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

#### 8.3.3.3 Expectedness

The site PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

### 8.3.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

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

### 8.3.5 Adverse Event Reporting

The investigator is responsible for close monitoring of the subject following administration of the IMP. If there are any findings on the pre-discharge assessment that are of concern to the investigator, even if they are not considered to represent an AE, monitoring of the subject should continue until the investigator is satisfied that there are no unresolved issues. At the discretion of the investigator, additional measurements of vital signs, 12-lead ECG, and oxygen saturation may be obtained. All such data should be recorded in the CRF.

Subjects will be closely observed and questioned for any kind of AE during the study procedures and throughout the study period with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report to the study staff any pre-administration events (any symptoms occurred before dosing) and post-administration signs (e.g., between formal observations).

If an AE has already been reported, it is not necessary to report each related sign and pre-administration event (any symptoms occurred before dosing) of that AE as a separate AE. For example, if a patient with neuroblastoma and frequently labile vital signs has a sudden increase in blood pressure and pulse following completion of PET/CT imaging, this would be classified as a single AE considered likely related to underlying disease; change in pulse and BP should not be recorded as separate AEs. However, increased blood pressure and increased body temperature could be reported as separate AEs if the investigator considered them related to different clinical conditions (e.g., neuroblastoma and infection).

All non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "Not Resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study.

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor according to the Medical Dictionary of Regulatory Activities (MedDRA).

### 8.3.6 Serious Adverse Event Reporting

The investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or Investigator's Brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

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

The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

SAEs will be recorded in the CRF if they occurred as follows:

- After a subject received $^{18}$F-*m*FBG and throughout the subject's follow-up period, *
- After the subject's follow-up period, and for which a causal relationship to $^{18}$F-*m*FBG cannot be ruled out.

*Follow-up period is defined as the protocol-stipulated period (until 24 hr post-injection) or, for subjects prematurely withdrawn from a study, the duration of a subject's participation.

Notification of SAEs should be sent as follows:

**Innervate Radiopharmaceuticals Pharmacovigilance**
**In care of:**
**Avance Clinical LLC**
**Email safety@avancecro.com**
**Fax +1 206-299-9118**

All serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "Not Resolved" is an acceptable final outcome for SAEs at database lock.

### 8.3.7 Reporting Events to Investigators

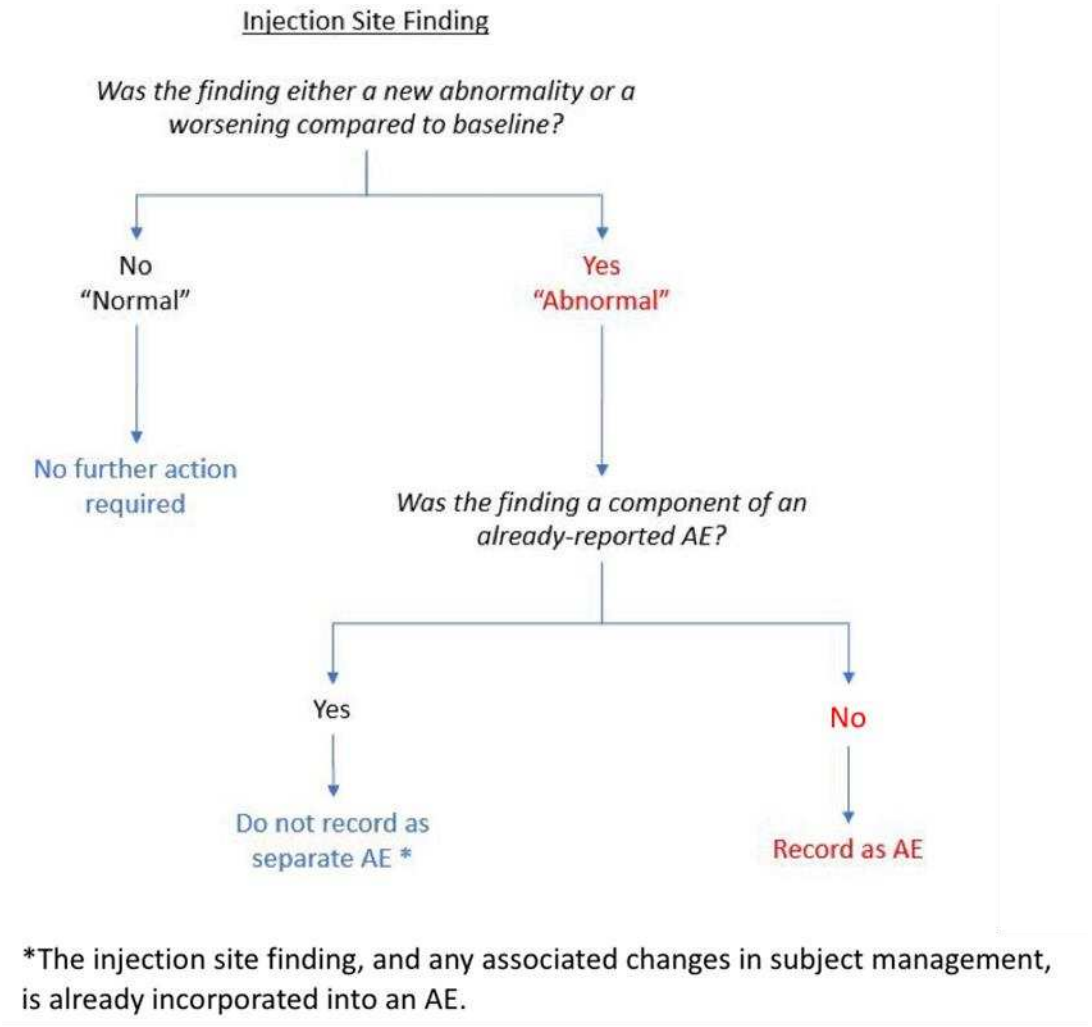
A summary of each reported SAE will be distributed within 15 working days of Sponsor receiving notification to all investigators, who should immediately forward them to their Independent Ethics Committee/Institutional Review Board (IEC/IRB) and local health authorities, according to local regulations.

### 8.3.8 Events of Special Interest

#### 8.3.8.1 Injection site monitoring

Injection site monitoring is only required if the IMP is administered via a peripheral vein. Abnormal injection site findings include, but are not limited to, hematoma, dermatitis, urticaria, extravasation, bleeding, redness, phlebitis, and infection. The injection site should be observed for any pre-administration abnormalities at baseline. Any abnormal finding observed post-administration that is new or represents a worsening from baseline is an AE (see decision algorithm below).

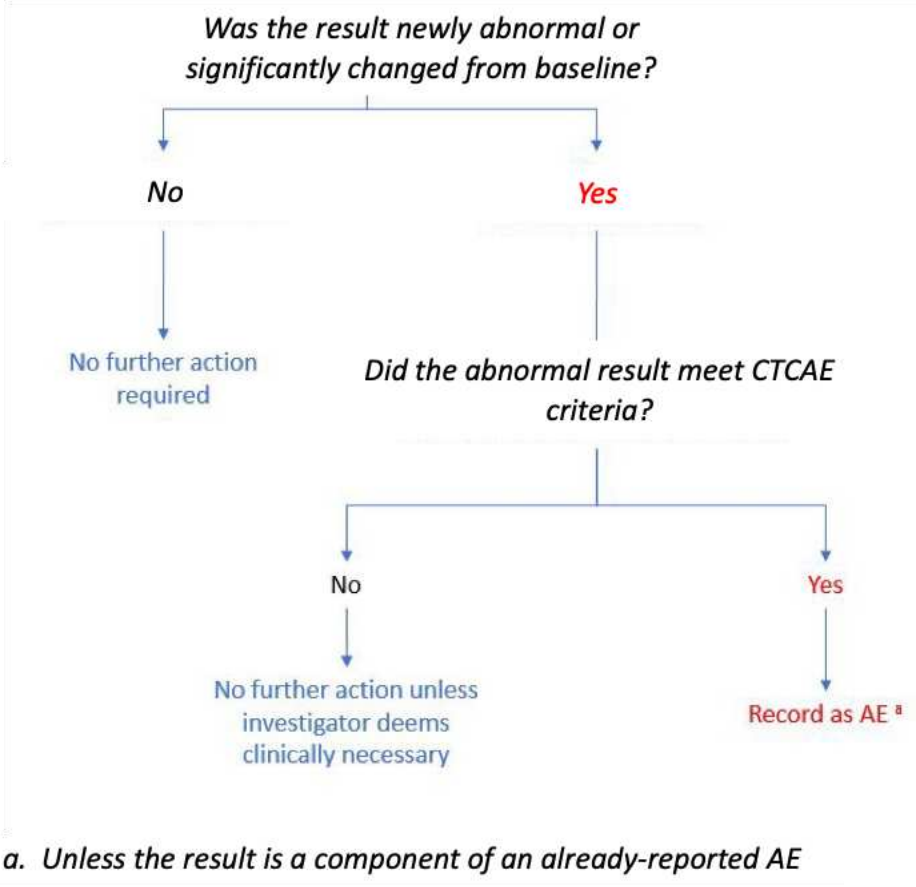
**Figure 2: Interpretation of Injection Site Findings in Conjunction with the Clinical Situation of the Subject**




