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STATISTICAL ANALYSIS PLAN **GE Healthcare**
GE-265-303

Title: A Phase 3, Open-Label, Multicentre Study of Flurpiridaz (^{18}F) Injection for Positron Emission Tomography (PET) Imaging for Assessment of Myocardial Perfusion in Patients Referred for Invasive Coronary Angiography Because of Suspected Coronary Artery Disease.

This Statistical Analysis Plan was prepared by the following personnel:

Name [redacted]
Title [redacted]
Company [redacted]

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REVISION HISTORY

Version	Date	Changes implemented
1.0	[redacted]	Not applicable.
2.0	Refer to the signature page.	Edits to the study schedule of events are incorporated (Table 1). Minor typographical edits and corrections. The analysis for some efficacy endpoints has been described in more detail. The analysis for several safety endpoints has been described in more detail (e.g., adverse events, vital signs).

ABBREVIATIONS

AE	Adverse event
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence Interval
ECG	Electrocardiogram
eCRF	Electronic case report form
FN	False negative(s)
FP	False positive(s)
ICA	Invasive coronary angiography
ICF	Informed consent form
IMP	Investigational medicinal product
ICL	Imaging core laboratory
IVUS	Intravascular Ultrasound
LV	Left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
MPI	Myocardial Perfusion Imaging
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
QCA	Quantitative coronary angiography
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Summed difference score
SMITT	Secondary modified intent-to-treat
SPECT	Single photon emission computed tomography
SRS	Summed rest score
SSS	Summed stress score
TEAE	Treatment-emergent adverse event
TN	True negative(s)
TP	True positive(s)
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

GE-265-303 is a Phase 3, prospective, open-label, international, multicentre study of Flurpiridaz (^{18}F) Injection for Positron Emission Tomography (PET) Myocardial Perfusion Imaging (MPI) in patients referred for Invasive Coronary Angiography (ICA) because of suspected Coronary Artery Disease (CAD). Five hundred and fifty-two (552) evaluable subjects will be enrolled in this study and will undergo Single Photon Emission Computed Tomography (SPECT) MPI and Flurpiridaz (^{18}F) Injection PET MPI, prior to ICA. Flurpiridaz (^{18}F) Injection is the IMP in this study.

This document presents the statistical analysis plan (SAP) for Study GE-265-303. Reference material for this SAP includes Protocol GE-265-303 CPR REV A03 Version 1.0.

The SAP will provide details to further elaborate statistical methods as outlined in the protocol and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report.

2 STUDY OBJECTIVES, DESIGN AND PROCEDURES

2.1 Objectives

Primary Objective:

- Assess the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET MPI in the detection of significant CAD, as defined by ICA, in patients with suspected CAD.

Secondary Objectives:

- Evaluate the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET MPI compared with that of SPECT MPI in the detection of CAD, as defined by ICA, in the following groups of subjects:
  - All subjects (key secondary endpoint)
  - Female subjects
  - Subjects with body mass index (BMI) ≥30 kg/m^2
  - Diabetic subjects
- Assess the safety of Flurpiridaz (^{18}F) Injection PET MPI.

Exploratory Objectives:

[redacted]

[redacted]

2.2 Study Design

This is a Phase 3, prospective, open-label, international, multicentre study of Flurpiridaz (^{18}F) Injection for PET MPI in patients referred for ICA because of suspected CAD.

This study will be conducted at approximately 60 centres in Europe and North America (United States and Canada).

The procedure order will not be randomised but will be dependent upon the presentation of the patient at the site; however, in all cases SPECT and Flurpiridaz (^{18}F) PET MPI must be performed within 60 days prior to ICA. Included in these 60 days are clinically indicated SPECT exams that may precede screening, which otherwise meet all study-specific imaging and stress testing criteria (hereby called "Off-study" SPECT exams) (see Study Diagram, Figure 1).

All subjects will be followed up for adverse events (AEs) within 2 days following Flurpiridaz (^{18}F) Injection administration, and for AEs and serious adverse events (SAEs) at approximately 2 weeks (14 to 17 days) following the last Flurpiridaz (^{18}F) Injection dose administration and at the time of their ICA.

Therefore, study subjects will participate in the study for up to 77 days.

Each subject will attend a Screening Visit up to 30 days prior to enrolment. The investigator will explain what participation in the study entails and check to determine that the subject meets all the inclusion criteria but none of the exclusion criteria.

Patients can be considered for enrolment if:

- They are being scheduled via written documentation at the time of enrolment to undergo ICA, and
- They have undergone a clinically indicated SPECT study which meets all study-specified imaging and stress testing criteria or are willing to undergo SPECT MPI for the purposes of the clinical study.

ICA represents the regulatorily-accepted truth standard for the determination of presence or absence of significant coronary stenosis.

