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A Prospective Image Reevaluation Study to Assess the Efficacy of ^{18}F-*m*FBG PET Imaging in Subjects with Neuroblastoma

Phase:	3
Investigational Product:	IRP101 [^{18}F-*m*FBG (meta-fluorobenzylguanidine)]
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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(R3): Good Clinical Practice (ICH GCP).

PROTOCOL SIGNATURE PAGE

Protocol Number: **IRP101-305**
Version 2.0

Protocol Title: **A Prospective Image Reevaluation Study to Assess the Efficacy of ^{18}F-*m*FBG PET Imaging in Subjects with Neuroblastoma**

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CT	Computed tomography
d	Day
DICOM	Digital Imaging and Communication in Medicine
dL	Deciliter
EDC	Electronic Data Capture
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
IRC	Independent Review Charter
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
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 Percent Agreement
PET	Positron Emission Tomography
PPA	Positive Percent Agreement
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SOPs	Standard operating procedures
SPECT	Single photon emission computed tomography
TN	True negative
TP	True positive

1 PROTOCOL SUMMARY

1.1 Synopsis

Study Title: A Prospective Image Reevaluation Study to Assess the Efficacy of ^{18}F-*m*FBG PET Imaging in Subjects with Neuroblastoma	
Name of Product: ^{18}F-*m*FBG	
Study Number: IRP101-305	**Study Phase:** 3
Clinical Sites: Multi-center	
Primary Objective: 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) on a subject-level in confirming or excluding the presence of neuroblastoma.	
Secondary Objectives: The secondary objective of this study are: a) 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)) on a region/organ system level in confirming or excluding the presence of neuroblastoma. b) To assess intra- and inter-reader variability.	
Study Design: This is a prospective image revaluation study designed to assess the performance of ^{18}F-*m*FBG PET imaging in detecting the presence of neuroblastoma. Eligible participants will have undergone ^{18}F-*m*FBG PET imaging in a research trial or locally-authorized clinical use and have: a) an established diagnosis of active neuroblastoma; or b) an established diagnosis of neuroblastoma in remission; or c) no history or current evidence of neuroblastoma based on signs, symptoms, imaging findings, and laboratory results. This is a study involving blinded interpretation of existing ^{18}F-*m*FBG PET images. No subjects will be administered ^{18}F-*m*FBG. Previously collected ^{18}F-*m*FBG PET studies will be evaluated by 5 independent radiologists and/or nuclear medicine physicians. They will have access to limited clinical information on the reason subject was undergoing evaluations at the time of ^{18}F-*m*FBG imaging but be blinded to all other subject information. Blinded readers will record the findings on ^{18}F-*m*FBG scans judged consistent with presence of neuroblastoma and the disease status (+ or -) of the subjects. Subject-level performance of ^{18}F-*m*FBG PET will be assessed on the basis of positive and negative percent agreement with presence of at least 1 lesion identified by a blinded reader confirmed as neuroblastoma on clinical standard-of-care imaging and histopathology evaluations. Region/organ system 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 in the corresponding region on clinical standard-of-care imaging and histopathology evaluations. Both assessments will	

utilize the clinical information gathered as part of the trials or locally-authorized clinical use in which the ^{18}F-*m*FBG scans were acquired and relevant clinical follow-up available at the imaging sites.

Study Population

The planned population will consist of subjects with previously established presence or absence of active neuroblastoma. Individuals enrolled as healthy controls in ^{18}F-*m*FBG trials may be included.

Inclusion Criteria:

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

a) The subject has undergone ^{18}F-*m*FBG imaging in a previous research trial (including as a non-disease control) or locally-authorized clinical use.

b) Disease status (+ or – for neuroblastoma) as of the date of ^{18}F-*m*FBG imaging was established based on data collected as part of the previous clinical trial or locally-authorized clinical use or during subsequent clinical follow-up.