### 8.3.8.2 Clinical Laboratory Abnormalities as AEs

Results of any laboratory tests performed from the time of IMP administration up to 24 hours post-administration should be reviewed promptly by the investigator and actions should be taken as deemed necessary to address any findings, in accordance with the algorithm in Figure 3. Any result meeting CTCAE v5.0 criteria should be recorded as an AE.

**Figure 3: Interpretation of Safety Monitoring Results in Conjunction with the Clinical Situation of the Subject**




#### 8.3.8.3 Vital Sign Abnormalities as AEs

Results of any vital signs performed, from the time of IMP administration to the conclusion of discharge, should be reviewed promptly by the investigator and actions should be taken as deemed necessary to address any findings of clinical concern. Any result meeting CTCAE v5.0 criteria (Figure 3) should be recorded as an AE.

If an immediate allergic or other reaction is noticed in vital sign readings while $^{18}$F-*m*FBG is being administered resulting in a termination of dosing, the investigator should record the AE as appropriate and reference the vital sign observations.

#### 8.3.8.4 ECG Abnormalities as AEs

Results of any 12-lead ECGs performed, from the time of IMP administration to the conclusion of discharge, should be reviewed promptly by the investigator and actions should be taken as deemed necessary to address any findings. Changes between pre- and post-$^{18}$F-*m*FBG administration exams meeting CTCAE v5.0 criteria (Figure 3) should be recorded as an AE. Any other ECG finding that the investigator deems to be an AE should also be recorded.

#### 8.3.8.5 Physical Examination Abnormalities as AEs

Results of any physical examinations performed, from the time of IMP administration to the conclusion of discharge, should be reviewed promptly by the investigator and actions should be taken in accordance with the algorithm below. Any result, which was either a new abnormality or a worsening compared to baseline (Figure 3) should be recorded as an AE.

### 8.3.9 Reporting of Pregnancy

If a subject deemed "Not pregnant" at the time of investigational drug administration reports that she is pregnant within 90 days of the baseline date, the site investigator will request information to determine if the subject might have been pregnant on the date of administration of the investigational drug. If there is definitive evidence that pregnancy occurred >24 hours post-administration, this information should be documented in the subject's medical record and no further action is required. If it cannot be determined with certainty that the subject was not pregnant on the date of administration of the investigational drug, the investigator should counsel the subject that any adverse effect on the fetus is extremely unlikely based on the low radiation dose and short half-life of the radioactive element. This counseling should be documented in the subject's medical record. She should also be advised that while no further evaluations are needed, she should inform her primary care and obstetrics/gynecology providers about her participation in this study in case they might have questions for the study investigator or sponsor.

## 8.4 Unanticipated Problems

### 8.4.1 Definition of Unanticipated Problems (UPs)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the sponsor. The UP report will include the following information:

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

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

- UPs that are SAEs will be reported to the IRB and to the data coordinating center/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 3 weeks; of the IRB's receipt of the report of the problem from the investigator.

### 8.4.3 Reporting Unanticipated Problems to Participants

If UPs are deemed to be reportable to OHRP, the sponsor will provide investigators with a letter describing the incidents as reported to OHRP as a letter to subjects. Investigators should have their IRB approve the letter prior to mailing to subjects who participated in the study. Site Informed Consent Forms should be updated to reflect any necessary communication to subjects and IRBs must approve any revisions to Informed Consent Forms.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

Tests on primary and secondary statistical measures endpoints will be 2-sided unless otherwise noted. Confidence intervals (CI) will be 2-sided at the 95% confidence level.

- Testing the following 2-sided hypotheses at the $\alpha$=0.05 and $\beta$=0.2 level, the primary hypotheses at the subject level are:
  - $H_0$: Positive Percent Agreement (PPA) = 50% vs. $H_1$: PPA ≠ 50%
  - $H_0$: Negative Percent Agreement (NPA) = 50% vs. $H_1$: NPA ≠ 50%
- Proof of efficacy is based on rejecting both null hypotheses with PPA and NPA >50% for PET imaging at 60 minutes post-administration of $^{18}$F-*m*FBG (details presented in Section 9.4.2).

## 9.2 Sample Size Determination

The study population will consist of subjects with known or presumed neuroblastoma.

The sample size determination is based on the expected values of PPA and NPA for $^{18}$F-*m*FBG PET.

Calculation of N is shown in Table 6 (37). Sample size is calculated using a 2-sided test at $\alpha$=0.05. The last column represents the smallest observed rate for which the lower bound of the 2-sided 95% confidence interval will be >50%.

**Table 6: Sample Size Calculation**

| | Alternative Hypothesis Rate | Required Sample Size | Smallest Observed Rate |
|---|---|---|---|
| **Power 80%** | 70.0% | 49 | 63.3% |
| | 72.5% | 37 | 64.9% |
| | 75.0% | 30 | 66.7% |
| | 77.5% | 25 | 72.0% |
| | 80.0% | 20 | 75.0% |
| | 82.5% | 17 | 76.5% |
| | 85.0% | 15 | 80.0% |
| | 87.5% | 12 | 83.3% |
| | 90.0% | 12 | 83.3% |
| | 92.5% | 9 | 88.9% |
| | 95.0% | 9 | 88.9% |

Expected PPA is 85%. Expected NPA is 80%. As such, the minimum required numbers of positive and negative cases are 15 and 20 respectively. Therefore, the minimum total sample size is 35 subjects.

Recruitment will continue until both of the following criteria have been met:

- A minimum of 15 subjects with positive SoR for neuroblastoma have completed the study.
- A minimum of 20 subjects with negative SoR for neuroblastoma have completed the study.

The total sample size will likely exceed the sum of these minima for several reasons.

- Subject enrollment will continue until the required numbers of positive and negative tumor diagnoses have been confirmed by the Expert Panel. As these latter evaluations may occur up to 3 months after IMP imaging, enrollment beyond the target numbers will have continued during this time interval.

- Whichever target is met first (most likely positive cases given the difference in required numbers), enrollment will continue and additional cases in both categories will be included. For example, if the 15$^{th}$ positive case is confirmed when only 12 negative cases have been confirmed, the subjects enrolled to identify the remaining 8 negative cases will almost certainly include additional positive cases.

- On the date both diagnosis targets are met, further enrollment will be terminated. However, there will likely be additional already-dosed subjects whose data have not yet been reviewed by the Expert Panel.

Based on the above, it is estimated that the number of dosed and evaluable subjects will be about 30-50% greater than the minimum requirement, for a total of 45-52 subjects.

Data for all subjects who received $^{18}$F-*m*FBG will be presented to the Expert Panel for determination of SoR.

## 9.3 Populations for Analyses

The following populations will be used for analyses purposes:

- **Intent-to-Image population (IIP):** All subjects receiving $^{18}$F-*m*FBG.
- **Diagnostic Efficacy Population (DEP**): All subjects who completed a $^{18}$F-*m*FBG scan at baseline and either complete the 3-month clinical follow-up period or discontinue the study prior to 3-months after $^{18}$F-*m*FBG imaging.

The IIP will be the primary population for assessment of the primary and key secondary efficacy endpoints and for safety. The primary and key secondary efficacy endpoints will also be assessed using the DEP as sensitivity analyses.

