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Statistical Analysis Plan

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Sponsor: Innervate Radiopharmaceuticals LLC

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

Protocol Number: **IRP101-301 (NANT 2020-01)**

Innervate Radiopharmaceuticals

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LIST OF ABBREVIATIONS

^{18}F-*m*FBG	meta-fluorobenzylguanidine (^{18}F)
^{123}I-*m*IBG	meta-iodobenzylguanidine (^{123}I)
ADaM	Analysis Data Model (CDISC)
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CSR	Clinical Study Report
CRF	Case Report Form
CT	Computed tomography
CTC	Common Terminology Criteria
DEP	Diagnostic Efficacy Population
eGFR	Estimated filtration rate
ECG	Electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IIP	Intent-to-Image Population
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NB	Neuroblastoma
NPA	Negative Percent Agreement
PET	Positron Emission Tomography
PPA	Positive Percent Agreement

PT	Preferred Term
QTc	Corrected QT interval
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SoR	Standard of Reference
TEAE	Treatment-emergent AE
uSoR	Updated Standard of Reference
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Innervate Radiopharmaceuticals LLC protocol IRP101-301, A Prospective Phase 3 Multi-center Study to Assess the Efficacy and Safety of ^{18}F-*m*FBG PET Imaging in Subjects with Neuroblastoma.

The structure and content of this SAP meets the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: E9 Guidance on Statistical Principles in Clinical Trials.

This SAP is based on the protocol Version 4.0 dated 05 Apr 2023. In the event of future amendments to the protocol, this SAP will be modified as necessary to account for changes relevant to the statistical analysis. Any updates to the SAP will be finalized prior to database lock and described in an Appendix to this document.

If there are any discrepancies between the protocol and SAP, the SAP will prevail. Any deviations from this SAP that are implemented in the final analysis will be documented in the Clinical Study Report (CSR).

2. TRIAL DESIGN

2.1 Trial Design

Study Design:

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.

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 imaging. 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 three 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.

Additional details on timing of study procedures are provided in the Schedule of Events (Protocol Table 1).

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.

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.

Standard of Reference (SoR):

Presence or absence of tumor will be determined by an Expert Panel of two 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 Panel will provide two assessments of disease status, one without functional imaging (i.e. ^{18}F-FDG and ^{123}I-*m*IBG) data included in their review (but including CT and MRI results), and one including functional imaging data in their review. The Panel assessment based on data including functional imaging will be considered the SoR.

^{18}F-*m*FBG PET studies and clinical ^{123}I-*m*IBG scans will be evaluated off-site by three independent radiologists and/or nuclear medicine physicians (readers) who are blinded to all subject information and the SoR. These 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 -). Image quality will be scored on a 4-point scale (1=poor, 2=fair, 3=good and 4=excellent).

Intra-reader variability:

Intra-reader variability will be examined by having each of the three independent blinded readers perform two 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 three readers, and the subject-level assessment at each evaluation will be listed side by side. Given the small sample size (approximately five for each imaging agent), no formal statistical tests will be conducted to assess intra-reader agreement. Only the first assessment of the duplicate images will be used in the analyses for the efficacy endpoints.

2.2 Primary Hypothesis

The co-primary hypotheses 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%

^{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 two out of three readers (or for all three readers).

2.3 Randomization

This study is not randomized in regard to treatment assignment. The order of the images read by the three independent readers will be randomized by the central imaging reading center. That is, the order of reading of ^{18}F-*m*FBG images will be randomized and the order of the reading of the ^{123}I-*m*IBG will also be (separately) randomized.

2.4 Sample Size Considerations

PPA is hypothesized to be 85%; NPA is hypothesized to be 80%. For 80% power, two-sided alpha-level equal to 0.05 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 determined. It is estimated that a total sample size up to 52 subjects might be required.

2.5 Post-Lock Changes

Due to an inconsistency between the IRP101-301 protocol and the Expert Panel Charter, it was found that not all of the follow-up information available for each subject was reviewed by the Panel (Protocol Clarification Letter 1; 12 Dec 2025). Therefore, the Expert Panel Charter was amended to require further review of all trial subjects including all data collected during the follow-up period (Expert Panel Charter, Version 3.0; 16 Dec 2025). To avoid potential bias, results for all trial subjects will be reviewed by the Expert Panel, including those for whom no clinical follow-up data were submitted. This updated SoR (uSoR) will be utilized to produce an additional dataset for analysis.

An additional aspect of the uSoR determination is the inclusion of a subcategory of Minimal Disease (MD) for neuroblastoma (NB)+ subjects. Defined as ≤5% NB cellularity on bone marrow examination without other evidence of macroscopic disease, this isolated finding is usually considered non-imageable with standard of care anatomic and functional imaging methods.

The final Clinical Study Report will include tables containing efficacy results for both the SoR and uSoR analyses. In addition, if any uSoR subjects are designated as MD, additional calculations will be performed with those subjects categorized as NB- to assess the effect on PPA and NPA determinations.

Subsequent to the initial evaluation of the ^{18}F-*m*FBG and ^{123}I-*m*IBG studies by the three blinded readers, major inconsistencies and errors in the ^{18}F-*m*FBG reads that impacted the primary efficacy results were noted for one of the three readers (Reader 3). These errors were identified in 11 (26%) of the study subjects, more than enough to affect the statistical significance of the results for that reader.

The unreliability of a subset of the ^{18}F-*m*FBG data provided by this reader has been clearly demonstrated by a root cause analysis and by an independent audit. The subset of image interpretations deemed unreliable was identified based on the audit findings. These findings included discrepancies between the images reviewed and the corresponding eCRFs completed, internal inconsistencies within eCRF responses (e.g., a subject classified as neuroblastoma-positive [NB+] with a Curie score of 0), and unexplained intra-reader inconsistencies, such as cases where two readers identified multiple metastatic lesions while another reader identified no lesions. These detailed evaluations demonstrated the validity of the results for the other two readers. However, based on feedback from the US Food and Drug Administration (FDA) Division of Imaging and Radiation Medicine (DIRM) and for completeness and data consistency, a GCP compliant re-read of the ^{18}F-*m*FBG images will be performed by all three readers (referred as new read). The original read of the ^{18}F-*m*FBG images (referred as original read) will also be used to for data analysis.

3. TRIAL OBJECTIVES

3.1 Primary Objectives

Efficacy: To demonstrate that ^{18}F-*m*FBG PET scintigraphy (PET/CT or PET/MR) is sensitive and specific on a subject level compared to the Standard of Reference (SoR) and the Updated Standard of Reference (uSoR) in confirming or excluding the presence of neuroblastoma.

3.2 Secondary Objectives

- To compare the performance of ^{18}F-*m*FBG and ^{123}I-*m*IBG imaging on a subject level with regards to disease presence or absence (PPA/NPA based on the SoR and uSoR).
- To assess the safety of ^{18}F-*m*FBG injection.

3.3 Exploratory Objectives

- 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 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 to PET/MR.

4. STUDY ENDPOINTS

4.1 Primary Endpoints

Efficacy: The positive and negative percent agreements between ^{18}F-*m*FBG and the SoR/uSoR for presence or absence of disease will be computed for each of the three independent readers, along with the corresponding exact binomial 2-sided confidence intervals.

4.2 Secondary Endpoints

Efficacy: The ^{18}F-*m*FBG and ^{123}I-*m*IBG findings will be compared for each reader and SoR/uSoR category based on whether the finding agreed or disagreed with SoR/uSoR.

Safety: Safety will be assessed based on adverse events, vital signs, laboratory tests, physical examinations 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).

4.3 Exploratory Endpoints

- Inter-reader variability will be assessed for each pair of blinded readers, utilizing both the original read data and the re-read data, based on Kappa statistics and the proportion of agreement
- Intra-reader variability will be assessed by comparing the percent agreement between the 10% sample of duplicate readings performed by each reader, by reader and type of image (^{18}F-*m*FBG or ^{123}I-*m*IBG) using original read data
- Frequency of potential change in therapeutic strategy based on ^{18}F-*m*FBG findings
- To evaluate the contribution of quantitation (absolute and in relation to lesion dimensions) in determining the presence or absence of active tumor
- PPA and NPA of PET/CT versus PET/MR will be assessed based on the primary endpoint if the number of exams is at least five for both PET/CT and PET/MR

5. ANALYSIS SETS

Analysis Set	Description
Enrolled Population	All subjects who sign the ICF
Intent to Image Population (IIP)	All enrolled subjects who receive one administration of ^{18}F-*m*FBG
Diagnostic Efficacy Population (DEP)	All enrolled 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

6. GENERAL ANALYSIS DEFINITIONS

6.1 General Considerations

Due to the small number of subjects at each investigational site, data will be pooled across sites for summary analyses.