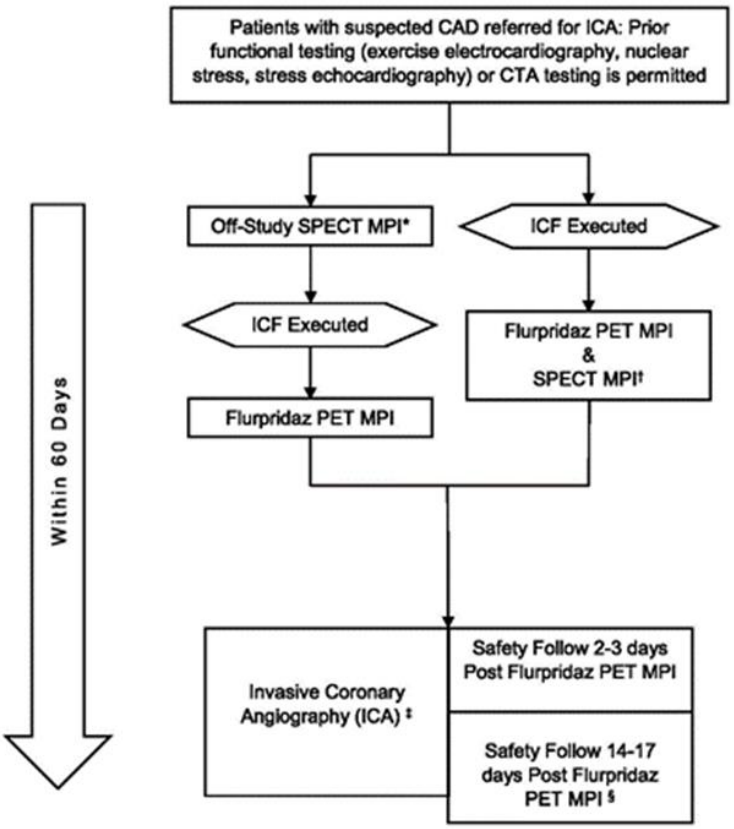
Study Population:

Five hundred and fifty-two (552) evaluable subjects will be enrolled in this study. Assuming a 15% dropout rate, 650 subjects will need to be enrolled initially.

While enrolment will not be formally stratified, enrolment will be monitored and the recruitment plan may be adjusted during the course of the study to ensure adequate representation of subjects aged ≥65 years of age and that at least one third of the enrolled subjects will be diabetic, one third but no more than one half will have BMI ≥30 kg/m^2, and one third will be women.

An overview of study procedures is presented in Figure 1. A schedule of study procedures is provided in Table 1.

Figure 1 Study Diagram



* Off-study SPECT MPI performed prior to signing of ICF, in accordance with the procedures developed by ICL and on a validated camera

† The Flurpridaz PET MPI and SPECT MPI may occur in any order and are unlikely to occur on the same day

‡ The ICA may occur during the safety follow up post Flurpiridaz PET MPI. The ICA must occur within 60 days of screening or Off-Study SPECT if this pathway is used.

§ The timing of the safety follow-up is 2-3 days and again 14-17 days after Flurpiridaz PET MPI. This follow up window may extend beyond the 60-day window defined by the initial screening or Off-Study SPECT occurrence.

Table 1 Study Schedule of Events

Variables	Screening	Baseline (≤30 days after Screening)	Can occur in either order. SPECT may precede Screening [a]		Safety Follow-up (2 to 3 days after PET MPI)	Safety Follow-up (14 to 17 days after PET MPI)	ICA (within 60 days of Screening or "Off-study" [a]
			Rest and Stress SPECT MPI	Rest and Stress PET MPI			SPECT)
Informed consent	X						
Entry criteria	X						
Pregnancy test [b]	X	X		X			
Demographic information	X						
Medical/surgical history	X						
Blood sampling	X[c]			X[d]			
Urine sampling	X			X[d]			
Seattle Angina Questionnaire	X						
Prior/concurrent medications	X	X	X	X	X	X	X[m]
Vital signs		X	X[e]	X[e]			X[m]
Pulse oximetry		X	X	X			X[m]
12-lead ECG recording	X[f]			X			
Physical examination [g]		X		X			
Full neurologic examination [h]		X		X			
Injection site monitoring				X[i]			
IMP administration				X			
Image acquisition			X[j]	X[k]			X
Adverse events (including AEs and SAEs)[l]	X	X	X	X	X	X	X

Table 1 Study Schedule of Events

Variables	Screening	Baseline (≤30 days after Screening)	Can occur in either order. SPECT may precede Screening [a]		Safety Follow-up (2 to 3 days after PET MPI)	Safety Follow-up (14 to 17 days after PET MPI)	ICA (within 60 days of Screening or "Off-study" [a] SPECT)
			Rest and Stress SPECT MPI	Rest and Stress PET MPI			

AE = adverse events; ECG = electrocardiogram; ICA = invasive coronary angiography; IMP = investigational medicinal product; MPI = myocardial perfusion imaging; PET = positron emission tomography; SAE = serious adverse events; SPECT = single photon emission computed tomography

a Results of "off-study" SPECT MPI that was performed prior to signing of the ICF but in accordance with procedures developed by the imaging core laboratory (ICL) and on a validated camera can be used. The "off-study" SPECT MPI must also achieve the minimal quality standard specified by the ICL in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study.