## 9.4 Statistical Analyses

### 9.4.1 General Approach

A separate document, the Statistical Analysis Plan (SAP), will provide additional details on the statistical analyses to be generated in support of this protocol. Any deviations from the statistical analysis outlined in the protocol and the Statistical Analysis Plan will be described, along with reasons for the deviations, in the final Clinical Study Report.

Tabulations of summary statistics, graphical presentations, and statistical analysis will be performed using SAS software. Outputs will present data pooled across study centers.

Prior to database lock, the sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the safety and efficacy evaluations due to a protocol violation that may have an impact on the scientific aspects and interpretation of the study results. The reason(s) for any exclusion will be described in the clinical study report.

Measurements used in the calculation of efficacy endpoints are described in Table 7.

**Table 7: Formulas for Calculating Endpoints**

| | **SoR Diagnosis Positive** | **SoR Diagnosis Negative** | |
|---|---|---|---|
| **Blinded Image Read Positive** | **a(TP)** | **b(FP)** | Positive Predictive Value TP / (TP + FP) |
| **Blinded Image Read Negative** | **c(FN)** | **d(TN)** | Negative Predictive Value TN / (TN + FN) |
| | PPA TP / (TP + FN) | NPA TN / (TN + FP) | Accuracy (TP+TN)/(TP+TN+FP+FN) |

PPA: (No. of True Positives) / (No. of subjects with positive SoR)

AND

NPA: (No. of True Negatives) / (No. of subjects with negative SoR),

WHERE:

- True Positive (TP) is defined as a subject with SoR diagnosis of active neuroblastoma and abnormal uptake on $^{18}$F-*m*FBG PET imaging identified as neuroblastoma.

- True Negative (TN) is defined as a subject in whom active neuroblastoma has been ruled out according to the SoR, and there is no abnormal uptake consistent with active tumor on $^{18}$F-*m*FBG PET imaging.

Exact binomial 2-sided 95% confidence limits will be estimated for PPA, NPA, positive predictive value (PPV), and negative predictive value (NPV) based on $^{18}$F-*m*FBG uptake assessments of the 60-minute post-administration PET images.

### 9.4.2 Analysis of Primary Efficacy Endpoint(s)

The primary endpoint, focal increased uptake (presence or absence) on PET/CT or PET/MR at 60 minutes post-administration of $^{18}$F-*m*FBG, will be used to determine the PPA and NPA of $^{18}$F-*m*FBG imaging for identification of the presence or absence of neuroblastoma (SoR) on a subject-level based on the IIP.

The results of the 3 independent readings of $^{18}$F-*m*FBG imaging will presented as independent measures. For each reader, PPA and NPA of $^{18}$F-*m*FBG for the diagnosis of neuroblastoma on a subject level will be calculated along with corresponding exact binomial 2-sided confidence limits.

For each reader, the primary analyses will test the hypothesis: $H_0$: $p_a = 0.50$ vs. $H_1$: $p_a \neq 0.50$, where PPA and NPA are as defined above.

$^{18}$F-*m*FBG imaging will be deemed diagnostically efficacious if lower bounds for 95% CIs about both subject-level PPA and NPA are greater than 50% for the same 2 out of 3 readers (or for all 3 readers).

If there are IIP subjects with missing scan data (scan not performed or incomplete/uninterpretable by a reader), two analyses will be performed, one assuming scans with missing data would have been interpreted positive for neuroblastoma and one assuming the scans would have been interpreted negative for neuroblastoma. If there are subjects with missing scan data, the success criterion described above must be met for both sets of sensitivity analyses.

There will be a separate presentation of subject-level PPA and NPA with 95% CIs using the DEP in order to assess the sensitivity of the primary efficacy analysis for the IIP.

The 0.50 (50%) thresholds for PPA and NPA under the null hypothesis were chosen because the values for sensitivity and specificity for the pharmacologically similar compound $^{123}$I-*m*IBG ranged from 82% to 88% for the tumors in the pivotal prospective trial (14,15). While it is expected that the PET compound $^{18}$F-*m*FBG will produce superior diagnostic imaging results compared to the conventional nuclear agent $^{123}$I-*m*IBG, the rarity of the tumors under investigation has necessitated a design with a small number of subjects. This small sample size amplifies the potential negative impact of an imaging outlier, especially for calculation of NPA. In addition, the upper limit of achievable PPA for $^{18}$F-*m*FBG will likely be in the 90-95% range because tumors with low expression of NET may not be detectable using NET-dependent agents, regardless of the nuclear imaging technology employed (16).

### 9.4.3 Analysis of Key Secondary Efficacy Endpoint

The key secondary endpoint, focal increased uptake (presence or absence) on $^{123}$I-*m*IBG scintigraphy consistent with active tumor, will be used to compare results of $^{123}$I-*m*IBG imaging with those of $^{18}$F-*m*FBG imaging based on the IIP. For each reader and each SoR category, McNemar's test will be used to test the null hypothesis that the marginal probabilities of a correct reading are equal for $^{18}$F-*m*FBG and $^{123}$I-*m*IBG, that is, pr(a+b) is equal to pr(a+c) in Table 8 below. The two-sided alternative hypothesis is that the marginal probabilities of a correct reading are not equal. For SoR positive, "correct" means the image interpretation is positive for tumor, while for SoR negative, it means the image interpretation is negative for tumor.

**Table 8. Agreement Between $^{18}$F-*m*FBG and $^{123}$I-*m*IBG Blinded Image Interpretations**

| | **$^{123}$I-*m*IBG Read Correct** | **$^{123}$I-*m*IBG Read Incorrect** |
|---|---|---|
| **$^{18}$F-*m*FBG Read Correct** | **a** | **b** |
| **$^{18}$F-*m*FBG Read Incorrect** | **c** | **d** |

A fixed sequence testing procedure will be used for the key secondary analysis in order to control the overall level of significance. Thus, if the primary analysis is not statistically significant, the results of the key secondary analysis will be considered exploratory.

#### 9.4.3.1 Additional efficacy analyses and summaries

Summaries based on tumor location will also be made on a by-reader basis. Tumor locations are defined as a combination of Anatomic Grid Location and Organ System identifiers as described Section 8.1.1. Overall disease extent score will be based on the 10-segment model (9 osteomedullary regions, 1 soft tissue) described in the BIE Manual.

Additional analyses performed but not indicated in previous sections will be considered exploratory.

### 9.4.4 Other Analyses

#### 9.4.4.1 Inter-reader variability

Variation of imaging assessments with respect to accuracy will be considered for each pair of independent blinded reviewers. A kappa statistic with a value > 0.40 for inter reader agreement will be considered acceptable, as per the suggested guidelines by Landis and Koch, where a value of 0.41 – 0.60 is considered as moderate level of agreement (38). The inter-reader agreement for 3 blinded readers will be compared between different pairs of readers using the kappa (κ) value, where the value of the z statistic is determined as:

$$z = (\kappa 1 - \kappa 2) / [\sigma 2 (\kappa 1) - \sigma 2(\kappa 2)]^{1/2}$$

Where $\kappa 1 = \kappa$ for A vs. B and $\kappa 2 = \kappa$ for B vs. C.

A value of $\kappa$ lower than 0.41 will be explored further to determine if there is an underlying cause for this low value.

Since $\kappa$ is highly dependent on marginal distributions, the proportion of agreement will also be used to assess inter-observer variation with respect to subject-level assessment. Agreement for normal and abnormal uptake will be considered separately, where the proportion of agreement for abnormal uptake is $p_a = pr[a/(a + b + c)]$, and the proportion of agreement for normal is $p_n = pr[d/(b + c + d)]$ (Table 9).

**Table 9: Agreement between Two Blinded Readers with Respect to Imaging Uptake**

| | | Reader 1 | |
|---|---|---|---|
| | | Abnormal | Normal |
| Reader 2 | Abnormal | a | b |
| | Normal | c | d |

To further characterize the proportion of agreement for abnormality and normality between each pair of reviewers, 2-sided 95% confidence intervals may be provided.

#### 9.4.4.2 Intra-reader variability

Intra-reader variability will be examined by having each of the 3 independent blinded readers perform 2 image evaluations on 10% of the $^{18}$F-*m*FBG and $^{123}$I-*m*IBG images. The same duplicated images will be assessed by all 3 readers, and the subject-level assessment at each evaluation will be listed side by side. Given the small sample size (approximately 5 for each imaging agent), no formal statistical tests will be conducted to assess intra-reader agreement. Only the first assessment of those duplicated images will be included in the efficacy analyses previously described.