For continuous variables, the following descriptive statistics will be presented: the number of subjects used in the calculation (n), mean, standard deviation (SD), median, minimum, and maximum values. All continuous summaries will display the minimum and maximum value with the same number of decimals collected in the data. The median and mean will display one greater decimal than the original data, and the SD will display two additional decimals. For all summary statistics, no more than three decimals will be presented.

For categorical variables, summaries will reflect frequencies and percentages, with the denominator for percentages being the number of subjects in the relevant study population. All percentages will be reported to one decimal except for percentages of 100% and 0% which will have no decimal place.

Duration for time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified.

Two-sided 95% exact binomial confidence intervals will be computed for the primary endpoint, with additional testing described below. There will be no adjustments made for multiple comparisons except as indicated in Section 7.7.2 below.

All data will be reflected in listings, sorted by site and subject number. Data collected at unscheduled visits will not be summarized (except as indicated below) but will be included in data listings.

6.2 Missing Data

Summaries of categorical variables will present the number of subjects with missing values, but percentages will be based on the number of subjects with non-missing data. Listings will indicate any missing data as missing, with no imputation performed.

6.2.1 Missing Dates

Partial and missing AE and concomitant medication dates will be imputed with maximum conservatism. In order to determine whether AEs are treatment-emergent and medications are concomitant, the following imputation will be used:

Start Date: If only DAY is missing, and the month and year are not the same as the month of first dose, then DAY will be imputed with '01'. Otherwise, if the month and year are the same as first dose date, first dose date will be used. If DAY and MONTH are missing and YEAR is not missing, then month and day will be imputed with month and day of first dose date (assuming the same YEAR). If the start date is completely missing, then the ^{18}F-*m*FBG dose date will be used.

Stop Date: If only DAY is missing, DAY will be imputed with last day of the month. If DAY and MONTH are missing and YEAR is not missing, then MONTH will be imputed with '12' and day will be imputed with '31' (or date of study discontinuation/completion if earlier than 12-31). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be imputed for ongoing AEs or concomitant medications.
For dates occurring in the past (such as birth date and dates associated with medical history) if day or month are missing, the following imputation will be used:

- if only the day is missing, day will be imputed as the 1st of the month
- if the month and day are missing, month and day will be imputed as January1st

6.2.2 Other Missing Data

AEs with missing relationship will be analyzed as related AEs. AEs with missing severity will be considered grade 3 AEs.

6.3 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to ^{18}F-*m*FBG injection.

6.4 Visit Windows

Visit windows are indicated in the Schedule of Activities found in Protocol section 1.3.

Subjects with data outside of the windows indicated for Safety Follow-up and Clinical follow-up will be reviewed prior to database lock to determine if the data can be included in the summary analyses for that visit. Data that is excluded due to being outside of visit windows will be reflected and flagged in data listings.

Note that 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.

6.5 Prior and Concomitant Medications

Prior medications are defined as medications with a stop date prior to the ^{18}F-*m*FBG injection.

Concomitant medications are defined as any medications ongoing on the day of the ^{18}F-*m*FBG injection or with a start date on or after the date of the ^{18}F-*m*FBG injection.

Any medication that cannot be confirmed as stopping before the ^{18}F-*m*FBG injection will be classified as both a prior and a concomitant medication.

Incomplete start or end dates will be imputed as described in section 6.2 above.

6.6 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that commence on, or after, the ^{18}F-*m*FBG injection up to the end-of-study (EOS) visit (inclusive).

AEs with incomplete start or end dates will be imputed as described in section 6.2. Any adverse event that cannot be confirmed as stopping before or starting after ^{18}F-*m*FBG administration will be classified as a treatment-emergent adverse event. If AEs start on the same day as the ^{18}F-*m*FBG injection without onset time, AEs will be defined as TEAEs unless the stop time indicates that the AEs stopped prior to the ^{18}F-*m*FBG injection.

6.7 Interim Analyses and Review Committees

No formal interim analyses are planned for this study.

6.8 Subgroups

Subgroup analyses for selected endpoints will be performed as indicated in Section 7.7.4. All subgroup analyses performed will be considered exploratory.

7. STATISTICAL ANALYSES

7.1 Protocol Deviations

Prior to database lock, Innervate 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.

Major protocol deviations are compliance issues that have an impact on subject safety or the scientific integrity of the study data. All protocol deviations will be recorded in an independent document (protocol deviation log) and evaluated and classified as major or minor by the study team before database lock.

The number of subjects with any protocol deviations will be summarized overall and by minor and major classifications for IIP subjects. The number of deviations across all subjects in major and minor categories may also be summarized.

If a subject has both minor and major deviations, that subject will be counted as having a major deviation in the summaries.

Full protocol deviation information will be provided in subject listings.

7.2 Subject Disposition

A summary based on the Enrolled Set of subjects will include the number of subjects screened and the number of screen failures. Summaries based on IIP subjects will include the number of subjects in the DEP population, study completion status (completed versus withdrawn), and frequencies of reason for study withdrawal.

7.3 Demographics and Baseline Characteristics

Descriptive statistics of general demographic and baseline characteristics will be generated based on IIP subjects.

Continuous baseline variables of age (years), height (cm), weight (kg), body mass index (BMI, kg/m^2), time since initial diagnosis, time since high-risk diagnosis, time since relapse, ECG PR interval, QRS interval, RR interval, QT interval and QTc interval (Bazett and Fridericia) will be summarized.

Frequency tables will be presented for baseline variables of gender, race, ethnicity, risk group (COG classification), disease stage (INSS and INRG), primary tumor site, INPC histopathology classification and subclassification, differentiation, mitosis-karyorrhexis index, MYC-N at initial diagnosis, metastatic bone disease at initial diagnosis, bone marrow involvement at initial diagnosis, progression to high-risk, relapse after high-risk diagnosis, and presence of ECG waveform abnormalities.

The following definitions and conversions will be used:

- Age (years) = (Informed Consent Date-Birthdate)/365.25 truncated to the lowest integer
- Height (in) *2.54 = height (cm)
- Weight (lb) / 2.2051 = weight (kg)
- BMI (kg/m^2) = weight (kg)/ height^2 (m^2)

7.4 Medical history

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher and summarized by System Organ Class (SOC), Preferred Term (PT), and treatment with counts and percentages in IIP subjects. A subject will only be counted once in a given SOC and an SOC/PT combination.

7.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug (WHODrug) Dictionary, Sep 2020 or later.

Using IIP subjects, summary tables of prior medications and concomitant medications will utilize Anatomical Therapeutic Chemical (ATC) Level 2 and Preferred term (PT) classifications. A

subject will only be counted once in an ATC class and an ATC class/PT combination. All medication data will be listed, including the WHO Drug ATC class, PT and the verbatim description of the medication.

7.6 Treatment Exposure

^{18}F-*m*FBG exposure summaries will be based on IIP subjects. Continuous summaries will reflect pre-injection syringe activity, post-administration activity, difference between decay-corrected pre- and post-administration activity (all in millicuries), and volume administered, in milliliters. Frequency analyses based on injection site, long-term venous access (LTVA) versus peripheral administration, LTVA type, lumens and side of injection (left versus right) will be generated.

7.7 Efficacy

Efficacy analyses will utilize IIP subjects. Sensitivity analyses of the primary and secondary endpoints may be generated based on the DEP set of subjects if the number of subjects in the IIP and DEP populations differs by at least five.

7.7.1 Primary Efficacy Endpoint

The primary endpoint, the results from the three independent readers, for both original and new reads, will be used to determine the PPA and NPA of ^{18}F-*m*FBG imaging based on of the presence or absence of neuroblastoma (SoR/uSoR) as defined in Table 7.1 below, on a subject level using IIP subjects.

The results of the three independent readings of ^{18}F-*m*FBG imaging will be presented separately. For each reader, PPA and NPA will be calculated along with corresponding exact 95% binomial two-sided confidence intervals.