b For women of childbearing potential, the results of either a urine or serum human chorionic gonadotropin pregnancy test (with the result known the day of radiopharmaceutical administration) must be negative.

c If for scheduling reasons, the study SPECT or PET MPI must occur rapidly after the screening visit (e.g., within 48 hours), an additional blood sample may be analysed by local labs to determine if the subject meets exclusion criteria. For all subjects, blood must be sent for central analysis for all protocol specified laboratory parameters, whether or not blood is sent to a local lab for limited biochemical analysis for screening purposes.

d Before the first IMP injection (blood and urine) and 1 hour after the last IMP injection (blood).

e For rest SPECT-MPI and rest PET-MPI, vital signs will be collected up to 20 minutes prior to dose and 30 (±5) minutes post-dose. For stress SPECT-MPI and stress PET-MPI, vital signs will be collected up to 20 minutes prior to dose (if >60 minutes between rest and stress injections) and 30 (±5) minutes post-dose.

f 12 lead ECG collected on local ECG machine and interpreted by the investigator or a designee at the investigative site. A clinically indicated ECG obtained up to 48 hours prior to Screening is acceptable.

g Physical examination will comprise a full examination with a specific focus on neurological and cardiovascular signs. During the Rest/Stress PET MPI Visit, a physical examination will be performed before the rest portion of the Flurpiridaz (^{18}F) Injection PET MPI and 1 hour after the stress portion of the Flurpiridaz (^{18}F) Injection PET MPI. Additionally, a focused clinical screen for new or worsening symptoms indicative of unstable coronary artery disease will be conducted prior to performing any procedures at the Flurpiridaz (^{18}F) PET Visit. If the clinical status screening is positive, the Flurpiridaz (^{18}F) PET Visit can either be rescheduled (up to 1 time) after symptoms stabilize or the subject can be discontinued from the study.

h If any neurologic abnormalities are noted during physical examination.

i Immediately prior to the first injection, and then immediately after the first injection of IMP for the rest exam, immediately after the second injection of IMP for the stress exam, and ultimately at 1 hour after the last injection of IMP.

j Rest SPECT MPI and then stress (exercise or physiologic) SPECT MPI, per the institution's standard practices (the same stressor used for PET MPI, if PET MPI precedes SPECT MPI).

k Rest PET MPI and then stress (exercise or physiologic, the same stressor used for SPECT MPI) PET MPI, per the institution's standard practices.

l All serious and non-serious AEs will be collected from the time of informed consent and followed for a final outcome until the end of the follow-up period.

m Pre-procedure vitals, pulse-oximetry and concomitant medications can be extracted from the clinical record.

2.3 Sample Size Calculation

The sample size was calculated to ensure that a sufficient number of evaluable negative and positive patients (by ICA) are enrolled to achieve 90% power at a 1-sided significance level of 0.025 for both sensitivity and specificity in the primary analysis. Assuming the true sensitivity and true specificity are both 70% and testing the hypothesis that they are both >60%, 237 negative and 237 positive patients in the MITT population are required. Assuming a prevalence of 43%, approximately 552 total patients will be enrolled to ensure there are ≥237 positive patients. Enrolment will be monitored and the recruitment plan may be adjusted during the course of the study to ensure an adequate number of diseased patients. Assuming a dropout rate of 15%, up to 650 total patients will be enrolled to ensure that there are at least 552 evaluable MITT patients.

2.4 Interim Analysis

No formal interim analyses will be performed in this study.

2.5 Randomisation and Blinding

This is a Phase 3, open-label study (Table 2).

Table 2 Blinded Personnel

Personnel	Blinded To:
Subjects, site personnel, contract research organisation (CRO), and Sponsor	Centrally read efficacy assessment of PET and SPECT MPI, intracoronary angiography (quantitative coronary angiography [QCA]) assessments (partial unblinding will occur with regards to the report of the prevalence of CAD+ patients to the Sponsor occurring in 1-month or 2-month increments after the first 100 patients have had QCA analysis)
Blinded independent image reviewers	Medical history (until staged unblinding), SPECT MPI results, and standard of truth Centrally read intracoronary angiography QCA assessments

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

The primary endpoints of the study are the sensitivity and specificity of Flurpiridaz (^{18}F) Injection PET MPI in the detection of significant CAD as defined by ICA.

Subjects will be considered to have CAD if QCA reveals ≥50% stenosis of ≥1 major coronary artery or major branch.

3.1.2 Secondary Efficacy Endpoints

The secondary endpoints of the study are the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET MPI compared to that of SPECT, when the diagnosis of CAD by ICA is the standard of truth, in the following:

- All subjects (key secondary endpoint)
- Female subjects
- Subjects with BMI ≥30 kg/m^2
- Diabetic subjects

3.1.3 Exploratory Efficacy Endpoints

[redacted]

[redacted]

3.1.4 Image Acquisition

Imaging procedures include PET MPI, SPECT MPI, and ICA.