Exclusion Criteria:

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

1. There is insufficient correlative imaging and clinical follow-up data to establish subject disease status as of the date of ^{18}F-*m*FBG imaging.
2. ^{18}F-*m*FBG imaging from the previous trial was judged incomplete or uninterpretable.

Planned Number of Subjects: 40-50

Test Product; Dose; and Mode of Administration:

Quantity of ^{18}F-*m*FBG administered to each subject was determined based on the protocol specifications of the original trial. No ^{18}F-*m*FBG will be administered in this study.

Disease Status:

Presence or absence of neuroblastoma tumor as of the date of ^{18}F-*m*FBG imaging study will be based on an independent assessment of data collected during the original trial and additional information collected subsequent to trial participation. The assessment will utilize a predefined decision algorithm for determining disease status.

Duration of Treatment:

No ^{18}F-*m*FBG will be administered in this trial.

Duration of Study Participation:

NA

Efficacy Assessments:

Primary Endpoint:

- Focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging, reported as PPA and NPA for detecting neuroblastoma as determined by comparing clinical standard of care imaging and/or histopathology with comparable anatomic regions judged positive/negative by ^{18}F-*m*FBG.

Secondary Endpoints:

- Focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging in prespecified anatomic regions, reported as PPA and NPA for detecting neuroblastoma as determined by comparison with clinical standard of care imaging and/or histopathology in those regions.
- To assess inter- and intra-reader variability

Safety Assessments: None.

Interim Analysis: None

1.2 Schedule of Activities (SoA)

Table 1: Study Schedule of Events

Procedure	Enrollment (site)	Blinded Reads (ICL)	Statistical Analysis (CRO)
Inclusion/Exclusion	X		
Medical History	X		
Disease Status Determination	X		
Availability of mFBG imaging digital files	X		
Image Interpretation		X	
Data Analysis			X

ICL: Imaging Core Laboratory; CRO: Clinical Research Organization

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 (*m*IBG) labeled with an isotope of iodine (^{123}I or ^{131}I), based on the analogy of *m*IBG with the neurotransmitter norepinephrine (NE), which is produced and released by most neuroblastoma tumors, *m*IBG scintigraphy has been a staple in diagnostic evaluations of neuroblastoma patients for 30 years, initially with planar ^{131}I-*m*IBG imaging and more recently with ^{123}I-*m*IBG employing planar, single-photon emission computed tomography (SPECT), and SPECT/CT techniques.

Positron-emission tomography (PET) has become the dominant oncology nuclear imaging technique in the past 2 decades based on its superior image quality and spatial resolution compared to imaging with gamma-emitters such as ^{123}I. As PET radiopharmaceuticals have progressively replaced SPECT tracers in clinical practice, interest in development of a suitable replacement for ^{123}I-*m*IBG in neuroblastoma has increased. This led investigators at Memorial Sloan Kettering Cancer Center (MSKCC) and multiple European and Chinese sites to compare ^{123}I-*m*IBG with the PET analog meta-fluorobenzylguanidine labeled with ^{18}F (^{18}F-*m*FBG). In aggregate, more than 200 neuroblastoma subjects have been studied to date, with the combined data showing that ^{18}F-*m*FBG PET consistently identified more neuroblastoma lesions than planar and SPECT ^{123}I-*m*IBG studies.

Innervate Radiopharmaceuticals LLC has completed a Phase 3 pivotal trial of ^{18}F-*m*FBG PET imaging in neuroblastoma subjects (IRP101-301). The objective of the present study is to develop a second ^{18}F-*m*FBG PET dataset in neuroblastoma to demonstrate the diagnostic performance of this imaging agent. This efficacy-only study will compare ^{18}F-*m*FBG PET findings in subjects with confirmed presence of neuroblastoma and subjects without neuroblastoma, including a small number of subjects studied for diseases other than neuroblastoma.

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, ^{123}I-*m*IBG was approved in 1994 (16) and ^{123}I -*m*IBG was approved in 2008 (17) for the diagnostic localization of neuroblastoma.