For each reader and measure (PPA or NPA), the primary analyses will test the null hypothesis H_0: $p_a = 0.50$ vs. the alternative hypothesis H_1: $p_a \neq 0.50$, where "p_a" corresponds to PPA or NPA. ^{18}F-*m*FBG imaging will be deemed diagnostically efficacious if lower bounds for 95% CIs for both PPA and NPA are greater than 50% for the same two out of three readers (or for all 3 readers).

If there are IIP subjects with missing ^{18}F-*m*FBG scan data (^{18}F-*m*FBG scan not performed or incomplete/uninterpretable by a reader), two analyses will be performed, one assuming scans

with missing data would have been interpreted as positive for neuroblastoma and one analysis assuming the scans with missing data would have been interpreted as negative for neuroblastoma. In the case of missing ^{18}F-*m*FBG scan data, the success criterion described above must be met for both sets of sensitivity analyses.

Table 7.1: Calculation of PPA and NPA

	SoR Diagnosis Positive	SoR Diagnosis Negative	uSoR Diagnosis Positive	uSoR Diagnosis Negative
Blinded Image Read Positive	a	b	a'	b'
Blinded Image Read Negative	c	d	c'	d'

PPA= a / (a+c) or a' / (a'+c')

NPA= d / (b+d) or d' / (b'+d').

If the IIP and DEP differ by at least five subjects, there will be a separate analysis of the primary efficacy endpoint using the DEP in order to assess the sensitivity of the primary efficacy analysis.

For descriptive information only, estimates of positive predictive value [a / (a+b)] or [a' / (a'+b')], negative predictive value [d / (c+d)] or [d' / (c'+d')] and accuracy [(a+d) / (a+b+c+d)] or [(a'+d') / (a'+b'+c'+d')] will be provided.

7.7.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint, presence or absence of disease based on ^{123}I-*m*IBG scintigraphy, 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/uSoR category (positive or negative), summary tables similar to Table 7.2 will be generated; 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 (original and new reads) and ^{123}I-*m*IBG [pr(a+b) is equal to pr(a+c)], while excluding inconsistency ^{123}I-*m*IBG image reads. The two-sided alternative hypothesis is that the marginal probabilities of a correct reading are not equal. For SoR/uSoR positive, "correct" means the

image (^{18}F-*m*FBG or ^{123}I-*m*IBG) interpretation is positive, while for SoR/uSoR negative, it means the image interpretation is negative.

Table 7.2. 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 secondary efficacy analysis in order to control the overall level of significance: if the primary analysis is not statistically significant, the analysis of the secondary efficacy endpoint will be considered exploratory.

Summaries of the secondary efficacy endpoint based on tumor location may also be generated on a by-reader basis. Tumor locations are defined as a combination of Region and Organ System identifiers described in Protocol Table 3 (Protocol Section 8.1.1). Summaries of the secondary efficacy variable will be generated only for tumor locations with at least five subjects.

7.7.3 Exploratory Endpoints

Descriptive summaries of each exploratory endpoint will be presented along with the associated statistical assessments indicated below.

7.7.3.1 Inter-reader variability

Variation of imaging assessments will be considered for each pair of independent blinded reviewers for original and new reads and type of scan (^{18}F-*m*FBG or ^{123}I-*m*IBG). 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. The inter-reader agreement for three blinded readers will be compared between different pairs of readers using the kappa (κ) value, where the value of κ is:

$\kappa = (p_o - p_e) / (1-p_e)$

where p_o is the relative observed agreement among raters and p_e is the hypothetical probability of chance agreement.

The relative observed agreement will be defined as $p_o = (a+d) / (a + b + c + d)$.

The hypothetical probability of chance agreement will be defined as $p_e = (a+b)(a+c) +(c+d)(b+d)/ (a + b + c + d)^2$.

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 for each pair of readers.

Table 7.3: 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 between each pair of reviewers, two-sided 95% confidence intervals may be provided.

7.7.3.2 Intra-reader variability

Intra-reader variability will be examined for the original reads by having each of the three independent blinded readers perform two 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 three readers, and the percent agreement (as defined for inter-reader analysis above) will be generated. Given the small sample size (approximately five for each imaging agent), no formal statistical tests will be conducted to assess intra-reader agreement.

Note that only the first assessment of the inter-reader duplicates will be included in the primary and secondary efficacy analyses previously described.

7.7.4 Subgroup Analyses

7.7.4.1 Estimated Glomerular Filtration Rate

A subgroup analysis comparing PPA and NPA in subjects with glomerular filtration rate (eGFR) ≥90 ml/min/1.73m2 versus subjects with eGFR <90 ml/min/1.73m2 may be performed if there are at least 10 subjects in the latter group. In these analyses, the Bedside Schwartz equation will be used to estimate eGFR.

In order to determine the effect of eGFR on reader image quality scores, a generalized linear model analysis of image quality scores for each reader will be generated separately, incorporating the eGFR as an independent variable.

7.7.4.2 Manufactured Precursor

A subgroup analysis comparing PPA and NPA for 18F-mFBG in subjects with well characterized precursor versus subjects with GMP precursor will be performed if there are at least 10 subjects in one group.

In order to determine the effect of GMP manufacturing procedure on reader image quality scores, a generalized linear model analysis of image quality scores for each reader will be generated separately, incorporating the GMP manufacturing procedure as an independent variable.

7.7.4.3 Confidence Score

Receiver operating characteristic (ROC) analysis will be performed to identify an optimal confidence score (from SoR at Pre-mIBG) threshold for discrimination of positive versus negative uSoR status. The threshold corresponding to the maximum Youden Index (sensitivity + specificity − 1) will be selected. Subjects will subsequently be categorized into high-confidence and low-confidence subgroups based on this threshold. All subgroup analyses comparing PPA and NPA for ^{18}F-*m*FBG re-read images based on the selected threshold will be considered exploratory.

The rationale for and results of any potential additional exploratory sub-group analyses will be described in the Study Report.

7.7.5 Analysis Combinations

The original analysis for all efficacy endpoints evaluated data derived from the original reads and the SoR. Following the availability of additional reader assessment data and the uSoR, five additional analysis combinations will be performed using the new data expanding beyond the original scope. These analyses are intended to evaluate the efficacy endpoints using the newly available data sources while preserving the original analysis as the primary analysis. The summary tables for the additional analysis combinations will retain the same table numbers as those used in the original analysis, with an additional suffix appended to distinguish each analysis combination, as described below.

1. Reader original reads vs uSoR
2. Reader original reads vs uSoR and MD subjects converted to NB-
3. Reader new reads vs SoR
4. Reader new reads vs uSoR
5. Reader new reads vs uSoR and MD subject converted to NB-

7.7.6 Sensitivity Analysis

In order to determine the effect of unreliable ^{123}I-*m*IBG reads, the analysis of agreement between ^{18}F-*m*FBG re-read image read and ^{123}I-*m*IBG will be performed on a selected subset of ^{123}I-*m*IBG interpretations, which are deemed reliable.

The uSoR results with determination uncertainties (subject 01-019, 02-005, 10-001 and 10-007) will be excluded from selected analysis to explore the effect of uSoR uncertainties when comparing to ^{18}F-*m*FBG image read. The details for characterizing uSoR determinations as uncertain are in Appendix 3.

7.8 Safety

All safety analysis will be carried out using IIP subjects.

7.8.1 Adverse Events

All AEs will be coded using MedDRA version 24.0 or higher.

An overall summary of TEAEs will be presented, including subjects with any TEAE, any TEAE severity (Mild, Moderate, Severe), any treatment-related TEAE, any treatment-related TEAE severity (Mild, Moderate, Severe), any serious TEAE, any treatment-related serious TEAE, any TEAEs leading to study withdrawal, any treatment-related TEAEs leading to study withdrawal and any injection site reactions.

A summary table will present the number and percentage of subjects with TEAEs by SOC and SOC/PT. Subjects with multiple TEAEs within an SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. This table will also present a summary of subjects with any TEAE. The number of TEAEs observed across all SOC/PT categories may also be presented.

Similar summaries will be presented for Serious TEAEs, treatment-related TEAEs, serious treatment-related TEAEs and TEAEs leading to study withdrawal.