### 9.4.5 Safety Analyses

Safety will be reported for the Intent-to-Image Population.

In addition to the investigator's evaluation of normal or abnormal, the sponsor will internally evaluate each vital sign result and ECG result for whether it reflects a new abnormality, and for numeric data, whether it reflects a significant worsening from baseline or an outlying result or extreme value. These terms are defined for vital sign results and ECG results as follows:

- A new abnormality will be any abnormal post-baseline result for a subject whose baseline was within normal limits.
- A significant worsening will be any numeric clinical laboratory result, vital sign result, or ECG interval measurement that represents a change from baseline by ≥25% of the baseline value, in the direction away from normal (i.e., in the direction that is clinically significant).

- An outlying result for any numeric vital sign result or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:
  - <25th Percentile - 1.5 * (interquartile range) OR
  - >75th Percentile + 1.5 * (interquartile range).
- An extreme value for any numeric vital sign result or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:
  - <25th Percentile – 3 * (interquartile range) OR
  - >75th Percentile + 3 * (interquartile range).

Subjects who demonstrate new abnormal results will be noted in data listings and reviewed by the sponsor. Outlying results will be identified and reviewed in the context of the subject's other abnormal results.

Post-administration changes from baseline will be summarized by mean, standard deviation, minimum, and maximum at each time point. Plots and shift tables of all post-administration changes from baseline versus time will be generated and examined for trends and relatively large individual changes from baseline.

#### 9.4.5.1 Clinical laboratory evaluation

Clinical laboratories available at screening and baseline (pre-administration) will be summarized. For subjects with both pre- and post-administration laboratory results, data from all measurements will be presented in tabular form and changes from baseline will be summarized. No summaries based on changes from screening will be performed.

A listing of clinical laboratory values, including identification of abnormal values, as identified by the local laboratories, will be presented. Clinical laboratory variables will be summarized using descriptive statistics for continuous variables. For each parameter, counts and percentages will be used to summarize the distribution of normal and abnormal values.

#### 9.4.5.2 Vital signs

For each vital sign or oxygen saturation variable and each time point, the following safety endpoints will be summarized by counts and percentages.

- The occurrence of one or more changes from baseline, at each post-administration time point, greater than a pre-specified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats per minute for heart rate, 1.5°C for body temperature, 10 breaths per minute for respiration rate, and 5% oxygen saturation).
- The occurrence of post-administration values outside the normal limits

#### 9.4.5.3 Electrocardiograms (ECGs)

Results from the ECG core laboratory reviews will be used for all statistical analyses.

For subjects with pre- and post-administration ECGs, the following safety endpoints will be summarized by counts and percents:

- The occurrence of a change from baseline in the PR interval within pre-specified increments of 4 msec (<4, 4 to 8, >8 to 12, >12), 10 msec (<10, 10 to 20, >20) and 25 msec (<25, 25 to 50, >50).
- The occurrence of a change from baseline in the QTc, QRS and RR interval within the following pre-specified increments:
    - <30 msec, 30 to 60 msec, and >60 msec increments for QTc interval;
    - <50 msec, 50 to 100 msec, and >100 msec increments for QRS interval;
    - <250 msec, 250 to 500 msec, and >500 msec increments for RR interval.
- The occurrence of post-administration values outside the normal limits in the PR, QTc, QRS or RR interval

Abnormal ECG waveforms will be summarized by counts and percentages.

#### *9.4.5.3.1 QTc-specific analyses:*

QTc will be summarized as:

1) Changes from baseline in the QTc interval, using the following categories: <30 msec; 30 to 60 msec; >60 msec
2) Number and percent of subjects with absolute QTc values >440 msec.

### 9.4.5.4 Physical examination

Number and percent of subjects with changes in the limited physical examination status from normal at baseline to abnormal at discharge from the clinic (approximately 2 hours ± 45 minutes post-administration of $^{18}$F-*m*FBG) and at the 24 ± 6 hours visit (if done) will be presented using counts and percentages.

### 9.4.5.5 Injection site reactions

The number of injection site reactions will be summarized as part of the AE listings and summaries.

### 9.4.5.6 Adverse events

The occurrence of one or more AEs or SAEs reported through the completion of the 24-hour follow-up visit will be summarized using counts and percentages. Adverse events will be summarized by: CTCAE criteria (or intensity), seriousness; relationship to the IMP; and time of occurrence.

AEs will be summarized as previously indicated. Exact 95% confidence intervals will be created for overall AE rates.

### 9.4.6 Baseline Descriptive Statistics

A table will be provided with the following information:

- Number of enrolled subjects.
- Number of subjects included in the Intent-to-Image, and Diagnostic Efficacy Populations.
- Number of subjects withdrawn from the study and the reasons for withdrawal.

Demographic information (age, height, and weight) will be summarized using descriptive statistics. Gender and race will be summarized by counts and percents.

Medical histories will be summarized by counts and percents. Concurrent medications will be recorded and coded using a standard classification system and grouped by primary and secondary classes if applicable.

### 9.4.7 Planned Interim Analyses

None.

### 9.4.8 Subgroup Analyses

None.

### 9.4.9 Tabulation of Individual Participant Data

Data will be presented in listings for all enrolled subjects. Sub-population data (e.g., intent-to-image and/or efficacy) may also be presented as additional listings.

### 9.4.10 Exploratory Analyses

Comparison of whole-body disease $^{18}$F-*m*FBG and $^{123}$I-*m*IBG scores will be presented in tables and listings.

Results for the exploratory assessment of the potential clinical implications of the difference between findings on $^{18}$F-*m*FBG and $^{123}$I-*m*IBG imaging will be tabulated from the CRFs completed by the clinical oncologists (Section 8.1.1.1). Subjects with only clinical $^{18}$F-FDG imaging results or no recent functional imaging results will be excluded from these analyses.

The following will be presented in tables and listings.

a) Difference in disease severity assessment between $^{18}$F-*m*FBG and $^{123}$I-*m*IBG imaging

b) Additional investigations that might be considered based on $^{18}$F-*m*FBG imaging findings

c) Frequency of a proposed change in management plan based on $^{18}$F-*m*FBG imaging findings

The relationship of quantitative analysis of $^{18}$F-*m*FBG PET lesions (SUV or TBR) and concordance/discordance with findings on $^{123}$I-*m*IBG will be explored in terms of correlative imaging and follow-up data confirming presence or absence of neuroblastoma at the identified sites. Appropriate analyses (e.g. Receiver Observer Characteristic curves) will be performed to determine the performance characteristics of various quantitative thresholds for discriminating benign from malignant lesions.

Additional exploratory analyses, as feasible, will be performed to investigate the following questions.

1) Is there any difference in PPA and/or NPA between subjects imaged with PET/CT vs. PET/MR?

2) In comparison to clinical $^{123}$I-*m*IBG imaging studies (as available for recording lesion-level findings on study CRF), did $^{18}$F-*m*FBG PET:

   a) identify at least 1 new lesion (primary or metastatic) confirmed as active tumor?

   b) provide an easier or more comfortable experience for the subject? This information will be collected from the subject (or legal guardian) in an exit interview following completion of $^{18}$F-*m*FBG imaging.

3) To the extent that tumor lesion dimensions can be quantified from CT and MR images, what is the relationship between SUV and lesion size? This analysis may include lesions detected on anatomic but not PET imaging to estimate a detection size limit for the latter modality.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Regulatory, Ethical and Study Oversight Considerations

### 10.1.1 Informed Consent Process

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study. The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the subject with the date and time of that signature indicated. The investigators will keep the original consent forms and copies will be given to the subjects.

#### 10.1.1.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### 10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND) sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and sponsor and will provide the

reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

### 10.1.3 Confidentiality and Privacy

The investigators must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In CRFs and other documents or image material (including materials from all CT, MR, nuclear, ultrasound examinations, etc.) submitted to the sponsor, subjects will not be identified by their names, but by an identification code (e.g., allocation number).

Personal medical information may be scrutinized for the purpose of verifying data recorded in the CRF. This may be done by the monitors, properly authorized persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

### 10.1.4 Future Use of Data

All data collected for this study will be the property of the sponsor. All data will be transferred to the sponsor and also stored at the investigational site as described in Section 10.1.9.2. After the study is completed, the de-identified, archived data will be transmitted to and stored at an appropriate Data Repository, as per institutional policies.