Image acquisition with SPECT and PET at rest and under stress procedures will be defined in the dedicated PET and SPECT Imaging Manual.

ICA will be performed in accordance with investigational site institutional practice.

Ventriculograms, when performed for clinical reasons, will also be included.

Doppler flow or pressure-wire measurements and/or Intravascular Ultrasound (IVUS) may also be performed at the time of the ICA. If a Doppler flow or pressure wire is used to measure fractional flow reserve (FFR), the measurements will be collected on the electronic case report form (eCRF).

The truth standard used in this study is the presence of CAD (i.e., disease-positive) as evidenced by the presence of stenosis of ≥50% in ≥1 major epicardial coronary artery or major branch by quantitative coronary angiography (QCA).

Further details of the ICA protocol will be provided in the Angiography Imaging Manual.

3.1.5 Image Interpretation and Correlation with Standard of Truth

Three qualified independent readers will perform a blinded assessment of each subject's PET image pair (rest and stress images) and each subject's SPECT image pair. Further details will be provided in the study PET and SPECT Independent Review Charter.

One blinded reviewer will perform QCA, according to the Angiography Independent Review Charter, for all ICA images.

3.2 Safety Endpoints

Subjects will be closely monitored for safety until completion of all study procedures. Safety monitoring will include AEs, medication errors, treatment-emergent adverse events (TEAEs), and SAE assessments, vital signs, electrocardiograms (ECGs), haematology, clinical chemistry laboratory tests, and urinalysis. All subjects will be followed up by telephone assessments for AEs within 2 days (+24 hours) following Flurpiridaz (^{18}F) Injection administration, and for AEs and SAEs at approximately 2 weeks (14 to 17 days) following the last Flurpiridaz (^{18}F) Injection dose administration. For subjects undergoing SPECT for the purposes of this clinical study, their safety will be monitored as per institutional standards.

The investigator(s) and the Sponsor/CRO will review the safety data. The following safety data will be collected and evaluated:

- Clinical laboratory parameters: serum biochemistry, haematology, and urinalysis
- Vital signs: systolic/diastolic blood pressure, heart rate, pulse oximetry, and intermittent respiration rate and body temperature
- Continuous ECG monitoring
- Lead II rhythm strip and 12-lead ECG
- Physical examination
- Injection site monitoring
- Post-treatment events (AEs and SAEs)

4 ANALYSIS POPULATIONS

4.1 Definition for Analysis Populations

4.1.1 Enrolled Population

The Enrolled population will consist of all subjects who signed the ICF.

4.1.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all enrolled subjects who received ≥1 dose of Flurpiridaz (^{18}F) Injection in the study.

4.1.3 Modified Intent-to-Treat (MITT) Population

The MITT population will include all ITT subjects who have completed the rest and stress Flurpiridaz (^{18}F) Injection PET MPI procedures and who have evaluable truth standard data. The MITT population will be the primary analysis set for the primary efficacy endpoints.

4.1.4 Secondary Modified Intent-to-Treat (SMITT) Population

The secondary MITT (SMITT) population will include the subjects in the MITT population who have completed the rest and stress SPECT MPI (if the subject's SPECT MPI is "off-study," that SPECT MPI must meet minimal quality standards, as specified by the ICL). The SMITT population will be the primary analysis set for the secondary efficacy and exploratory efficacy endpoints unless otherwise specified.

A summary of subject disposition, including the number and percentage of ITT subjects who do not have evaluable results for PET or the truth standard or who are not in the MITT analysis set, will be provided, with the reasons for non-evaluability.

4.1.5 Determination of Safety Population

The Safety Population will include all subjects who have received ≥1 dose of Flurpiridaz (^{18}F) Injection in the study. All safety data will be summarised for the Safety Population.

5 ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the ICH M2 Guidelines [ICH 2008]. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name, including the path that generates the output;
3. Any other output-specific details that require further elaboration.

Three (3) table formats will be followed for data summary:

1. For background data, including demography, medical history, prior medications, and concomitant medications, one column will be presented for all enrolled patients. In addition, the safety population, MITT population and SMITT population will be presented side-by-side as 3 additional columns, where appropriate.
2. For all safety data, 1 column displaying values for patients who have received ≥1 dose of Flurpiridaz (^{18}F) Injection will be presented.
3. For some efficacy-related tables, when comparing SPECT MPI and PET MPI, SPECT MPI and PET MPI will be presented side-by-side, where appropriate.

The summary tables will clearly indicate the number of patients to which the data apply, and *unknown* or *not performed* will be distinguished from *missing* data.

Supportive individual Patient Data Listings, as a minimum, will be sorted and presented by the study arm, patient number, and visit date, if applicable.

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- Summary statistics for categorical variables will consist of the number and percentage of responses in each level. The number and percentage of responses will be presented in the form XX (XX.X%).
- Summary statistics for continuous variables will consist of the sample size (n), mean, median, standard deviation (SD), minimum, and maximum values.
- All mean and median values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- All p-values, if applicable, will be rounded to 4 decimal places. All p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.0000 will be

presented as '>0.9999'. One-sided P-values < 0.025 will be considered to be statistically significant unless otherwise specified.