An additional summary table of TEAEs will be presented summarizing the TEAE severity (Mild, Moderate, Severe) associated with each SOC and SOC/PT. A subject will be counted only once for an SOC or an SOC/PT combination: if a subject experiences multiple events in the same SOC or SOC/PT the highest recorded grade will be reflected in the summary table.

A summary table of TEAEs will be presented by the relationship to study drug (related or not related). For this summary, TEAEs that are indicated as being "Definitely", "Probably" or "Potentially" related will be classified as "Related", and "Unlikely" and "Not Related" will be analyzed as "Unrelated". A subject will be counted only once for an SOC or an SOC/PT combination. If a subject experiences multiple events in the same SOC or SOC/PT the closest relationship to study drug will be reflected in the summary table.

All adverse event data will be listed by subject (in order of adverse event start date). AEs that are not TEAEs will be flagged. Separate listings of AEs leading to death and AEs leading to study termination will also be generated.

7.8.2 Clinical Laboratory Tests

Laboratory data (hematology, chemistry, and urine catecholamine metabolites, if collected) will be summarized descriptively by time point. For lab tests collected post-screening, changes from baseline will be presented along with observed value at each time point. Summaries will reflect conventional units and local laboratory assessments except where indicated.

The estimated glomerular filtration rate (eGFR) will be calculated using the Bedside Schwartz formula:

eGFR (mL/min/1.73 m^2) =0.413*height (cm) / (serum creatinine in mg/dl)

Shift tables will be presented for the hematology and chemistry laboratory parameters based on laboratory normal ranges and clinical assessment (low and not clinically significant, low and clinically significant, normal, high and not clinically significant, high and clinically significant). The shift tables will compare post-baseline assessment (excluding unscheduled visits) to baseline assessment.

- Hematology: hematocrit, hemoglobin, white blood cell (WBC) count and platelet count.
- Chemistry: creatinine, chloride, urea nitrogen, bicarbonate, sodium, potassium, glucose, alkaline phosphatase, aspartate transaminase, alanine transaminase, bilirubin (total) and lactic dehydrogenase.

Laboratory results including symbols ("<" or ">", for example) will not be used in summary analyses. Values including symbols will be reflected in listings of the data.

All clinical laboratory results will be listed; these listings will include low and high value flags based on local laboratory normal ranges.

7.8.3 Vital Signs

Vital signs include heart rate, systolic and diastolic blood pressures, respiration rate, and body temperature. Vital signs will be analysed descriptively based on observed values at each visit, and the corresponding change from baseline. In the descriptive summaries, temperature will be presented in Celsius.

Summary counts and percentages will be generated at each post-administration time point for each vital sign based on the occurrence of one or more changes from baseline 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 and 10 breaths per minute for respiration rate). The occurrence of post-administration vital sign values outside of the normal limits will also be generated based on the normal ranges indicated in Table 7.4. The normal range for temperature (Celsius) is 36.3 to 37.6.

Table 7.4: Vital Sign Normal Ranges

Age (yr)	Heart Rate (bpm)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Respiratory Rate (bpm)
0-1	100-160	72-104	37-56	30-53
1-2	98-140	86-106	42-63	20-30
3-5	80-120	89-112	46-72	20-28
6-11	75-118	97-120	57-80	18-25
12-15	60-100	110-131	64-83	12-20
≥16	60-100	80-120	60-80	12-20

Height (in centimeters), weight (in kilograms) and BMI are only measured at pre-injection visit and will be summarized in the baseline characteristics table.

7.8.4 O2 Saturation

O_2 saturation is assessed 1 hour pre-injection and 20 minutes and 2 hours post-injection. O_2 saturation will be summarized descriptively as a continuous variable, reflecting values at each visit as well as change in O_2 saturation between the two post-injection assessments. In addition, frequencies of the number of subjects with greater than a 5% change in O_2 saturation and number of subjects with O_2 values <90% will be generated.

7.8.5 Electrocardiograms (ECGs)

ECGs will be measured 1-hour pre-^{18}F-*m*FBG injection and 2 hours post-^{18}F-*m*FBG injection until a total of 25 subjects have undergone these exams. Results from the ECG core laboratory reviews will be used for all statistical analyses.

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

- PR interval: The occurrence of a change from baseline 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)
- QTc: The occurrence of a change from baseline of <30 msec, 30-60 msec or >60 msec, for both Bazett and Fridericia corrections
- QRS: The occurrence of a change from baseline of <50 msec, 50 to 100 msec, >100 msec

- RR interval: The occurrence of a change from baseline of <250 msec, 250 to 500 msec, >500 msec
- QTc: Number and percentage of subjects with absolute QTc values > 440 msec.

Abnormal ECG waveforms will be summarized by counts and percentages.

Table 7.5: Criteria for Normal Limits and Clinically Notable Limits for ECGs in Pediatric Subjects

	Normal Limits (msec)		Notable Limits (msec)	
PR interval	**Low**	**High**	**Low**	**High**
Newborn (0-1 month)	70	140	<70	>140
Infant (2-<12 months)	70	150	<70	>150
Toddler (≥1-3 years)	80	150	<80	>150
Preschooler (4-5 years)	80	160	<80	>160
School Age (6-11 years)	90	170	<90	>170
Adolescent (12-18 years)	90	180	<90	>180
QRS interval				
Newborn (0-1 month)	40	80	<40	>80
Infant (2-<12 months)	40	80	<40	>80
Toddler (≥1-3 years)	40	80	<40	>80
Preschooler (4-5 years)	50	90	<50	>90
School Age (6-11 years)	50	90	<50	>90
Adolescent (12-18 years)	50	100	<50	>100
RR interval				
Newborn (0-1 month)	330	600	<330	>600
Infant (2-<12 months)	330	600	<330	>600
Toddler (≥1-3 years)	330	600	<330	>600
Preschooler (4-5 years)	400	1000	<400	>1000
School Age (6-11 years)	460	1200	<460	>1200
Adolescent (12-18 years)	600	1200	<600	>1200
QTc interval				
All	NA	≤440	NA	>440

REF: Van Hare GF, Dubin AM. The normal electrocardiogram. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, editors. Moss and Adams' Heart Disease in Infants, Children, and Adolescents Including the Fetus and Young Adult, Vol 1, 6th Ed. Philadelphia: Lippincott Williams & Wilkins, 2001:425-442.

8. ADDITIONAL EXPLORATORY ANALYSES

Summary table will be generated comparing the SoR assessments (Positive, Negative) and change of confidence scores (increased, decreased, unchanged) between two adjudications.

9. SOFTWARE AND PROGRAMMING SPECIFICATIONS

9.1 Statistical Software

All statistical analyses will be performed using SAS 9.4 or higher.

9.2 General Programming Specifications

All tables, listings and figures will include the sponsor name, protocol ID, and "Draft" or "Final" in the header.

The following two footers lines will be included:

1. Data Source: (ADaM dataset reference for tables, Table or Listing reference for Figures) left justified
2. "Creation Date/Time: DDMMMYYYY HH:MM" left justified, "Confidential" in the middle, and "Page X of Y" right justified

10. References

1. C.J Clopper, E. S. Pearson. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

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

3. Sean Wallis, Binomial Confidence Intervals and Contingency Tests: Mathematical Fundamentals and the Evaluation of Alternative Methods. Journal of Quantitative Linguistics, 2013; 20 (3): 178-208

11. Appendices

Appendix 1. Changes from Previous Version of SAP

SAP Version	Date (DDMMMYYYY)	Change(s) from Previous Version	Reason	Revised SAP Sections
1.0	18 Jun 2021	Original		
2.0	21 Dec 2023	Revision	1) The subjects enroll in the study changed. 2) Selected endpoints will be analyzed separately for the non-GMP precursor versus GMP precursor subgroups. 3) Diagnostic Efficacy Population definition changed. 4) MedDRA updated to 24.0 or higher. 5) Removed "these measures at post-baseline visits will only be presented in subject listings" due to weight, height and BMI only measuring at pre-injection. 6) ECG normal ranges added. 7) Defined TEAE when AEs happened the same day as ^{18}F-*m*FBG injection without onset time 8) Change of confidence sores added in additional exploratory analyses	1) 2.1 2) 6.8; 7.7.4 3) 5 4) 7.4; 7.8.1 5) 7.8.3 6) 7.8.5 7) 6.6 8) 8