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 30 years ago, and its biodistribution is very similar to *m*IBG (24-26). However, animal and human experience demonstrates more rapid clearance of ^{18}F-*m*FBG from blood and certain target organs 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). The expected advantages of ^{18}F as a positron emitter over the single-photon emitter ^{123}I, including higher resolution and superior image quality of PET compared to SPECT, have been confirmed in direct comparisons between ^{123}I-*m*IBG and ^{18}F-*m*FBG (26-31).

Multiple investigators have performed clinical trials of ^{18}F-*m*FBG imaging in neuroblastoma patients (27-31). Based on PET/CT imaging at 60-90 minutes post-administration, image quality was distinctly superior to contemporaneous ^{123}I-*m*IBG imaging of the same subjects. Analysis of ^{18}F-*m*FBG images at a lesion-level also demonstrated that more lesions were detected in almost every patient compared to ^{123}I-*m*IBG, images (27-31). In all published series, image interpretations were performed by on-site investigators.

The primary objective of the present prospective image reevaluation study is to provide additional data supporting the use of ^{18}F-*m*FBG for imaging neuroblastoma subjects using central blinded image interpretations that are compared to standard of reference data (disease status positive/negative). Effectiveness will be judged on both a subject- and anatomic region-level in terms of the identification of abnormal uptake of the radioactive compound in one or more anatomic locations where tumor has been identified at surgery, biopsy (bone marrow or tissue), by CT/MRI, or functional imaging (^{123}I-*m*IBG, ^{18}F-FDG, or dotatate PET), 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 provide an unambiguous measurement of the diagnostic efficacy of the ^{18}F-*m*FBG imaging method. The null hypothesis is that the positive and negative percent agreements (PPA and NPA) of ^{18}F-*m*FBG imaging compared to the established neuroblastoma disease diagnosis will each be greater than 50%.

As no subjects will be administered investigational product (IP) (^{18}F-*m*FBG) in this study, no safety data will be collected.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

None.

2.3.2 Known Potential Benefits

Benefits of ^{18}F-*m*FBG have not been established. The following summarizes the expected benefits of additional controlled data to supplement the prospective Phase 3 study performed by the sponsor (IRP101-301).

An expected potential benefit of ^{18}F-*m*FBG PET is more accurate identification of anatomic sites of active tumor for neuroblastoma disease status evaluation. The results of the present study are expected to provide further validation for the findings on the utility of ^{18}F-*m*FBG PET described in numerous recent single-center publications (27-31).

2.3.3 Assessment of Potential Risks and Benefits

As an image review study, there are neither risks nor benefits to the subjects whose images are being reread. As such, assessment of risk to benefit ratio is moot.

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 for detecting the presence of neuroblastoma. These data will be used to support an NDA submission.

The primary endpoint is focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging, reported as PPA and NPA for detecting neuroblastoma as determined by comparing clinical standard of care imaging and/or histopathology with comparable anatomic regions judged positive/negative by ^{18}F-*m*FBG.

3.2 Secondary Objectives

A secondary objective is to demonstrate that ^{18}F-*m*FBG PET scintigraphy (PET/CT or PET/MR) is sensitive and specific on a region/organ system-level in confirming or excluding the presence of neuroblastoma. The secondary efficacy endpoint will be focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging in prespecified anatomic regions, reported as PPA and NPA for detecting neuroblastoma as determined by comparison with clinical standard of care imaging and/or histopathology in those regions.

Another secondary objective is to assess inter-reader variability. Data from the primary endpoint will be used in these analyses.

3.3 Tertiary / Exploratory Objectives and Endpoints

None.

4 STUDY DESIGN

4.1 Overall Design

This is a prospective image re-evaluation study assessing ^{18}F-*m*FBG PET scintigraphic imaging for evaluation of neuroblastoma. The study is powered on PPA and NPA. Each eligible subject will have received an injection of ^{18}F-*m*FBG as part of a previous clinical research study or locally-authorized clinical use. Imaging will have been performed as per specifications in the original study protocols.