- All summary tables will include the analysis population sample size (i.e., number of patients).
- Study Day 1 is defined as the date at which the patient received the IMP, Flurpiridaz (^{18}F) Injection. All study days are determined relative to Day 1.
- Study days prior to Day 1 will be calculated as:
  - Study Day = Assessment Date – Date of IMP received
- Study days after Day 1 will be calculated as:
  - Study Day = Assessment Date – Date of IMP received + 1.
- Baseline values will be defined as the last non-missing value recorded prior to IMP received.
- Change from baseline will be calculated as follows:
  - Change = Post-baseline value - baseline value.
- All pre- and post-enrolment assessments including unscheduled or repeat assessments will be included in the data listings.
- Date variables will be formatted as YYYY-MM-DD for presentation.
- Tables, figures, and listings will be presented in landscape orientation.
- SAS® Version 9.4 or higher will be the statistical software package used for all data analyses.

5.1 Definition of Analysis Windows

There are no visit windows for this study. For the statistical analyses, data will be analyzed by the nominal visit that was collected on the eCRF.

Unscheduled visits will not be used in the by-visit analysis but will be used for the following where appropriate: 1) derivations of baseline/last on-treatment measurements; 2) derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses; 3) data listings.

5.2 Definition of Missing Data Imputation

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

5.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances.

6 STATISTICAL ANALYSES

6.1 Subject Disposition

A table will be provided with the following information:

- Number of subjects enrolled.
- Number of subjects included in the efficacy analysis populations (ITT, MITT, SMITT).
- Number of subjects included in the safety analysis population.
- Number of subjects withdrawn from the study and the reason for withdrawal.

6.2 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

6.2.1 Demographic and Baseline Characteristics

Demographic information (age, height, weight, and BMI) will be summarised by using descriptive statistics. Sex, ethnicity, race, and history of Diabetes Mellitus will be summarised by counts and percentages.

6.2.2 Medical/Surgical History

The subjects' relevant medical and surgical history as recorded at Screening will be summarised and the data will be presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system.

The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

6.2.3 Prior and Concomitant Medications

Prior and concomitant medications are defined relative to Flurpiridaz administration. Any medications taken by the subject within 12 hours before the screening or the SPECT stress test if it precedes screening, at the time of ICA and up to study completion will be summarized by counts and percentages using the World Health Organization Drug Dictionary (WHO-DD) March 2021 version, and grouped by primary and secondary classes, if applicable.

A *prior* medication is defined as any medication taken prior to the start of the first dose of Flurpiridaz. A *concurrent* medication is a new medication started after the start of the first dose of Flurpiridaz or a prior medication but continued to post Flurpiridaz administration.

If the medication was taken prior to Flurpiridaz administration and no information on its use is available after the imaging (i.e., no end date), the medication will be assumed to be ongoing

and therefore considered as both prior and concurrent medications. If the medication was being taken after the start of Flurpiridaz administration and there is no information on its use prior to Flurpiridaz administration (i.e., no start date), the medication will be considered as both prior and concurrent medications.

Table 3 Classification of prior and concurrent medications

Start date \ End date	Before start of IMP administration	On or after start of IMP administration	Missing
Before start of IMP administration	Prior	Prior/Concurrent	Prior/Concurrent
On or after start of IMP administration	–	Concurrent	Concurrent
Missing	Prior	Prior/Concurrent	Prior/Concurrent

6.3 Study Drug Exposure

Treatment exposure (SPECT agent or Flurpiridaz (^{18}F) injected dose in mCi or MBq) will be summarized by descriptive summary statistics. Summary statistics will be presented by each dose: rest, stress (exercise and pharmacological), and total exposure. A summary of each subject's dosing information will be presented in a listing.

Treatment exposure for Flurpiridaz (^{18}F) will be calculated using the following formula for decay correction:

$$A_{injected} = A_{measured} \cdot e^{-0.0063 \cdot \Delta T_{measured-injection}} - A_{residual} \cdot e^{0.0063 \cdot \Delta T_{injection-residual}}$$

Effective dose will be calculated as the product of the dose/unit activity and the administered activity. For Flurpiridaz (^{18}F) injected doses, the dose per unit injected activity depends on whether the study is a rest (0.071 rem/mCi), pharmacologic stress (0.069 rem/mCi) or exercise stress (0.054 rem/mCi) exam. For SPECT studies, the dose per unit injected activity depends on whether the study is a Tetrofosmin (Rest: 0.0296 rem/mCi or Stress: 0.0255 rem/mCi) or Sestamibi (Rest: 0.0333 rem/mCi or Stress: 0.0292 rem/mCi) exam.