All $^{18}$F-*m*FBG PET images will be retained at the investigational site for a minimum of 5 years or until either 2 years after approval of the last regulatory submission or until 2 years after the sponsored research program is terminated and FDA is notified.

### 10.1.5 Key Roles and Study Governance

The investigational site will be responsible for the processing and quality control of the data. Data management will be carried out in accordance with the standard operating procedures (SOPs) of the sponsor's designated clinical research organizations (CROs).

The handling of data, including data quality control, will comply with national and local regulatory requirements and the CROs' SOPs.

The site principal investigator has ultimate responsibility for oversight of all aspects of the performance of this study. This includes designation of appropriately trained individuals to oversee efficacy and safety aspects of the study. In consideration of the benign safety profile of PET imaging agents, an external panel to monitor safety data (such as a Data Safety Monitoring Board) will not be utilized.

### 10.1.6 Safety Oversight

The principal investigator (PI) will review all reports provided by the on-site ECG reader(s) and AE and SAE reports. The PI is responsible for verifying that all potential safety issues have been thoroughly investigated and reported to the appropriate local and national authorities. The PI has the prerogative to solicit input from additional clinical and safety authorities as needed to insure the study is performed in accordance with national and local regulatory requirements, International Conference on Harmonisation (ICH) E6-good clinical practice (GCP), and the sponsor's quality standards and SOPs.

### 10.1.7 Clinical Monitoring

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

Study Monitoring will be performed in accordance with ICH E6-GCP, sponsor's or the CRO's SOPs, the protocol, and applicable local regulations.

The monitors, auditors, personnel authorized by the sponsor, and health authority inspectors or their agents will be given direct access to source data and documentation (e.g., medical charts/records, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

According to ICH E6-GCP, the sponsor or the authorized personnel on behalf of the sponsor may audit the investigational site to compare raw data, source data, and associated records with the interim or final report of the study to assure that data have been accurately reported.

The investigators must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

### 10.1.8 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be investigated for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### 10.1.9 Data Handling and Record Keeping

#### 10.1.9.1 Data Collection and Management Responsibilities

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

Any data recorded directly in the CRF, for which no other written or electronic record will be maintained in the subject's medical record, will be considered source data and should be signed by the investigator(s) (e.g., results of physical examinations, vital signs testing, or the IMP administration procedure). It is recommended that source data not be recorded directly in the CRF.

Trained site personnel will enter data into CRFs with reasons given for any missing data. Any errors should be corrected within the CRF data correction procedures. There will be an audit trail of date and time of the correction, and the person correcting the error.

The investigational site will be responsible for the processing and quality control of the data. Data management will be carried out in accordance with applicable sponsor and CRO SOPs for clinical studies. The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6-GCP, and local regulations where applicable) and the CRO's or investigational site's SOPs.

#### 10.1.9.2 Study Records Retention

All study documentation at the investigator site will be archived in accordance with ICH GCP E6 and the site's record retention SOPs.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

### 10.1.10 Protocol Deviations

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

Any significant deviation from the protocol when no approved amendment exists, particularly if it could have a negative impact on the scientific aspects and interpretation of the study results, will be recorded as a protocol violation and will be addressed as such during the reporting of the study. Prior to database lock, the sponsor will make and justify any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the safety and efficacy evaluations as a result of protocol violations.

### 10.1.11 Publication and Data Sharing Policy

At the completion of this study, the investigators from all participating institutions (as a group) shall have the right to publish the results of the work conducted under this protocol, guided by the study Lead Investigator. The sponsor will be given the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor will make every reasonable effort to consider and release each proposed publication within 30 days or each proposed abstract within 15 days of submission.

### 10.1.12 Conflict of Interest Policy

According to 21 CFR, Part 54, the sponsor is required to completely and accurately disclose or certify information concerning the financial interests of a clinical investigator (or investigating institution) who is not a full-time or part-time employee to the FDA. Therefore, the investigators (or investigating institutions) must provide the sponsor with sufficient, accurate financial certification that none of the following financial

arrangements (further defined in 21CFR Part 54.2) exist with the sponsor or fully disclose the nature of the arrangement. This financial disclosure also applies to any financial arrangements that exist between the sponsor and the investigator's spouse(s) or dependent children.

- Compensation for participation in the study is affected by the outcome of the study.
- Significant equity (greater than $50,000) interest in the sponsor's company.
- Proprietary interest in the tested product.
- Significant payments of other sorts, exceeding a monetary value of $25,000.

## 10.2 Additional Considerations

### 10.2.1 Insurance

This study is covered under Innervate Radiopharmaceuticals' Liability Insurance Policy. A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

### 10.2.2 BIE Manual

A BIE Manual describing operational procedures for the blinded image evaluations in greater detail will be provided to independent image reviewers at the ICL prior to the first reading session. This manual will be reviewed with the readers prior to each subsequent reading session to ensure continuing compliance with all study procedures. Completion of these reviews will be documented at the ICL.

### 10.2.3 Charter for the Expert Panel

The Expert Panel will act independently of the sponsor to evaluate the available clinical and imaging information on all subjects enrolled into the study to confirm the presence or absence of active tumor. The responsibility of the Expert Panel will be to review all pertinent data and arrive at a conclusion concerning whether these subjects did or did not have active tumor at the time of IMP administration in this study. Expert Panel members will be blinded to all information concerning the imaging results from study IMP administration.

The following subsections present general guidelines for the Expert Panel process. Refer to the Expert Panel Charter that supports this protocol for detailed descriptions of Expert Panel procedures.

#### 10.2.3.1 Membership

The Expert Panel will consist of 2 pediatric oncologists to assess data on enrolled subjects with known or presumed neuroblastoma. The members of the panel will constitute a quorum and will function completely independently of the investigators and will have no financial, scientific or other conflict of interest with the sponsor.

The qualifications of each panel member will be confirmed by the sponsor to ensure relevant clinical expertise and familiarity with clinical trial methodology.

#### 10.2.3.2 Committee Process

An initial tele- or video conference between panel members and sponsor representatives or CRO designees will take place prior to the first data review meeting. At this conference, the remit of the panel will be reviewed, and the members will discuss guidelines for presentation of information and resolving disagreements. Any decision rules established will be recorded and sent to the sponsor.

The Expert Panel will meet with frequency necessary to complete review of all subject data by a date agreed upon in advance with the sponsor. The first review meeting of the Expert Panel will occur once data-review packages for the first 10 enrolled subjects are complete. Thereafter, the Panel will meet after approximately each subsequent group of 10 subjects have complete data packages. Based on the expected study enrollment of 45-52 subjects, the final Panel meeting, which may include review of less or more than 10 subjects, will occur following assemblage of the data package for the last subject enrolled and dosed in the trial. Depending upon the number of subjects whose data must be reviewed, additional meetings may be scheduled to facilitate determination of whether targets for positive and negative diagnoses have been met.

Sponsor representative(s) or its designee(s) will be present at every meeting to assist with administrative tasks only. Said representative will be blinded to all $^{18}$F-*m*FBG image read information (both on-site and independent reader) and will not be an investigational site monitor.

All Expert Panel meetings shall be closed to the public because discussions will address confidential subject information. If necessary, an emergency teleconference between the Panel and the sponsor may be scheduled at any time to discuss issues concerning rates of subject recruitment and quality of data being submitted by investigational sites.

#### 10.2.3.3 Meeting Format

Each Expert Panel meeting will consist of review and discussion of the available data on a predetermined list of subjects. The estimated maximum number of subjects whose data will be reviewed during a meeting day is 15.

The initial data package provided to the Expert Panel members will include information up to the date of $^{18}$F-*m*FBG imaging. This will include data recorded on the CRF (demographics, medical history, laboratory and imaging results) and copies of source documents (e.g., laboratory, histopathology, diagnostic imaging reports) supporting or elaborating on data supplied in the CRF. In order to quantify the impact of functional imaging results on the Panel decision, the results of the most recent $^{123}$I-*m*IBG or $^{18}$F-FDG studies will be excluded from the initial information package. The members will then reach a consensus decision concerning the presence or absence of active tumor, and this will be recorded in the CRF. The recent functional imaging results will then be provided and the disease evaluation repeated. The results of this second consensus evaluation will be recorded in the CRF as the SoR. For each determination, the Panel will record a numeric confidence score (maximum value 100%).