SAP Version	Date (DDMMMYYYY)	Change(s) from Previous Version	Reason	Revised SAP Sections
			according to protocol version 4.0	
2.1	22 Jan 2024	Revision	1) Use severity grade instead of CTCAE grade for adverse events as CTCAE grade did not capture. 2) Use clinical assessment instead of CTCAE grade for laboratory parameter shift table as CTCAE grade did not capture.	1) 7.8.1 2) 7.8.2
2.2	02 Jul 2026	Revision	1) Included uSoR based on Protocol Clarification Letter 1 2) Included re-reading data for all three readers 3) Added five additional efficacy analysis combinations incorporating newly available data 4) Added two sensitivity analyses to explore the impact of unreliable ^{123}I-*m*IBG and uSoR results	1) 2.1, 7.7.1, 7.7.2, 7.7.3, 7.7.4 2) 2.1, 7.7.1, 7.7.2, 7.7.3, 7.7.4 3) 7.7.5 4) 7.7.6

Appendix 2. Changes from Protocol

Protocol	Change(s) in SAP	Reason	SAP Sections
In section 9.4.10, additional exploratory analyses were planned if feasible	The Additional exploratory analyses are not included	No CRF was design to capture the additional exploratory analyses information	8
In section 8.2, Adverse events were planned be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5	The severity grade will be used	CTCAE grade did not capture	7.8.1
The original analysis for all efficacy endpoints evaluated data derived from the SoR	uSoR will be used for additional analysis	Based on Protocol Clarification Letter 1 and Expert Panel Charter (Version 3.0), expert panel data will be updated	2.5
The original analysis for all efficacy endpoints evaluated data derived from the original reads	New reader reads will be used for additional analysis	Reader re-reads were requested by the FDA	2.5
NA	Five additional analysis combinations and sensitivity analysis will be performed using the new data	Analyses will be consistent with the new reader reads and uSoR	7.7.1, 7.7.2, 7.7.3, 7.7.4, 7.7.5, 7.7.6

Appendix 3. Justification For Characterizing uSoR Determinations As Uncertain:

1. Subject 01-019:

For this subject, the Expert Panel adjudicated Part 1 as negative with 90% confidence. Functional imaging was cited as the most important contributor to the adjudication, based on the FDG PET/CT performed on 29 August 2023, which reported no evidence of FDG-avid recurrence or metastatic disease and unchanged mild diffuse-to-moderate bone marrow FDG uptake, considered probably reactive.

Part 2, corresponding to the SoR, was subsequently classified as positive based on functional imaging, with 100% confidence. The mIBG SPECT/CT performed on 21 September 2023 reported overall unchanged sites of mIBG uptake compared with 30 March 2023, including residual faint uptake in the right sacrococcygeal spine. The reported total Curie score was 6, comprising craniofacial region 3, lumbar/sacral spine (faint uptake in L3 transverse process, L5 and left sacrum) 2, and pelvis (left wing uptake) 1, all unchanged from the previous assessment.

Part 3, corresponding to the uSoR, remained positive, although a subsequent FDG PET/CT performed on 20 December 2023 was negative.

The oncology PI considered the subject most likely to be in remission. Given the discordance between the persistent site-read *m*IBG findings and the negative FDG PET/CT assessments, and considering that the *m*IBG findings may have reflected reactive bone or marrow changes rather than active disease, the uSoR conclusion for this subject is considered uncertain.

2. Subject 02-005

For this subject, the Expert Panel adjudicated Part 1 as positive with 60% confidence. Functional imaging was cited as the most important contributor to the adjudication, based on the *m*IBG scan performed on 17 August 2023, which reported mIBG-avid malignancy in the left posterior aspect of L3 and the left side of T12, consistent with findings seen on multiple previous examinations. The reported Curie score was 2.

Part 2, corresponding to the SoR, was also classified as positive based on functional imaging, with 100% confidence. The *m*IBG SPECT/CT performed on 26 October 2023 was reported as virtually identical to the previous examination.

Part 3, corresponding to the uSoR, remained positive, although two subsequent follow-up *m*IBG scans performed on 4 January 2024 and 22 February 2024 were interpreted as negative.

The oncology PI considered the subject to have stable disease as of May 2024.

The apparent rationale for the Expert Panel assessment was that the persistently positive *m*IBG findings up to the time of trial participation reflected active disease, while the subsequent negative follow-up examinations indicated a complete response to therapy. However, no corresponding anatomic imaging, such as CT or MRI of the spine, was available to confirm the *m*IBG findings. Therefore, because the uSoR conclusion was based exclusively on serial site-read mIBG interpretations, the uSoR conclusion for this subject is considered uncertain.

3. Subject 10-001

For this subject, the Expert Panel adjudicated Part 1 as negative with 50% confidence. Anatomic imaging was cited as the most important contributor to the adjudication, based on the brain MRI performed on 14 July 2022, which reported findings corresponding to the area of uptake on the nuclear medicine *m*IBG scan dated 29 December 2021, possibly reflecting treated disease, with no evidence of progressive tumour.

Part 2, corresponding to the SoR, was classified as positive based on functional imaging, with 75% confidence. The *m*IBG SPECT/CT performed on 15 July 2022 reported redemonstration of *m*IBG uptake along the right lateral orbit, with increased intensity compared with 30 December 2021, although the Curie score remained unchanged at 1.

Part 3, corresponding to the uSoR, remained positive, with the follow-up *m*IBG scan performed on 27 October 2022 interpreted as unchanged from previous examinations.

The subject was not receiving therapy at the time of *m*FBG imaging, and the oncology PI indicated that the subject was likely in remission despite the site-read *m*IBG findings. Given that the MRI findings were equivocal and biopsy of the skull lesion was not pursued, the uSoR conclusion for this subject is considered uncertain.

4. Subject 10-007

For this subject, the Expert Panel adjudicated Part 1 as positive based on functional imaging, with 60% confidence. The *m*IBG scan performed on 2 August 2023 reported a Curie score of 0 on planar imaging, with SPECT imaging increasing the Curie score to 4.

Part 2, corresponding to the SoR, remained positive based on functional imaging, with confidence increasing to 90%. This was supported by the *m*IBG scan performed on 3 November 2023, which was interpreted as unchanged and positive.

Part 3, corresponding to the uSoR, also remained positive, although the follow-up *m*IBG scan performed on 7 February 2024 was interpreted as negative.

The apparent rationale for the Expert Panel assessment was that normalization of the site-read *m*IBG findings during follow-up represented evidence of response to therapy. However, serial whole-body CT scans showed no corresponding change, and no histopathology assessment was available to confirm the imaging findings. Therefore, based on the available evidence, it cannot be determined whether the positive uSoR conclusion accurately reflected active disease followed by treatment response. The uSoR conclusion for this subject is considered uncertain.

Data Display Plan

Sponsor Name	Innervate Radiopharmaceuticals LLC
Protocol ID	IRP101-301
Protocol Version	4.0 (date: 05-Apr-2023)
SAP Version	2.2 (date: 08-Jul-2026)
Study Name	IRP101-301
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
CRF Version	5.0 (date: 18-OCT-2023)
Document ID	IRP101-301_Data Display Plan (Amendment)_Final Version_2.2_08Jul2026
Document Version	#2.2

		Signature and Date
Author:	Andrea Peng Senior Biostatistician III/SME Process Management	Signed by: Andrea Peng Signer Name: Andrea Peng Signing Reason: I am the author of this document Signing Time: 08-Jul-2026 | 12:56:24 ACST 0338ADB9FE544C1AA800AE513B7A6B65
Reviewer:	Nelson Onyango Senior Biostatistician II	Signed by: Nelson Onyango Signer Name: Nelson Onyango Signing Reason: I have reviewed this document Signing Time: 13-Jul-2026 | 11:48:47 ACST B2A54A8DAE754CA2B7E4424D14CEC10B
Approver:	Arnold Jacobson Sponsor	Signed by: Arnold J Jacobson Signer Name: Arnold Jacobson Signing Reason: I approve this document Signing Time: 08-Jul-2026 | 01:59:02 PDT 150DD1B58020486D89F0369549FB8481

Collaboration

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collaboration

1 Study Introduction

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

Due to an inconsistency between the IRP101-301 protocol and the Expert Panel Charter, it was found that not all of the follow-up information available for each subject was reviewed by the Panel (Protocol Clarification Letter 1; 12 Dec 2025). Therefore, the Expert Panel Charter was amended to require further review of all trial subjects including all data collected during the follow-up period (Expert Panel Charter, Version 3.0; 16 Dec 2025). To avoid potential bias, results for all trial subjects will be reviewed by the Expert Panel, including those for whom no clinical follow-up data were submitted. This updated SoR (uSoR) will be utilized to produce an additional dataset for analysis.