No ^{18}F-*m*FBG will be administered in this study. Therefore, no safety data will be collected.

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

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 imageable tumor.

No safety monitoring plan is required for this image-review-only study.

4.3 Justification for Dose

The ^{18}F-*m*FBG activity administered to each subject was determined in accordance with the protocol in which the subject participated. Those activities will be summarized and potential effects on image quality assessments by the blinded readers will be examined.

4.4 End of Study Definition

A subject is considered to have completed the study once his/her images have been evaluated by all blinded readers. The end of the study is defined as either when image reads for all subjects have been completed 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 undergone ^{18}F-*m*FBG imaging in a previous research trial (including as a non-disease control) or locally-authorized clinical use.
2. Disease status (+ or – for neuroblastoma) as of the date of ^{18}F-*m*FBG imaging was established based on data collected as part of the previous research trial or locally-authorized clinical use and during subsequent clinical follow-up.

5.2 Exclusion Criteria

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

1. There is insufficient correlative imaging and clinical follow-up data to establish subject disease status as of the date of ^{18}F-mFBG imaging.
2. ^{18}F-mFBG imaging from the previous trial was judged incomplete or uninterpretable.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

Each investigator contributing images is responsible for ensuring that: a) informed consent provided by subjects in the original clinical trial allows provision of the images from that trial for independent review in the present study; b) deliveries of image files and associated clinical data are in accordance with regulatory guidelines (e.g., International Conference on Harmonisation [ICH] E6-Good Clinical Practice [GCP] and the Code of Federal Regulations), and the specifications of this protocol.

6.1.1 Study Intervention Description

Imaging procedures were performed in accordance with clinical practice for PET/CT (or PET/MR) at the original study sites.

6.1.1.1 Imaging Procedures

All ^{18}F-*m*FBG imaging studies were performed on clinical PET/CT or PET/MR systems using standard technical parameters used at the investigational site. At a minimum, whole-body imaging was performed from the skull vertex to below the pelvis. Images were reconstructed using manufacturer-provided iterative reconstruction algorithms and attenuation, deadtime, randoms, and scatter corrections similar to ^{18}F-FDG imaging. The submitted whole-body tomographic images will be viewable in standard axial, coronal, and sagittal projections, or as rotating maximum intensity projection (MIP) displays. Displays of fused PET/CT or PET/MR images will also be available.

Imaging will have commenced at the time post-administration of ^{18}F-*m*FBG specified in the protocol in which the scan was acquired.

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.

- Each participating investigator must send reconstructed PET image files to the sponsor or the designated imaging core laboratory (ICL).
- The digital files must be of acceptable quality in accordance with protocol specifications. Specifically, there must be:
  - Complete coverage of anatomical regions from vertex to at least inferior to the pelvis.
  - Adequate image counts.
  - No or minimal subject motion.

6.1.1.3 General Guidelines for Image Submissions

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

Investigators will be required to submit imaging data in DICOM 3.0 or higher format through a digital portal. All image data must be anonymous, with no reference to the subject's identity. The data must only be labelled with the original site or study identifier and the exam date.

6.1.2 Dosing and Administration

Details of ^{18}F-*m*FBG administered as part of the original image acquisition will be recorded on the case report form (CRF). These will include activity administered and date of administration.

6.1.3 Clinical Follow-up

There is no follow-up specifically for this study. All data will be those collected as part of the original trials in which ^{18}F-*m*FBG was administered. Additional follow-up data collected by the original trial investigators for neuroblastoma disease confirmation may be submitted as deemed appropriate.

6.2 Preparation / Handling / Storage / Accountability

6.2.1 Acquisition and Accountability

Not applicable.

6.2.2 Formulation, Appearance, Packaging and Labelling

Not applicable.

6.2.3 Product Storage and Stability

Not applicable.

6.2.4 Preparation

Details of the preparation of ^{18}F-*m*FBG in the original trials will be available on request to the investigator.