6.4 Primary Efficacy Analyses

6.4.1 Efficacy Variables

6.4.1.1 Myocardial Perfusion Imaging Evaluations

Three qualified readers (independent from the study) will perform independent blinded and unblinded reads of all MPI images. The PET MPI and SPECT MPI reads will be performed by the same set of readers in cross-over sessions independent of one another. In each session, PET and SPECT images will be displayed in a randomised order, non-sequentially, with PET

and SPECT MPI exams corresponding to individual subjects randomly allotted into reading session batches. For each modality, perfusion and gated acquisitions of rest and stress images will be rated for image quality and reviewed. After the results of each blinded interpretation of individual MPI (PET or SPECT) scans are locked as the "blinded" read, then clinical information will be provided. The reader will then be given the opportunity to submit a revised assessment of the existence of any perfusion defects as an "unblinded" read.

The primary efficacy read for MPI status will be the overall qualitative diagnosis of the paired Flurpiridaz (^{18}F) PET MPI (rest/stress) using perfusion and gated assessments from independent blinded reads. The overall qualitative diagnosis will be scored by each reader for each subject as normal, ischaemic, ischaemic + scar, or scar on the basis of the perfusion + gated images. These scores will be dichotomised into MPI negative (normal) and MPI positive (ischaemic, ischaemic + scar, or scar) for each subject and reader.

6.4.1.2 Coronary Angiography Evaluations

All coronary angiograms will be performed within 60 days of screening or SPECT if SPECT occurs prior to informed consent. ICA data for the diagnosis of CAD will be generated by QCA.

6.4.1.3 Image Quality

The data on image quality and interpretability will be collected separately during the blinded read and will be analysed separately by modality.

6.4.2 Primary Efficacy Endpoints Analyses

The primary efficacy endpoints of the study are the sensitivity and specificity of Flurpiridaz (^{18}F) Injection PET MPI in the detection of significant CAD as defined by ICA. The truth standard used in this study is the presence of CAD as evidenced by the presence of stenosis of ≥50% in ≥1 coronary artery or major branch of a coronary artery as determined by QCA analysis.

For each of the 3 readers, a binary decision will be derived by using the overall qualitative diagnosis criteria as MPI-negative or MPI-positive; sensitivity and specificity will then be calculated for each of the 3 readers.

Sensitivity and specificity are defined as follows:

- True Positives (TP): Subjects with abnormal PET MPI and disease positive by the truth standard
- True Negatives (TN): Subjects with normal PET MPI and disease negative by the truth standard
- False Positives (FP): Subjects with abnormal PET MPI and disease negative by the truth standard

- False Negatives (FN): Subjects with normal PET MPI and disease positive by the truth standard
- Sensitivity: TP/(TP + FN)
- Specificity: TN/(TN + FP)
- Accuracy: TN + TP/(TN + TP + FN + FP)

A dosed subject whose PET MPI images are incomplete (i.e., a missing rest and/or stress image) will be excluded from the MITT analysis population. Also, a subject with a missing truth standard will be excluded from the MITT analysis population. A summary of reasons for all missing data will be provided, with number and percent in each category. To eliminate bias between modalities, once a subject is included in the MITT population, the readers will be asked to read SPECT MPI and PET MPI images and to classify the images as normal or abnormal, regardless of image quality and interpretability. To indicate when a diagnosis is forced, the reader will record in the blinded-read CRF which images are considered uninterpretable. The data on image quality and interpretability will be collected separately during the blinded read and will be analysed separately by modality.

In addition, sensitivity and specificity using the majority rule (the majority rule uses for each subject the judgement [positive or negative] given by at least 2 of the 3 readers) will be calculated.

6.4.3 Statistical Hypothesis, Model, and Method of Analysis

The 2 primary efficacy endpoints are calculated as follows from different subsets of the population:

- The calculation of sensitivity of Flurpiridaz (^{18}F) Injection PET MPI includes data only from subjects with CAD, per the standard of truth.
- The calculation of specificity of Flurpiridaz (^{18}F) Injection PET MPI includes data only from subjects without CAD, per the standard of truth.

Let s_1 = true sensitivity of Flurpiridaz (^{18}F) Injection PET MPI:

Let p_1 = true specificity of Flurpiridaz (^{18}F) Injection PET MPI:

The criteria for primary efficacy will be proving the statistical superiority of both the true specificity and sensitivity to a threshold of 60% in Flurpiridaz (^{18}F) Injection PET MPI. To meet the criteria for success in this study, both the sensitivity and the specificity of Flurpiridaz (^{18}F) Injection PET MPI must exceed 60%. Thus, the lower bound of the 2-sided 95% confidence interval (CI) for both sensitivity and specificity must exceed 60%.

Therefore, the tests of hypotheses will be as follows:

H_{01} : $s_1 \leq 0.60$; H_{02}: $p_1 \leq 0.60$, where s_1 is sensitivity in Flurpiridaz (^{18}F) Injection PET MPI and p_1 is specificity in Flurpiridaz (^{18}F) Injection PET MPI.