An additional aspect of the uSoR determination is the inclusion of a subcategory of Minimal Disease (MD) for neuroblastoma (NB)+ subjects. Defined as ≤5% NB cellularity on bone marrow examination without other evidence of macroscopic disease, this isolated finding is usually considered non-imageable with standard of care anatomic and functional imaging methods.

The final Clinical Study Report will include tables containing efficacy results for both the SoR and uSoR analyses. In addition, if any uSoR subjects are designated as MD, additional calculations will be performed with those subjects categorized as NB- to assess the effect on PPA and NPA determinations.

Subsequent to the initial evaluation of the ^{18}F-*m*FBG and ^{123}I-*m*IBG studies by the 3 blinded readers, major inconsistencies and errors in the ^{18}F-*m*FBG reads that the impacted the primary efficacy results were noted for one of the three readers (Reader 3). These errors were identified in 11 (26%) of the study subjects, more than enough to affect the statistical significance of the results for that reader.

The unreliability of a subset of the ^{18}F-*m*FBG data provided by this reader has been clearly demonstrated by a root cause analysis and by an independent audit. These detailed evaluations demonstrated the validity of the results for the other two readers. However, based on feedback from the US Food and Drug Administration (FDA) Division of Imaging and Radiation Medicine (DIRM) and for completeness and data consistency, a GCP compliant re-read of the ^{18}F-*m*FBG images will be performed by all 3 readers (referred as new read). The original read of the ^{18}F-*m*FBG images (referred as original read) will also be used for data analysis.

2 Population Definitions

Enrolled Population: All subjects who sign the ICF.

Intent to Image Population (IIP): All enrolled subjects who receive an administration of ^{18}F-*m*FBG.

Diagnostic Efficacy Population (DEP): All enrolled 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.

3 Conventions Regarding Data Presentation

3.1 General

All outputs will be presented in Times New Roman font, Size 8. Outputs will be created in rich text file (.rtf) format with one file created for each output.

Due to programming constraints, tables with many columns may require some columns be displayed on a separate page. In such cases, all identifier columns must be repeated across pages.

All listings will display information in the order of Site and Subject Identifier followed by remaining information as applicable.

Note that the mock shells serve as general structural guidance for programming purposes. The actual outputs are subject to change depending on the actual data and might differ from the mock shells' font, margin, footnotes and other non-substantial features.

Primary and secondary efficacy endpoint tables will be repeated for DEP population, if the number of subjects in the IIP and DEP populations differs by at least 5.

3.2 Output Headers and Footers

Header for all the tables, listings and figures will be consistent using the following labels.

Protocol: IRP101-301 **IRP101-301 - Tables, Listings, and Figures**
Sponsor: Innervate Radiopharmaceuticals LLC **Version: Draft/Final**

Column header labels will be consistent and presented in "bold" font across all TLFs.

Include the following footnotes for all TLFs. Refer corresponding SAP sections for the reference listing numbers.

```
Abbreviations: (as appropriate)

Reference Listing: 16.X.X.X; Source Dataset: ADaM.ADXX
Creation Date/Time: DDMMMYYYY HH:MM          Confidential          Page X of X
```

Footnotes will use same verbiage and order consistently across all TLFs. All outputs will contain corresponding population definitions in the footer as per Section 2.

3.3 Sorting

For by-subject listings, the sort order will be site, Subject Number and Date of Assessment.

4 Scope of the Data Display Plan

This amendment Data Display Plan is limited to those tables and listings impacted by the amendment. Outputs not requiring modification are excluded from the scope of this plan and will be generated using the previously provided formats to maintain consistency.

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Agreement between ^{18}F-mFBG Imaging Original Read and uSoR
(Intent to Image Population)

Blinded Image Reader	Blinded Reader Result	Subjects with missing ^{18}F-mFBG scan data as Positive						Subjects with missing ^{18}F-mFBG scan data as Negative					
		uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value	uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value
1	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
2	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
3	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Exact binomial two-sided 95% CIs are presented for PPA and NPA. P-values are from Normal z-test testing whether the proportion (PPA or NPA) equals 0.5.

PPA = a / (a+c)
NPA = d / (b+d)

Abbreviation: PPA = Positive Predictive Agreement; NPA = Negative Predictive Agreement; uSoR = Updated Standard of Reference; CI = Confidence Interval; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.1-1 and 16.2.6.2

Programming Note: If it is confirmed that there are no missing scan data after DBL, only columns under "**Subjects with missing ^{18}F-mFBG scan data as Positive**" table header should be retained with this table header removed.

Table 14.2.1.1.1-2a
Agreement between ^{18}F-mFBG Imaging Original Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.1.1-3a
Agreement between ^{18}F-mFBG Imaging New Read and SoR
(Intent to Image Population)

Reference Listing: 16.2.6.1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.1.1-4a
Agreement between ^{18}F-mFBG Imaging New Read and uSoR
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.1.1-5a
Agreement between ^{18}F-mFBG Imaging New Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.1.1-6a
Agreement between ^{18}F-mFBG Imaging New Read and uSoR Excluding Subjects with uSoR Determination Uncertainties
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Subjects with uSoR Determination Uncertainties include 01-019, 02-005, 10-001 and 10-007.

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.1.2-1a
Agreement between ^{18}F-mFBG Imaging Original Read and uSoR by ^{18}F-mFBG Manufactured Precursor
(Intent to Image Population)

Subgroup: GMP Precursor / Well Characterized

Blinded Image Reader	Blinded Reader Result	Subjects with missing ^{18}F-mFBG scan data as Positive						Subjects with missing ^{18}F-mFBG scan data as Negative					
		uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value	uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value
1	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
2	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
3	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Exact binomial two-sided 95% CIs are presented for PPA and NPA. P-values are from Normal z-test testing whether the proportion (PPA or NPA) equals 0.5.

Well Characterized precursor subgroup includes subjects who were injected with ^{18}F-mFBG on or before 3-JAN-2023 and GMP precursor includes those injected after 3-JAN-2023.

PPA = a / (a+c)
NPA = d / (b+d)

Abbreviation: PPA = Positive Predictive Agreement; NPA = Negative Predictive Agreement; uSoR = Updated Standard of Reference; CI = Confidence Interval; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.1-1 and 16.2.6.2.

Programming Note: If it is confirmed that there are no missing scan data after DBL, only columns under "Subjects with missing 18F-mFBG scan data as Positive" table header should be retained with this table header removed.

Table 14.2.1.1.2-3a
Agreement between New ^{18}F-mFBG Imaging Read and SoR by ^{18}F-mFBG Manufactured Precursor
(Intent to Image Population)

Reference Listing: 16.2.6.1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.2-1a to replace the relevant information.

Table 14.2.1.1.2-4a
Agreement between New ^{18}F-mFBG Imaging and Read uSoR by ^{18}F-mFBG Manufactured Precursor
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.2-1a to replace the relevant information.

collaboration

Table 14.2.1.1.3-1a
Predictive Values and Accuracy between ^{18}F-mFBG Imaging Original Read and uSoR
(Intent to Image Population)

Blinded Image Reader	Blinded Reader Result	Subjects with missing ^{18}F-mFBG scan data as Positive					Subjects with missing ^{18}F-mFBG scan data as Negative				
		uSoR Diagnosis Positive	uSoR Diagnosis Negative	Positive Predictive Value	Negative Predictive Value	Accuracy	uSoR Diagnosis Positive	uSoR Diagnosis Negative	Positive Predictive Value	Negative Predictive Value	Accuracy
1	Positive	XX[a]	XX[b]	XX.X	XX.X	XX.X	XX[a]	XX[b]	XX.X	XX.X	XX.X
	Negative	XX[c]	XX[d]				XX[c]	XX[d]			
2	Positive	XX[a]	XX[b]	XX.X	XX.X	XX.X	XX[a]	XX[b]	XX.X	XX.X	XX.X
	Negative	XX[c]	XX[d]				XX[c]	XX[d]			
3	Positive	XX[a]	XX[b]	XX.X	XX.X	XX.X	XX[a]	XX[b]	XX.X	XX.X	XX.X
	Negative	XX[c]	XX[d]				XX[c]	XX[d]			

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Positive Predictive Value = a / (a+b)

Negative Predictive Value = d / (c+d)
Accuracy = (a+b) / (a+b+c+d)

Abbreviation: uSoR = Updated Standard of Reference; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.1-1 and 16.2.6.2

Programming Note: If it is confirmed that there are no missing scan data after DBL, only columns under "**Subjects with missing ^{18}F-mFBG scan data as Positive**" table header should be retained with this table header removed.