6.3 Measures to Minimize Bias: Randomization and Blinding

As a trial utilizing existing images, selection of studies for inclusion could be a source of bias. Whereas participants were entered in the previous trials or locally-authorized clinical use in accordance with specific enrolment criteria, the primary basis for inclusion of images in the present study was the ability

of site investigators to release those images in compliance with institutional policies and maintenance of subject anonymity. As partial mitigation, the choice of submitted images was made by the site investigator, not the study sponsor. The study design also provides partial mitigation, in that the presence or absence of tumor was established in the original trials (or clinically-authorized use) by accepted medical methods, prior to development of the present trial protocol. A final mitigation is that only images from subjects whose neuroblastoma disease status was unequivocally established at the trial sites will be utilized in this study.

6.3.1 Method of Assigning Subject Numbers

A unique allocation number will be assigned to each subject whose images are included in the study. No subject may be entered into the study more than once.

The allocation number will be unique for each subject in the study and will consist of 5-digits: 2 for the center and 3 for the subject (e.g., 02001: first subject at center No. 2).

Once an allocation number is assigned, it cannot be reassigned even if the subject image files are deemed unusable. Allocation numbers will be assigned by the Sponsor.

6.3.2 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 Section 6.1.1.2 and Section 6.1.1.3. ^{18}F-*m*FBG images will be qualitatively examined by 5 independent readers. Readers will be aware that the trial involves neuroblastoma subjects. The readers will be informed of the reason the subject was undergoing evaluations at the time of ^{18}F-*m*FBG imaging, in accordance with instructions in the Independent Review Charter (IRC) supporting this protocol. The readers will be blinded to all other clinical information. Readers will have access to anatomic cross-sectional images (CT or MRI) acquired as part of the PET exam.

All activities of each reader will be overseen by ICL personnel in accordance with the IRC.

6.4 Study Intervention Compliance

Not applicable.

6.5 Concomitant Therapy

Not applicable.

6.5.1 Rescue Medications

Not applicable.

6.5.2 Prohibited Medications

Not applicable.

7 STUDY INTERVENTION, DISCONTINUATION, AND PARTICIPATION

7.1 Discontinuation of Study Intervention

There are no formal termination criteria for the study. The sponsor reserves the right to stop the study for any reason.

7.2 Participant Discontinuation / Withdrawal from Study / Rescreening

Not applicable.

7.3 Lost to Follow-up

Not applicable.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

8.1.1 Onsite assessment of imaging data

Not applicable.

8.1.2 Offsite assessment of imaging data

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 5 independent readers with minimal knowledge of the clinical status of the subjects. Each reader will assess the image quality on a 4-point scale (1-poor; 2-fair; 3-good; 4-excellent) or designate the scan as "Not evaluable". For scans judged evaluable, the reader will 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.

Blinded image evaluation procedures for ^{18}F-*m*FBG are described in detail in the IRC supporting this protocol.

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.

Readers will also record: a) presence of abnormal ^{18}F-*m*FBG uptake in accordance with the 10-segment model (9 osteomedullary regions, 1 soft tissue) (Curie score) routinely employed with ^{123}I-*m*IBG image assessments (15); b) presence of abnormal ^{18}F-*m*FBG uptake in the prespecified anatomic regions defined in the IRC. The image review CRF will be completed in accordance with rules presented in the IRC.

8.1.3 Final Disease Status Determination & Standard of Reference (SoR) Assessments

An experienced pediatric radiologist/nuclear medicine specialist will record presence or absence of tumor on a CRF based on a decision algorithm described in detail in the Objective Standard of Reference (OSoR) Charter associated with this trial. In brief, for imaging studies involving subjects with an established diagnosis of neuroblastoma, disease status will be based on results of a structured review of the histopathology and aggregate available imaging (functional and anatomic) and clinical follow-up information. The highest value information will be from procedures performed within ±3 months of the ^{18}F-*m*FBG study. Results from each procedure will be scored as either:

a) Consistent with neuroblastoma;
b) Abnormal but equivocal for active tumor (e.g., potentially reflecting effects of prior therapies);
c) Negative for findings suggestive of neuroblastoma.