H_{a1}: $s_1 > 0.60$; H_{a2}: $p_1 > 0.60$

Since sensitivity and specificity are calculated for separate subsets of the MITT analysis population, and since both null hypotheses need to be rejected for the study to be considered a success, each of the above endpoint comparisons will be performed by using a 1-sided 1-sample test with type 1 error (α)= 0.025. The test will be based on the 1-sample z-test for proportions, using the normal approximation to the binomial distribution. The analysis will be done for each reader and for all readers. If each null hypothesis is rejected in the analysis of all readers or by the same 2 out of 3 readers, the study will be considered a statistical success.

There will be no formal interim efficacy analysis for this study.

A summary of diagnostic efficacy including sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) will be provided along with 2-sided 95% CIs based on the normal approximation to the binomial distribution (for each of sensitivity and specificity, if the null hypothesis above is rejected by the z-test, then the lower bound of the 2-sided 95% CI will mathematically be above the threshold of 60%).

6.4.4 Primary Efficacy Endpoint Subgroup Analysis

The summary in the last paragraph of Section 6.4.3 will also be provided for the following subgroups:

- Age groups (<65 years and ≥65 years)
- BMI <30 kg/m^2 and BMI ≥30 kg/m^2
- Diabetic and nondiabetic
- Sex (male and female)
- Race (White, Black or African-American, Asian, other)
- Presence or absence of multivessel CAD (per the standard of truth)
- Presence or absence of renal impairment (i.e., serum creatinine level at pre-dose evaluation is above normal range)
- Presence or absence of hepatic impairment (i.e., either ALT or AST value at pre-dose evaluation is above normal range)
- Type of stress test (pharmacological (Adenosine, Dipyridamole, and Regadenoson), exercise)

There are some subjects who took a pharmacological stress test during the SPECT procedure but an exercise stress test during the PET procedure. For the subgroup analysis, the subjects who took different stress tests will be excluded.

- Some patients took both exercise and pharmacological stress tests during both SPECT and PET procedures; these subjects will be classified as 'pharmacological'

The primary analysis will be repeated in the MITT population using as the SOT the presence of stenosis of ≥30% in ≥1 coronary artery or major branch of a coronary artery as determined by QCA analysis. The analysis will also be repeated using stenosis of ≥70% as the SOT.

The primary analysis will be repeated for SPECT MPI where SPECT MPI alone is compared to the truth standard using the SMITT population.

Additionally, sensitivity and specificity of PET MPI and SPECT MPI based on the unblinded reads with clinical information will be summarised. The percentage of read results that were changed after clinical information was made available will be presented by modality.

6.4.5 Reader Difference

The inter-reader agreement and intra-reader reproducibility of blinded visual interpretations of PET MPI and SPECT MPI will be reported as percent agreement and kappa scores. Intra-reader reproducibility will be determined based on a re-read of images from approximately 10% of the subjects, selected at random from all study subjects. Each reader will re-read the same subset of images.

6.4.6 Handling of Missing Values/Censoring/Discontinuations

To explore the extent of missing data, a summary of baseline characteristics will be created to compare groups of subjects with non-missing results with those who have missing results to assess if there is a significant difference between the two groups. This summary will be performed separately in ITT subjects who are missing PET MPI results, missing ICA results, or missing both PET MPI and ICA results.

For subjects who have ICA results available as a standard of truth but are missing PET MPI results, a sensitivity analysis will be performed to explore the potential impact of missing data on the primary analysis. In this analysis, the missing PET MPI results will be imputed by using the opposite result of ICA in order to obtain the conservative results for sensitivity analyses of the primary endpoint. PET MPI will also be imputed to match the ICA results in a separate summary to provide a range of possible outcomes.

6.4.7 Handling of Uninterpretable Images

Once a subject is included in the MITT population, the readers will be asked to read PET MPI images and to classify the images as normal or abnormal, regardless of image quality and interpretability.

6.5 Secondary Efficacy Analyses

6.5.1 Secondary Efficacy Endpoint Analyses

The secondary endpoints in this study are the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET MPI compared to that of SPECT MPI, when the diagnosis of CAD by ICA is the standard of truth, in the following:

- All subjects (key secondary endpoint)
- Female subjects
- Subjects with BMI ≥30 kg/m^2
- Diabetic subjects

To control the false-positive rate at a 1-sided 0.025 level across the testing of the secondary endpoints, the secondary efficacy endpoints will be tested hierarchically in the order given above. Each endpoint will be tested sequentially at a 1-sided 0.025 level of significance; when a statistical test for a given endpoint fails to reach statistical significance in the appropriate direction, testing on all remaining secondary endpoints in the hierarchy will cease and the study will be considered successful on all secondary endpoints up to that point.

6.5.2 Hypothesis Testing for the Key Secondary Endpoint

In the secondary efficacy analysis, the criteria for success will be the statistical superiority of sensitivity in Flurpiridaz (^{18}F) Injection PET MPI over that of SPECT MPI, and the noninferiority of specificity in Flurpiridaz (^{18}F) Injection PET MPI over that of SPECT MPI, when the detection of CAD by ICA is the standard of truth. Since the sensitivity calculation includes only the subjects with CAD and the specificity analysis includes only the subjects without CAD, the analysis of sensitivity and specificity will be separate, as follows:

Let s1 = sensitivity in Flurpiridaz (^{18}F) Injection PET MPI, and s2 = sensitivity in SPECT MPI.