If the members judge that the available information is insufficient to provide a reliable conclusion regarding subject tumor status, they will request the sponsor's representative to obtain additional information from the investigational site to assist the deliberations. The final decision for the subject will then be deferred until data collection for the subject 3-month follow-up is completed and summarized. This additional information will be provided to the Panel at the next available meeting. Following this review, the Panel will make a final decision. If the initial review of the deferred case is at the final scheduled Panel meeting, the second review can be done on an ad hoc basis as soon as possible thereafter.

All Panel SoR determinations must be either positive or negative. A disease status characterization as "Indeterminate" will not be accepted.

#### 10.2.3.4 Reports

Results of the Expert Panel review will be recorded on the CRF for each subject. A general report for each Expert Panel meeting will also be prepared by the sponsor (or designee) for signature by the Panel members, documenting the number of subjects reviewed and any issues that arose that might affect future performance of the study. This report will be circulated to the Panel members for editing and approval within 2 weeks of the meeting date.

Reports and minutes are considered strictly confidential.

#### 10.2.3.5 Sponsor Responsibilities

Prior to each meeting, the sponsor (or designee) is required to generate and distribute to the Expert Panel members a report indicating the number of subjects whose data will be available for review at the next scheduled meeting. Should this number be judged inadequate, the members may request a postponement until a specified larger number of records are available. The sponsor will then reschedule the meeting in accordance with such a request.

#### 10.2.3.6 Confidentiality

All materials, discussion, and proceedings of the Expert Panel are completely confidential. Members and other participants in Expert Panel meetings should not discuss the results of Expert Panel meetings with anyone other than official representatives of the sponsor.

## 10.3 Revision History

10.3.1 Reasons for Amendments

Version 1.1: Changes made as a result of: i) protocol and informed consent template review by WIRB; ii) Administrative addition of NANT protocol number to Title page.

Version 2.0: Changes made in response to: i) FDA clinical/statistical suggestions/recommendations following review of IND submission; ii) Administrative addition of NCT number to Title page; iii) Administrative addition of Protocol Signature Page.

Version 3.0: Changes made to: i) Remove the absolute requirement for completing baseline procedures within 30 days of informed consent by defining the screening interval as the 30-days prior to the baseline date; ii) Clarify procedures for rescreening if the baseline visit must be rescheduled and requirements for recording results from within the new screening interval; iii) Add specific language covering the possibility that investigational medicinal product (IMP) may be provided in a syringe or a vial; iv) Add references to additional external documents (Radiopharmacy Manual; Expert Panel Charter) that support the protocol; v) Replace multiple uses of the term investigational medicinal product with the acronym IMP; vi) Acknowledge change of Sponsor name from Illumina Radiopharmaceuticals to Innervate Radiopharmaceuticals since approval of protocol v2.0; vii) Update the Schema, the Schedule of Activities and its footnotes; viii) Correct minor errors in the body of the protocol.

Version 4.0: Changes made to: i) Redefine Inclusion criterion 2 (now subpart a) as subjects who had undergone neuroblastoma therapy within the previous 36 months and allow qualifying $^{123}$I-*m*IBG or $^{18}$F-FDG exams either before or after the baseline date; ii) Add new subpart b to Inclusion criterion 2, allowing enrollment of subjects in durable remission (no objective evidence of disease for at least 36 months) with most recent imaging evaluation within 12 months of baseline; iii) Clarify instructions for collection of imaging and histopathology results within 12 months prior to baseline; iv) Clarify requirements for in-person 24-hour safety assessments to include subjects with unresolved post-dose AEs at discharge on baseline date; v) Increase the allowed time interval for pre-administration baseline safety assessments; vi) Update name of Pharmacovigilance and Clinical CRO.

| **Protocol Version and Date** | **Protocol Section** | **Description of Change(s)** | **Reason for Change(s)** |
|---|---|---|---|
| **1.0**<br><br>**18Dec2020** | | Original Version | N/A |
| **1.1** | Title Page | Title page includes NANT Study Number | Administrative update |
| **24Jan2021** | 1.1 | Replace "primary or metastatic" with "presence of". | Correction of synopsis to be consistent with body of protocol |

| | | | |
|---|---|---|---|
| | 1.1 | Addition of Assent as part of informed consent process for children age 7-17. | Request from WIRB during review of informed consent template. |
| | 5.1 | Addition of Assent as part of informed consent process for children age 7-17. | Request from WIRB during review of informed consent template. |
| **2.0**<br><br>**18Mar2021** | Protocol Signature Page | Addition of Protocol Signature Page | Administrative update |
| | 1.1; 2.1; 2.3.1; 2.3.1.1; 3.3; 6.1.1; 6.3.3; 8.4.3; 9.4.2 | "patient" changed to "subject" | Consistency of designation for trial participants |
| | 1.1 | Addition of "SoR" in multiple locations and mIBG included in SoR | Clarity in definition of PPA and NPA and role of mIBG in SoR |
| | 1.1 | Change "understand" to "assess" | Consistency with body of protocol |
| | 1.1 | Reverse the order of IIP and DEP to change primary analysis population to IIP | Response to Feb 26 FDA request |
| | 2.1 | Change "18" to "16" | Correct typographical error |
| | 2.1 | Add definition of tumor | For clarity regarding use of word "tumor" throughout protocol |
| | 3.1 | Change "a" to "an" Article with NDA | Grammatical correction |
| | 4.3 | Revision of subgroup c) by addition of explanatory text describing circumstances under which image acquisition time might be increased to assure satisfactory image quality. | Response to Feb 9 FDA request |

| | | | |
|---|---|---|---|
| | 6.1.1.2.1 | Add periods at end of list items | Grammatical consistency |
| | 6.1.1.2.2 | Add periods at end of list items | Grammatical consistency |
| | 6.3.3 | Revisions relating to ICL for consistency | Generalize blinded read description relative to ICL personnel oversight without committing to in-person reads at ICL |
| | 7.1 | Added text on termination criteria | Response to Feb 9 FDA request |
| | 8.1.1 | Replace "designated …" with ICL | Consistency with prior terminology |
| | 8.1.2 | Revisions regarding ICL role | For consistency with revised 6.3.3 |
| | 8.1.3 | Text revised, removing reference to definitive histology and adding current histopathology to list of data used by Expert Panel. | For greater clarity in adjudication of SoR. |
| | 8.2 | Addition of "will be recorded" at the end of paragraph | Inadvertent omission |
| | 9.1 | Added text regarded SAP | Response to Feb 26 FDA comment |
| | 9.2 | Revisions in text regarding sample size | Improved clarity |
| | 9.3 | Changes in IIP and DEP descriptions to add mention of sensitivity analysis | Response to Feb 26 FDA request |
| | 9.4.1 | Text rearranged and reference to SAP added | Improved clarity |
| | 9.4.2 | Statistical descriptions revised | Response to Feb 26 FDA request |
| | 9.4.3 | Addition of "based on the IIP" to clarify final sentence | Response to Feb 26 FDA request |
| | 9.4.4.1 | Delete "standard error for each" | Improved clarity |
| | 9.4.5.1 | Add "changes from baseline …" for laboratory results | Inadvertent omission |
| | 10.2.3.3 | Sentence added regarding SoR | Clarification in response to FDA Feb 26 comment |
| **3.0**<br><br>**18 Mar2022** | Title page; Signature page; Investigator Declaration; | Illumina Radiopharmaceuticals replaced with Innervate Radiopharmaceuticals LLC | Reflects company name change on October 1, 2021 |