The algorithm will provide guidance for categorizing subjects with only category b findings on 1 or multiple procedures.

The Curie score region(s) of OSoR positive findings (confirmed disease) will be recorded to facilitate determination of the primary efficacy PPA and NPA of blinded image interpretations based on sites of increased ^{18}F-*m*FBG uptake. Anatomic/region-level determinations of disease presence or absence (secondary efficacy) will also be recorded where feasible (based on availability of correlative procedure information).

For ^{18}F-*m*FBG studies performed on subjects with no history or suspicion of neuroblastoma (including those enrolled in studies investigating diseases other than neuroblastoma), disease status will be recorded as negative for neuroblastoma without application of the decision algorithm.

8.2 Safety and Other Assessments

Not applicable.

8.3 Adverse Events and Serious Adverse Events

Not applicable.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

Not applicable.

8.4.2 Unanticipated Problem Reporting

As no investigational product will be administered in this trial, no unanticipated problems are expected.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Tests on primary 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 α=0.05 level of significance, 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%
- For a given reader, proof of efficacy is based on rejecting both null hypotheses with PPA and NPA >50% for ^{18}F-*m*FBG PET imaging (details presented in Section 9.4.2).
- Region-level (secondary efficacy) testing will apply the same hypotheses as for the primary analyses.

9.2 Sample Size Determination

The study population will consist of subjects with known neuroblastoma and subjects with no history or suspicion of 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 2 (32). These sample size estimates provide 80% power to demonstrate that the lower limit of the two-sided 95% exact binomial confidence interval is greater than 50%. The last column displays the smallest observed rate for which the lower bound of the two-sided 95% confidence interval will be >50%.

Table 2: Sample Size Calculation

Power 80%	Alternative Hypothesis Rate	Required Sample Size	Smallest Observed Rate
	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%

Based on experience with trials involving blinded image evaluations (PPA tending to be lower than for informed image reads), expected PPA is 80%. Expected NPA is 85%. As such, the minimum required numbers of positive and negative cases is 20 and 15 respectively. Therefore, the minimum total sample size is 35 subjects.

As a prospective image reevaluation study, adequate correlative information from the original trials and associated clinical follow-up will be available to allow definitive determination of the disease status of all subjects. Sufficient images will be collected to assure that the numbers of positive and negative disease status cases meet the minimum criteria specified above. It is estimated that the number of dosed and evaluable subjects included in this study will be between 40 and 50.

9.3 Populations for Analyses

The following population will be used for analyses purposes:

- **Diagnostic Efficacy Population (DEP)**: All subjects who completed a ^{18}F-*m*FBG scan in the previous trials and whose images were available for blinded interpretation.

The primary and secondary efficacy endpoints will be assessed using the DEP.

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 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 3.

Table 3: Formulas for Calculating Endpoints

	Disease Status (OSoR) Positive	**Disease Status (OSoR) 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 Disease Status)
AND
NPA: (No. of True Negatives) / (No. of subjects with negative Disease Status),

WHERE:

- True Positive (TP) is defined as a subject with Disease Status 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 Disease Status, 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 submitted PET images.

9.4.2 Analysis of Primary Efficacy Endpoint

The primary endpoint is focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging, reported as subject-level PPA and NPA for detecting neuroblastoma as determined by comparing clinical standard of care imaging and/or histopathology with comparable anatomic regions judged positive/negative by ^{18}F-*m*FBG. A correct interpretation by a reader requires either: a) identification of abnormal ^{18}F-*m*FBG uptake in an anatomical (Curie score) region in which neuroblastoma was identified in the OSoR assessment (OSoR+); or b) no identification of abnormal ^{18}F-*m*FBG uptake in any anatomical (Curie score) region in a subject with OSoR-.