Table 14.2.1.1.3-2a
Predictive Values and Accuracy between ^{18}F-mFBG Imaging Original Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2

Programming Note: using the same format for Table 14.2.1.1.3-1a to replace the relevant information.

Table 14.2.1.1.3-3a
Predictive Values and Accuracy between ^{18}F-mFBG Imaging New Read and SoR
(Intent to Image Population)

Reference Listing: 16.2.6.1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.3-1a to replace the relevant information.

Table 14.2.1.1.3-4a
Predictive Values and Accuracy between ^{18}F-mFBG Imaging New Read and uSoR
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.3-1a to replace the relevant information.

Table 14.2.1.1.3-5a
Predictive Values and Accuracy between ^{18}F-mFBG Imaging New Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1 and 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.3-1a to replace the relevant information.

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Table 14.2.1.2-1a
Agreement between ^{18}F-mFBG Original Read and ^{123}I-mIBG Blinded Image Read Interpretations Excluding Unreliable ^{123}I-mIBG
(Intent to Image Population)

Blinded Image Reader	uSoR Category	Blinded Reader ^{18}F-mFBG Result	Blinded Reader ^{123}I-mIBG Result		p-value
			^{123}I-mIBG Read Correct	^{123}I-mIBG Read Incorrect	
1	Positive	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	
	Negative	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	
2	Positive	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	
	Negative	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	
3	Positive	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	
	Negative	^{18}F-mFBG Read Correct	XX	XX	X.XXX
		^{18}F-mFBG Read Incorrect	XX	XX	

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Note: For SoR positive, "correct" means the image (^{18}F-mFBG or ^{123}I-mIBG) interpretation is positive, while for SoR negative, "correct" means the image interpretation is negative. P-value is from McNemar test. Subjects with missing scan data for either scan are excluded from this analysis. Subjects with unreliable ^{123}I-mIBG are excluded.

Abbreviation: uSoR = Updated Standard of Reference; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F); ^{123}I-mIBG = meta-iodobenzylguanidine (^{123}I).

Reference Listing: 16.2.6.1-1, 16.2.6.2, 16.2.6.3

Table 14.2.1.2-4a
Agreement between ^{18}F-mFBG New Read and ^{123}I-mIBG Blinded Image Read Interpretations Excluding Unreliable ^{123}I-mIBG
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1, 16.2.6.3

Programming Note: using the same format for Table 14.2.1.2-1a to replace the relevant information.

collaboration

Table 14.2.1.3.1-1
Agreement between Blinded Readers New Read with Respect to Imaging Uptake (Reader 1 vs. Reader 2)
(Intent to Image Population)

Reader	Image Reader Result	Image Reader 2			
		^{18}F-mFBG Result			
		Abnormal	Normal	k	p_o
Image Reader 1	Abnormal	XX[a]	XX[b]	X.XX	X.XX (X.XXX, X.XXX)
	Normal	XX[c]	XX[d]		

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Kappa Statistic (κ) = (p_o - p_e) / (1-p_e), where p_o = observed agreement among raters and p_e = probability of chance agreement.

Proportion of Agreement (p_o) = [(a+d)/(a + b + c + d)] As per Landis and Koch guidelines, k value between 0.41 and 0.60 is considered as moderate level of agreement.

Abbreviation: ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.2-1

collaboration

Table 14.2.1.3.2-1
Agreement between Blinded Readers New Read with Respect to Imaging Uptake (Reader 1 vs. Reader 3)
(Intent to Image Population)

Programming Note: Repeat Table 14.2.1.3.1 for readers 1 vs. reader 3.

Table 14.2.1.3.3-1
Agreement between Blinded Readers New Read with Respect to Imaging Uptake (Reader 2 vs. Reader 3)
(Intent to Image Population)

Programming Note: Repeat Table 14.2.1.3.1 for readers 2 vs. reader 3.

collaboration

Table 14.2.1.5a-1
Summary of Scan Image Quality for New Read by eGFR Category
(Intent to Image Population)

eGFR Category	Scan Quality	^{18}F-mFBG
eGFR ≥90 ml/min/1.73m^2	Excellent	XX (XX.X%)
	Good	XX (XX.X%)
	Fair	XX (XX.X%)
	Poor	XX (XX.X%)
	Uninterpretable	XX (XX.X%)
eGFR <90 ml/min/1.73m^2	Excellent	XX (XX.X%)
	Good	XX (XX.X%)
	Fair	XX (XX.X%)
	Poor	XX (XX.X%)
	Uninterpretable	XX (XX.X%)

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG.

eGFR (mL/min/1.73 m^2) =0.413*height (in cm) / serum creatinine (in mg/dl).

Abbreviation: eGFR = Estimated Glomerular Filtration Rate; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.2-1

Programming Note: Populate this table even if there are less than 10 subjects in an eGFR category.

collaboration

Table 14.2.1.5b-1
Summary of Scan Image Quality for New Read by ^{18}F-mFBG Manufactured Precursor (Well Characterized vs GMP Precursor)
(Intent to Image Population)

Manufactured Precursor	Scan Quality	^{18}F-mFBG
GMP Precursor	Excellent	XX (XX.X%)
	Good	XX (XX.X%)
	Fair	XX (XX.X%)
	Poor	XX (XX.X%)
	Uninterpretable	XX (XX.X%)
Well Characterized	Excellent	XX (XX.X%)
	Good	XX (XX.X%)
	Fair	XX (XX.X%)
	Poor	XX (XX.X%)
	Uninterpretable	XX (XX.X%)

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG.

Well characterized subgroup includes subjects who were injected with ^{18}F-mFBG on or before 3-JAN-2023 and GMP precursor includes those injected after 3-JAN-2023.

Abbreviation: ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Listing: 16.2.6.2-1

collaboration

Table 14.2.1.6-1
Generalized Linear Model Assessing the Effect of eGFR on Image Quality Score for New Read
(Intent to Image Population)

Blinded Image Reader	Statistic	Result
1	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX
2	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX
3	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG.

eGFR (mL/min/1.73 m^2) =0.413*height (in cm) / serum creatinine (in mg/dl).

Regression Model: Reader image quality score = eGFR.

Abbreviation: CI = Confidence Interval; SE = Standard Error; eGFR = Estimated Glomerular Filtration Rate.

Reference Listing: 16.2.8.2, 16.2.4.1 and 16.2.6.2-1

Collaboration

Table 14.2.1.7-1
Generalized Linear Model Assessing the Effect of ^{18}F-mFBG Manufactured Precursor (Well Characterized vs GMP Precursor) on Image Quality Score for New Read
(Intent to Image Population)

Blinded Image Reader	Statistic	Result
1	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX
2	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX
3	Estimate (SE)	XX.XXX (X.XXXX)
	95% CI	XX.XXX, XX.XXX
	Adjusted R-square	X.XXX
	p-value	X.XXX

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG.

Regression Model: Reader image quality score = ^{18}F-mFBG Manufactured Precursor.

Abbreviation: CI = Confidence Interval; SE = Standard Error.

Reference Listing 16.2.6.2-1

Collaboration

Table 14.2.1.10-1
Agreement between ^{18}F-mFBG Imaging Original Read and uSoR excluding Subjects with uSoR Determination Uncertainties
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.1.1-1a to replace the relevant information.

Table 14.2.1.10-2
Agreement between ^{18}F-mFBG Imaging Original Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative excluding Subjects with uSoR Determination Uncertainties
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2

Programming Note: using the same format for Table 14.2.1.10-1 to replace the relevant information.