| | | | |
|---|---|---|---|
| | List of Abbreviations; 2.2; 6.2.1; 8.3.6; 10.2.1 | | |
| | 1.1 Synopsis | Second paragraph: "or are scheduled to undergo" deleted and "of" changed to "prior to" | To clarify that functional imaging must be completed prior to administration of $^{18}$F-*m*FBG |
| | 1.2 | Text in Screening Visit box changed from "(-30 to -3 days prior to baseline)" to "(to be completed between -30 and -1 day prior to baseline)" | To eliminate requirement that screening evaluations be completed by 3 days prior to $^{18}$F-*m*FBG administration |
| | 1.3 Schedule of Activities | Addition of a "Subject Enrollment" column; Change of subheading for "Screen Pre-dose" column; revision of footnotes 6 and 8; new footnote 15 | Changes for consistency (moving Informed Consent to separate column before Screening) and clarification of Screening Interval and possibility of rescreening |
| | 2.3.1 | Paragraph 3 revised to indicate need for aseptic conditions for "any manipulation of the subject dose". Wording also changed regarding product supplied in a vial. | To generalize instructions applicable to IMP provided in either a single-use syringe or a vial |
| | 5.2: Exclusion criterion 4) | Changed "approximately" to "up to" | Clarification that 30 minutes is maximum expected scan time rather than the approximate time for all subjects |
| | 6.2.1 | Paragraph 2: Change "ready-to-use container" to "syringe or vial". Add sentence concerning Radiopharmacy Manual | More specific description of how IMP is provided. Reference to external manual with additional guidance |
| | 6.2.2 | Batch" replaced by "Lot". "End-of-synthesis" replaced by "calibration" | Modifications for consistency with terminology of IMP |

| | | |
|---|---|---|
| | | label |
| 6.2.4 | Text revised to provide more specific instructions regarding handling of syringes with greater than needed activity | Addressing a contingency when IMP is provided in a ready-to-use syringe |
| 6.4 | batch" replaced by "lot". | For consistency with terminology of IMP label |
| 7.2 | "/Rescreening" added to title. Ending of Bullet 5 modified. New fifth paragraph added | To clarify criteria for subject withdrawal and for rescreening if Baseline visit must be rescheduled |
| 8.1.2 | Paragraph 5: Removed "(1-4 scale)" | Correction of error in description of blinded image evaluation intensity score |
| 8.2 | Table 4: Addition of row for "Informed Consent". Change in Screening Period to -30 to -1 day before Baseline. Deletion of text describing requirements for ordering IMP | Changes for consistency with Schedule of Activities and revised definition of "screening interval". Deletion of instructions that are presented in detail in Radiopharmacy Manual |
| 10.2.3 | Addition of new second paragraph | Indicate that the following text is descriptive, and the approved Expert Panel Charter is a separate document |
| 10.3 | Summary of changes in protocol version | Overview of changes itemized in this table |
| 6.1; 6.1.2; 6.2.1; 6.2.2; 6.2.4; 6.3; 7.2; 8.2.1; 8.3.5; 8.3.8.2; 8.3.8.3; 8.3.8.4; 8.3.8.5; 9.2; 9.4.5.6; 10.1.9.1 | Investigational medicinal product replaced with IMP | Consistency with inclusion of IMP in Abbreviations list |
| Title page; 8.3.6 | C3 Research Associates replaced with Avance Clinical LLC; safety email address changed from safety@c3- | To reflect acquisition of C3 Research Associates by Avance Clinical |

**4.0**
**05 April 2023**

| | | |
|---|---|---|
| | research.com to safety@avancecro.com. | LLC as of September 6, 2022. |
| 1.1 Synopsis | "Study Design":<br>Paragraph 2 modified to include both recently-treated subjects undergoing routine functional imaging and those in durable remission for whom frequency of imaging for disease surveillance is reduced.<br>Paragraph 3: Reference to Table I added<br>"Study Population": Inclusion Criterion 2 modified to define 2 groups: recently-treated subjects undergoing routine functional imaging; and subjects in durable remission who undergo surveillance imaging less frequently. | To expand eligible population to include subjects in remission for whom diagnostic imaging is performed less frequently. |
| 1.2 Figure 1 Schema | Time interval for baseline pre-dose safety assessments increased from 1 hr±30 min to 0-3 hr. | To provide greater flexibility in relation to time of administration of IMP. |
| 1.3 Schedule of Activities | a) Column header for Baseline Pre-dose changed from 1 hr±30 min to 1 hr +2 to -1hr.<br>b) Footnotes revised.<br>1. "Unresolved AE post-dose" added as criterion for performing in-person visit at 24 hours.<br>6. Changed to indicate results of all imaging studies performed within 1 year prior to baseline should be recorded during the screening period. For subjects in durable remission, if most recent functional imaging was >1 year before baseline, results for that scan should also be recorded.<br>8. Modified to indicate that: a) provisions apply only to subjects with treatment within previous 36 months; b) $^{18}$F-*m*FBG scan can be performed before or after $^{123}$I-*m*IBG or $^{18}$F-FDG.<br>15. Modified to indicate that requirements for $^{123}$I-*m*IBG or $^{18}$F-FDG scan only apply to subjects with treatment within previous 36 months. | a) To provide greater flexibility in timing of baseline safety assessments in relation to time of administration of IMP.<br>b) 1. To clarify AE monitoring requirements.<br>6. To assure all relevant imaging data are recorded for later review by the Expert Panel.<br>8 & 15. To make clear the specific requirements that apply to subjects meeting Inclusion Criterion 2a. |
| 2.2 | Paragraph 8 modified in accordance with addition of Inclusion Criterion 2b. Definition of "durable remission" added. | Changes for consistency with revision of Inclusion Criterion 2. |

| | | | |
|---|---|---|---|
| | 5.1 Inclusion criterion 2 | Original criterion modified and new part b). | To expand eligible population to include subjects in remission for whom diagnostic imaging is performed less frequently. |
| | 8.2 Table 4 | Screening Period: New bullet added to clarify expanded instructions for recording imaging and histopathology history data during this time period.<br>Baseline: 1 hour ± 30 minutes changed to 0-3 hr.<br>Safety Follow-up: Text revised to include unresolved AE at discharge as basis for in-person 24-hour visit. | For consistency in assuring collection of 1-year of imaging and histopathology results prior to baseline in support of Expert Panel process.<br>To provide greater flexibility in relation to time of administration of IMP.<br>To clarify specifications for in-person 24-hour safety visit. |
| | 9.4.10 | Paragraph 2: "or no recent functional imaging results" added to second sentence. | To make clear that subjects enrolled under new Inclusion Criterion 2b) will not be included in the Exploratory Analyses described in section 8.1.1.1. |

# 11 REFERENCES

1. Maguire LH, Thomas AR, Goldstein AM. Tumors of the neural crest. Common themes in development and cancer. Developmental Dynamics 2015; 244:311–322.

2. Newman EA, Nuchtern JG. Recent biologic and genetic advances in neuroblastoma: Implications for diagnostic, risk stratification, and treatment strategies. Semin Pediatr Surg. 2016 Oct;25(5):257-264.

3. Fishbein L. Pheochromocytoma and paraganglioma: Genetics, diagnosis, and treatment. Hematol Oncol Clin North Am. 2016 Feb;30(1):135-50.

4. Pfluger T, Piccardo A. Neuroblastoma: MIBG imaging and new tracers. Semin Nucl Med. 2017 Mar;47(2):143-157

5. Society of Nuclear Medicine and Molecular Imaging. Procedure: 123I-MIBG Scintigraphy. Accessed August 2, 2017.

6. Streby KA, Shah N, Ranalli MA, Kunkler A, Cripe TP. Nothing but NET: a review of norepinephrine transporter expression and efficacy of 131I-mIBG therapy. Pediatr Blood Cancer. 2015 Jan;62(1):5-11.

7. Kiratli Po, Tuncel M, Bar-Sever Z. Nuclear medicine in pediatric and adolescent tumors. Sem Nucl Med. 2016; 46:308-323.

8. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, et al. Scintigraphic localization of pheochromacytoma. N Engl J Med. 1981;305(1):12-17.

9. Corbett R, Oliff J, Fairley N, Moyes J, Husband J, Pinkerton R, et al. A prospective comparison between magnetic resonance imaging, meta-iodobenzylguanidine scinitgraphy and marrow histology/cytology in neuroblastoma. Eur J Cancer 1991;27:1560-1564.

10. Shulkin BL, Shapiro B. Current concepts on the diagnostic use of MIBG in children. J Nucl Med. 1998;39:679-688.

11. Wale DJ, Wong KK, Viglianti BL, Rubello D, Gross MD. Contemporary imaging of incidentally discovered adrenal masses. Biomed Pharmacother. 2017 Mar;87:256-262.

12. Liu B, Zhuang H, Servaes S. Comparison of [$^{123}$I]MIBG and [$^{131}$I]MIBG for imaging of neuroblastoma and other neural crest tumors. Q J Nucl Med Mol Imaging. 2013 Mar;57(1):21-8.