The results of the 5 independent readings of ^{18}F-*m*FBG imaging will be presented as independent measures. For each reader, PPA and NPA of ^{18}F-*m*FBG for identification of neuroblastoma at a subject-level will be calculated along with corresponding exact binomial 2-sided confidence limits.

For each reader, each 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 3 out of 5 readers (or for 4 or all 5 readers).

If there are DEP subjects with missing scan data (scan considered incomplete or Not evaluable 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 reader success criteria described above must be met for both sets of sensitivity analyses.

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 were 88% and 83% respectively for the tumor in the pivotal prospective trial (14). 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 Secondary Analyses

9.4.3.1 Anatomic Region-Level Efficacy

The secondary efficacy endpoint will be focal increased uptake (presence or absence) on ^{18}F-*m*FBG PET/CT or PET/MR imaging in prespecified anatomic regions, reported as PPA and NPA for detecting neuroblastoma as determined by comparison with clinical standard of care imaging and/or histopathology in those regions. For each prespecified anatomic region in a subject, a correct interpretation by a reader requires either: a) identification of abnormal ^{18}F-*m*FBG uptake in the region with neuroblastoma identified on the OSoR assessment (OSoR+); or b) no identification of abnormal ^{18}F-*m*FBG uptake in the region with no evidence of neuroblastoma on the OSoR assessment. Secondary efficacy analyses will be performed when feasible, i.e., when there is correlative imaging or histopathology results for comparison with ^{18}F-*m*FBG scan findings.

9.4.3.2 Inter-reader variability

Variation of primary efficacy 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 (33). The inter-reader agreement for 5 blinded readers will be compared between each of the 10 possible 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 κ lower than 0.41 will be explored further to determine if there is an underlying cause for this low value.

Since κ 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.

9.4.3.3 Additional efficacy analyses and summaries

Summaries based on Curie scores will also be made on a by-reader basis. Curie scores designations are defined in the IRC. Analyses of these data or others not described in previous sections will be considered exploratory.

9.4.4 Safety Analyses

No safety analyses will be performed in this study.

9.4.5 Baseline Descriptive Statistics

A table will be provided with the following information:

- Number of enrolled subjects.
- Number of subjects included in the Diagnostic Efficacy Populations.

Demographic information (age, gender) and relevant neuroblastoma histories will be summarized using descriptive statistics, i.e., counts and percents.

9.4.6 Planned Interim Analyses

None.

9.4.7 Subgroup Analyses

None.

9.4.8 Tabulation of Individual Participant Data

Data will be presented in listings for all enrolled subjects.

9.4.9 Exploratory Analyses

None planned.

9.4.10 Criteria for Objective SoR

A detailed description of the methodology for determination of the Objective SoR (OSoR) is presented in the OSoR Charter associated with this protocol.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical and Study Oversight Considerations

10.1.1 Informed Consent Process

Subjects provided written informed consent for participation in the original trials and will not be reconsented for this study. Images from a site without ability to provide images to the Sponsor without additional subject consent will not be included in this study.

10.1.2 Study Discontinuation and Closure

There are no circumstances under which the study would need to be discontinued prematurely.

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 submitted to the sponsor, subjects will not be identified by their names, but by an identification code (e.g., allocation number).

Medical information obtained in the original studies may be scrutinized for the purpose of verifying data recorded in the CRF. Original source data from investigational sites will not be reviewed.

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.

10.1.5 Key Roles and Study Governance

The investigational sites were responsible for the processing and quality control of the data in the original studies. 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.

10.1.6 Safety Oversight

Not applicable.

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 limited to confirmation that data provided by sites to the sponsor are accurately transferred into the trial database. This will be performed in accordance with ICH E6-GCP, sponsor's or the CRO's SOPs, the protocol, and applicable local regulations.

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 that will be generated. Any missing data or data anomalies will be investigated for clarification/resolution.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection in the original studies was the responsibility of the clinical trial staff at the sites under the supervision of the principal investigators. Data recorded in the CRF should be consistent with the data provided to the sponsor by those investigators as recorded in accordance with the original protocols.