Table 14.2.1.10-4
Agreement between ^{18}F-mFBG Imaging New Read and uSoR excluding Subjects with uSoR Determination Uncertainties
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.10-1 to replace the relevant information.

Table 14.2.1.10-5
Agreement between ^{18}F-mFBG Imaging New Read and uSoR with Minimal Disease Converted to Neuroblastoma Negative excluding Subjects with uSoR Determination Uncertainties
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.10-1 to replace the relevant information.

collaboration

Table 14.2.1.11
Summary of Receiver Operating Characteristic (ROC) Analysis on Confidence Scores at Pre-mIBG to uSoR
(Intent to Image Population)

Confidence Score at Pre-mIBG	Sensitivity	Specificity	Youden Index
XX	XX.X	XX.X	XX.X
XX	XX.X	XX.X	XX.X
XX	XX.X	XX.X	XX.X

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Youden Index is sensitivity + specificity - 1. Confidence Score (%) at Pre-mIBG is from the original expert panel assessment.

Abbreviation: uSoR = Updated Standard of Reference; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F); ^{123}I-mIBG = meta-iodobenzylguanidine (^{123}I); AUC = Area Under Curve.

Reference Listing: 16.2.6.1-1

Programming Note: Confidence Score at Pre-mIBG is from original data. uSoR is the updated SoR.

collaboration

Table 14.2.1.12-1
Agreement between ^{18}F-mFBG Imaging Original Read and uSoR by Confidence Score Cut Off Point at Pre-mIBG
(Intent to Image Population)

Subgroup: Confidence Score <XX / Confidence Score >= XX

Blinded Image Reader	Blinded Reader Result	Subjects with missing ^{18}F-mFBG scan data as Positive						Subjects with missing ^{18}F-mFBG scan data as Negative					
		uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value	uSoR Diagnosis Positive	uSoR Diagnosis Negative	PPA (95% CI)	PPA p-value	NPA (95% CI)	NPA p-value
1	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
2	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				
3	Positive	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX	XX[a]	XX[b]	XX (XX.X, XX.X)	X.XXX	XX (XX.X, XX.X)	X.XXX
	Negative	XX[c]	XX[d]					XX[c]	XX[d]				

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Confidence Score (%) at Pre-mIBG is from the original expert panel assessment. Exact binomial two-sided 95% CIs are presented for PPA and NPA. P-values are from Normal z-test testing whether the proportion (PPA or NPA) equals 0.5.

PPA = a / (a+c)
NPA = d / (b+d)

Abbreviation: PPA = Positive Predictive Agreement; NPA = Negative Predictive Agreement; uSoR = Updated Standard of Reference; CI = Confidence Interval; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Reference Table: 14.2.1.13 Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: If it is confirmed that there are no missing scan data after DBL, only columns under "Subjects with missing 18F-mFBG scan data as Positive" table header should be retained with this table header removed.

Table 14.2.1.12-2
Agreement between ^{18}F-mFBG Imaging New Read and uSoR by Confidence Score Cut Off Point at Pre-mIBG with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2

Programming Note: using the same format for Table 14.2.1.12-1 to replace the relevant information.

Table 14.2.1.12-3
Agreement between ^{18}F-mFBG Imaging New Read and SoR by Confidence Score Cut Off Point at Pre-mIBG
(Intent to Image Population)

Reference Listing: 16.2.6.1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.12-1 to replace the relevant information.

Table 14.2.1.12-4
Agreement between ^{18}F-mFBG Imaging New Read and uSoR by Confidence Score Cut Off Point at Pre-mIBG
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.12-1 to replace the relevant information.

Table 14.2.1.12-5
Agreement between ^{18}F-mFBG Imaging New Read and uSoR by Confidence Score Cut Off Point at Pre-mIBG with Minimal Disease Converted to Neuroblastoma Negative
(Intent to Image Population)

Reference Listing: 16.2.6.1-1, 16.2.6.2-1

Programming Note: using the same format for Table 14.2.1.12-1 to replace the relevant information.

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Listing 16.2.6.1-1
Updated Expert Panel Assessment Data
(Intent to Image Population)

Subject ID	Confidence Score (%) at Pre-mIBG	Neuroblastoma Tumor Status	Did the additional follow-up information change the Part 2 assessment? (specify)	If uSoR is Positive for Neuroblastoma, did subject status qualify as MD on the reference date?
XXX	XXX	Present	Yes (XXX)	Yes
XXX*	XXX	Absent	No	No
XXX*	XXX	Absent	No	No

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Confidence Score (%) at Pre-mIBG is from the original expert panel assessment.

Abbreviations: ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F); MD = Minimal Disease; uSoR = Updated Standard of Reference

Programming Notes: Sort order: Subject ID; Grouping variables: -; Missing data representation: Represent missing data as '-'; Other notes: -.

Listing 16.2.6.2-1
^{18}F-mFBG Blinded Reader New Read
(Intent to Image Population)

Subject ID	Subgroup	Reader Identifier	Visit Date	Scan Quality	If Neuroblastoma is Present	Grid Zone	Neuroblastoma Disease Classification	Location of Metastasis	Number of Type 1 Lesions	Number of Type 2 Lesions	Comment	Organ System	Curie Scores	Total Curie Score
XXX	GMP Precursor	1	DD-MMM-YYYY	Good	Yes	XXX	Primary tumor, no metastasis		XX	XX	XXX	XXX	X	XX
		2	DD-MMM-YYYY	Fair	No	XXX	Primary tumor, metastasis	Both	XX	XX	XXX	XXX	X	XX
		3	DD-MMM-YYYY	Fair	Yes	XXX	Primary tumor, no metastasis		XX	XX	XXX	XXX	X	XX
XXX*	Well Characterized	1	DD-MMM-YYYY	Good	Yes	XXX	Primary tumor, no metastasis		XX	XX	XXX	XXX	X	XX
		2	DD-MMM-YYYY	Good	Yes	XXX	Primary tumor, no metastasis		XX	XX	XXX	XXX	X	XX
		3	DD-MMM-YYYY	Good	Yes	XXX	Primary tumor, metastasis	Soft Tissue	XX	XX	XXX	XXX	X	XX

Note: Intent to Image Population includes all enrolled subjects who receive an administration of ^{18}F-mFBG. Curie scores are presented from region 1 to region 10. Diagnostic efficacy population includes all enrolled subjects who completed a ^{18}F-mFBG scan at baseline and either complete the 3-month clinical follow-up period or discontinue the study prior to 3-months after ^{18}F-mFBG imaging. * denotes subjects in diagnostic efficacy population.

Well Characterized precursor subgroup includes subjects who were injected with ^{18}F-mFBG on or before 3-JAN-2023 and GMP precursor includes those injected after 3-JAN-2023.

Curie Score: 0 - No mFBG uptake 1 - One mFBG-avid lesion 2 - More than one lesion 3 - mFBG avidity in >50% of that region

Abbreviations: CT = Computerized Tomography; MR = Magnetic Resonance; ^{18}F-mFBG = meta-fluorobenzylguanidine (^{18}F).

Programming Notes: Sort order: Subject ID, Reader Identifier; Grouping variables: Subject ID; Missing data representation: Represent missing data as '-'; Other notes: present curie scores as comma separated from region 1 to 10.

8 References

Statistical Analysis Plan v2.2 dated 08-Jul-2026

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9 Change Log

Version	Author	Change Date	Description	Reviewer	Review Date
1.00	Sangli Therasanathan	18-OCT-2022	First approved version	Madhangi Priyadharshini Gandhi	11-Oct-2022
1.01	Divya Anthony	04-Jan-2024	Updated based on SAP Version 2.0	Sangli Therasanathan	05-Jan-2024
1.02	Divya Anthony	11-Jan-2024	Updated as per internal review comments	Sangli Therasanathan	11-Jan-2024
1.03	Divya Anthony	16-Jan-2024	Updated as per second round internal comments	Sangli Therasanathan	16-Jan-2024
1.04	Divya Anthony	30-Jan-2024	Updated as per Sponsor comments and SAP Version 2.1	Sangli Therasanathan	30-Jan-2024
2.20	Andrea Peng	08-Jul-2026	Updated based on PCL1 and reader re-reading data	Nelson Onyango	08-Jul-2026

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