13. Jacobson AF, Deng HW, Lombard J, Lessig HL, Black RR. 123I-mIBG scintigraphy for the detection of neuroblastoma and pheochromocytoma: Results of a meta-analysis. J Clin Endoc Metab 2010; 95:2596-2606.

14. Vik TA, Pfluger T, Kadota R, Castel V, Tulchinsky M, Farto JC, Heiba S, Serafini A, Tumeh S, Khutoryansky N, Jacobson AF. (123)I-mIBG scintigraphy in patients with known or suspected neuroblastoma: Results from a prospective multicenter trial. Pediatr Blood Cancer. 2009; 52:784-790.

15. Matthay KK, Shulkin B, Ladenstein R, Michon J, Giammarile F, Lewington V, Pearson AD, Cohn SL. Criteria for evaluation of disease extent by (123)I-metaiodobenzylguanidine scans in neuroblastoma: a report for the International Neuroblastoma Risk Group (INRG) Task Force. Br J Cancer. 2010 Apr 27;102(9):1319-26.

16. CIS-US. Iobenguane [mIBG (131-I-meta-iodobenzylguanidine sulfate)]. NDA 20-084, 1994.

17. GE Healthcare. AdreView (Iobenguane I 123 Injection) for Intravenous Use Initial U.S. Approval: 2008.

18. Kwon HW, Becker AK, Goo JM, Cheon GJ. FDG Whole-Body PET/MRI in oncology: a systematic review. Nucl Med Mol Imaging. 2017 Mar;51(1):22-31.

19. Subramaniam RM. Precision medicine and PET/computed tomography: Challenges and implementation. PET Clin. 2017 Jan;12(1):1-5.

20. Jones T, Townsend D. History and future technical innovation in positron emission tomography. J Med Imaging (Bellingham). 2017 Jan;4(1):011013.

21. Garcia EV. Proceedings of the cardiac PET summit meeting 12 May 2014: Cardiac PET and SPECT instrumentation. J Nucl Cardiol. 2015 Jun;22(3):563-70.

22. Rufini V., Treglia G., Castaldi P., Perotti G., Giordano A. Comparison of metaiodobenzylguanidine scintigraphy with positron emission tomography in the diagnostic work-up of pheochromocytoma and paraganglioma: a systematic review. Q J Nucl Med Mol Imaging. 2013 Jun;57(2):122-33.

23. Balogova S, Talbot JN, Nataf V, Michaud L, Huchet V, Kerrou K, Montravers F. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur J Nucl Med Mol Imaging. 2013 Jun;40(6):943-66.

24. Garg PK, Garg S, Zalutsky MR. Synthesis and preliminary evaluation of para- and meta-[18F]fluorobenzylguanidine. Nucl Med Biol. 1994 Jan;21(1):97-103.

25. Zhang H, Huang R, Pillarsetty N, Thorek DL, Vaidyanathan G, Serganova I, Blasberg RG, Lewis JS. Synthesis and evaluation of 18F-labeled benzylguanidine analogs for targeting the human norepinephrine transporter. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):322-32.

26. Zhang H, Huang R, Cheung NK, Guo H, Zanzonico PB, Thaler HT, Lewis JS, Blasberg RG. Imaging the norepinephrine transporter in neuroblastoma: a comparison of [18F]-MFBG and 123I-MIBG. Clin Cancer Res. 2014 Apr 15;20(8):2182-91.

27. Pandit-Taskar N, Zanzonico P, Staton KD, et al. Biodistribution and dosimetry of 18F-Meta Fluorobenzyl Guanidine (MFBG): A first-in-human PET-CT imaging study of patients with neuroendocrine malignancies. J Nucl Med 2018; 59:147-153.

28. Hu B, Vāvere AL, Neumann KD, Shulkin BL, DiMagno SG, Snyder SE. A practical, automated synthesis of meta-[(18)F]fluorobenzylguanidine for clinical use. ACS Chem Neurosci. 2015 Nov 18;6(11):1870-9.

29. Dubois SG, Matthay KK. Radiolabeled metaiodobenzylguanidine for the treatment of neuroblastoma. Nucl Med Biol. 2008 Aug;35 Suppl 1:S35-48.

30. Delbeke D, Coleman RE, Guiberteau MJ, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. Approved by the Board of Directors of the Society of Nuclear Medicine on February 11, 2006. Accessed August 2, 2017.

31. Schillaci O. Use of dual-point fluorodeoxyglucose imaging to enhance sensitivity and specificity. Semin Nucl Med 2012; 42(4):267-80.

32. Gelfand MJ, Parisi MT; Treves ST. Pediatric radiopharmaceutical administered doses: 2010 North American consensus guidelines. J Nuc Med 2011;52:318-322.

33. Gelfand MJ. Dose reduction in pediatric hybrid and planar imaging. Q J Nucl Med Mol Imaging. 2010;54:379–388.

34. Jacobson AF, Travin MI. Impact of medications on mIBG uptake, with specific attention to the heart: Comprehensive review of the literature. J Nucl Cardiol 2015; 22(5):980-93.

35. Jacobson AF, White S, Travin MI, Tseng C. Impact of concomitant medication use on myocardial $^{123}$I-*m*IBG imaging results in patients with heart failure. Nucl Med Commun 2017; 38(2):141-148.

36. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events version 5.0, DCTD, NCI, DHHS, November 27, 2017. ((http//cyep.cancer.gov).

37. Karimollah HT. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomedical Informatics 2014; 48:193-204.

38. Landis RJ, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33:159-174.

# 12 ACTIVITY ADMINISTRATION GUIDELINES FOR PEDIATRIC SUBJECTS

For pediatric subjects, a fraction of the adult reference activity should be chosen, dependent upon body weight. The recommended activities are as follows (Table 10).

**Table 10: Activity Administration for Pediatric Subjects**

| Weight (kg) | Fraction of adult activity | $^{18}$F-*m*FBG pediatric activity (mCi) | $^{18}$F-*m*FBG pediatric activity (MBq) |
|---|---|---|---|
| 3 | 0.04 | 1.0* | 37* |
| 4 | 0.06 | 1.0* | 37* |
| 6 | 0.09 | 1.0* | 37* |
| 8 | 0.11 | 1.0* | 37* |
| 10 | 0.14 | 1.1 | 41 |
| 12 | 0.17 | 1.3 | 48 |
| 14 | 0.20 | 1.6 | 59 |
| 16 | 0.23 | 1.8 | 67 |
| 18 | 0.26 | 2.1 | 78 |
| 20 | 0.29 | 2.3 | 85 |
| 22 | 0.31 | 2.5 | 92 |
| 24 | 0.34 | 2.7 | 100 |
| 26 | 0.37 | 3.0 | 111 |
| 28 | 0.40 | 3.2 | 118 |
| 30 | 0.43 | 3.4 | 126 |
| 32 | 0.46 | 3.7 | 137 |
| 34 | 0.49 | 3.9 | 144 |
| 36 | 0.51 | 4.1 | 152 |
| 38 | 0.54 | 4.3 | 159 |
| 40 | 0.57 | 4.6 | 170 |
| 42 | 0.60 | 4.8 | 178 |
| 44 | 0.63 | 5.0 | 185 |
| 46 | 0.66 | 5.3 | 196 |
| 48 | 0.69 | 5.5 | 202 |

| Weight (kg) | Fraction of adult activity | $^{18}$F-*m*FBG pediatric activity (mCi) | $^{18}$F-*m*FBG pediatric activity (MBq) |
|---|---|---|---|
| 50 | 0.71 | 5.7 | 211 |
| 52 | 0.74 | 5.9 | 218 |
| 54 | 0.77 | 6.2 | 230 |
| 56 | 0.80 | 6.4 | 237 |
| 58 | 0.83 | 6.6 | 244 |
| 60 | 0.86 | 6.9 | 255 |
| 62 | 0.89 | 7.1 | 263 |
| 64 | 0.91 | 7.3 | 270 |
| 66 | 0.94 | 7.5 | 277 |
| 68 | 0.97 | 7.8 | 289 |

For intermediate weights between those listed, the formula Activity = Body mass (kg) * 8 mCi)/70 kg can be used (32).

*minimum activity (32)