Trained 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.

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 investigational 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 efficacy evaluations as a result of protocol violations.

10.1.11 Publication and Data Sharing Policy

At the completion of this study, the results will be used to support the Sponsor's regulatory submission for the Investigational Product. Publication of results from the original studies remains in the purview of the original study investigators. No further publication of the results generated in this study is planned.

10.1.12 Conflict of Interest Policy

Financial agreements under which data (including images) were provided to the sponsor will be documented in the Clinical Study Report (CSR). Any components of those arrangements that could represent a conflict of interest will be disclosed in accordance with local, national, and international regulations.

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 IRC

An IRC describing operational procedures for the blinded image evaluations in greater detail will be the basis for training of the independent image reviewers by Sponsor and ICL personnel prior to the first reading session. The training materials will be reviewed with the readers prior to subsequent reading sessions as judged necessary to ensure continuing compliance with all study procedures. Completion of these reviews will be documented by the ICL.

10.3 Revision History

Protocol Version and Date	Protocol Section	Description of Change(s)	Reason for Change(s)
1.0 17Nov2025		Original Version	N/A
2.0 6April2026	**Abbreviations**	PPA and NPA changed; IRTM deleted; IRC added	"P" changed from "Predictive" to "Percent" for consistency with usage throughout protocol; Image Review Training Manual (IRTM) replaced by Independent Review Charter (IRC) to reflect document being used by imaging CRO.
	1.1 Synopsis: Study Design;	Number of independent readers changed to "5" from "a minimum of 3"; Exclusion Criterion #1 changed: "uncertainty about" replaced by	To be specific about the number of image readers; To clarify the relationship

	Exclusion Criteria; Planned Number of Subjects	"insufficient correlative imaging and clinical follow-up data to establish". Planned Number of Subjects: Minimum increased from 30 to 40.	between this Exclusion criterion and Inclusion criterion b). To reflect reduction in expected NPA from 85% to 80%.
	2.1 Study Rationale	Minor edits to third paragraph.	Make clear that images from non-disease control subjects would be included in the study.
	3.2 Secondary Objectives	Remove reference to intrareader variability from second paragraph.	This assessment will not be performed in the study.
	5.2 Exclusion Criteria	Exclusion criterion #1 revised	To clarify the relationship between this criterion and Inclusion Criterion 2.
	6.3.2 Independent Image Review	Number of readers changed to "5". Nomenclature changed from Image Review Training Manual (IRTM) to Image Review Charter (IRC).	Clarification of planned reader number; Updated nomenclature reflecting new imaging CRO.
	8.1.2 Offsite assessment of imaging data	Number of readers changed to "5". Nomenclature changed from Image Review Training Manual (IRTM) to Image Review Charter (IRC).	Clarification of planned reader number; Updated nomenclature reflecting new imaging CRO.
	9.1 Statistical Hypotheses	"For a given reader" added to beginning of second major bullet.	To clarify that the stated success criteria apply to each individual image reader.
	9.2 Sample Size Determination	Changes in paragraph 4, with more conservative estimate of PPA as 80% rather than 85% and increase in lower bound of number of subjects from 30 to 40.	To reflect likely lower PPA based on previous trial experience and effect of blinded read method on study statistics.
	9.4.2 Analysis of Primary Efficacy Endpoint	Replacement of paragraph 4 with text describing study success criterion based on majority of 5 readers. Replacement of term "uninterpretable by "Not evaluable".	Response to request from FDA. Correction to reflect terminology used in IRC.
	9.4.3.2 Interreader Variability	Paragraph 1 modified to specify all possible interreader tests for the 5 designated independent readers.	For consistency with specification of 5 readers rather than a minimum of 3.
	9.4.3.3 Intrareader Variability	Section deleted.	This assessment will not be performed in the study.
	10.2.2 IRC	Section renamed IRC and revised to reflect procedures employed by imaging CRO.	For consistency with reader training procedures used by the imaging CRO.

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