Let p1 =specificity in Flurpiridaz (^{18}F) Injection PET MPI, and p2 = specificity in SPECT MPI.

Therefore, the test of hypotheses will be as follows:

H_{01}: $s1 - s2 \leq 0$, H_{02}: $p1 - p2 \leq -0.1$

H_{a1}: $s1 - s2 > 0$, H_{a2}: $p1 - p2 > -0.1$

Each of the above endpoint comparisons will be performed with a 1-sided paired test with a type 1 error (α) = 0.025.

The tests of comparisons are based on paired responses, as the Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed on a within-subject basis, and the images will be read by the same readers in a cross-over design. The test of sensitivity comparison between

Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a 1-sided McNemar's test at $\alpha = 0.025$. Similarly, the test of specificity noninferiority between Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a paired test for noninferiority [Liu et al 2002] at a 1-sided $\alpha = 0.025$. The criterion for the demonstration of diagnostic efficacy for the secondary endpoints will be meeting the tests of hypotheses for both sensitivity and specificity for all 3 or the same 2 of the 3 readers for whom the null hypotheses were rejected in the analysis of the primary endpoint.

6.5.3 Hypothesis testing for other secondary endpoints

The methodology used for evaluating diagnostic efficacy within these populations will be similar to that used for analysis of the key secondary endpoint.

6.6 Exploratory Analyses

6.6.1 Exploratory Endpoints:

[redacted]

[redacted]

[redacted]

[redacted]

6.7 Safety Variables and Analyses

Safety Endpoint(s): Descriptive summary statistics will be reported for AEs, TEAEs, and SAEs, changes from baseline for clinical laboratory tests, ECGs, physical examination, and vital signs for all treated subjects.

Post-administration changes from baseline will be summarised by mean, SD, minimum, and maximum at each time point.

6.7.1 Analysis of Adverse Events

An AE is defined as any untoward medical occurrence or an already present event that worsens in intensity after signing informed consent to the end of study. A TEAE is defined as an AE with an onset date on or after the first injection of IMP up to the end of the last injection of IMP + 17 days (inclusive) or from first injection of IMP to the time of first injection of the SPECT MPI agent--whichever interval is shorter. A TEAE does not necessarily have to have a causal relationship with exposure to the investigational agent. A TEAE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to the IMP, whether or not considered related to that product.

AEs and SAEs will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later, and all reported events will be listed for the safety population.

The following table summarizes all analyses for AEs and TEAEs:

Treatment-emergent Adverse Events (TEAEs)	Adverse Events (AEs)
Overall summary of TEAEs for safety population	Overall summary of AEs for all enrolled patients
	Overall summary of AEs for safety population
TEAEs by SOC and PT for safety population	AEs by SOC and PT for safety population
Serious TEAEs by SOC and PT for safety population	Serious AEs by SOC and PT for safety population
Severe TEAEs by SOC and PT for safety population	Severe AEs by SOC and PT for safety population
Drug-related TEAEs by SOC and PT for safety population	Drug-related AEs by SOC and PT for safety population
Common TEAEs (>5%) by SOC and PT for safety population	Common AEs (>5%) by SOC and PT for safety population
Common Serious TEAEs (>5%) by SOC and PT for safety population	Common Serious AEs (>5%) by SOC and PT for safety population
TEAEs by SOC, PT and Severity for safety population	AEs by SOC, PT and Severity for safety population
Serious TEAEs by SOC, PT and Severity for safety population	Serious AEs by SOC, PT and Severity for safety population
TEAEs by SOC, PT and Relationship for safety population	AEs by SOC, PT and Relationship for safety population

Treatment-emergent Adverse Events (TEAEs)	Adverse Events (AEs)
Serious TEAE by SOC, PT and Relationship for safety population	Serious AEs by SOC, PT and Relationship for safety population
TEAE leading to treatment discontinuation by SOC and PT	AEs leading to treatment discontinuation by SOC and PT
TEAE leading to death by SOC and PT	AEs leading to death by SOC and PT

If more than one event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to the IMP.

6.7.2 Clinical Laboratory Evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline (Table 4). In addition, for each clinical laboratory variable and each time point, the following safety endpoints will be summarised by counts and percentages:

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than 40% and 80% of the span of the normal limits (not applicable to qualitative parameters).

- The occurrence of post-administration values outside the normal limits (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

Table 4 Clinical Laboratory Parameters

Serum Biochemistry	Haematology	Urinalysis
Alanine aminotransferase (ALT)	Haematocrit	Bilirubin
Albumin	Platelet count	Glucose
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Ketone
Bicarbonate		Occult blood
Bilirubin (total)		pH
Calcium		Protein
Chloride		Specific gravity
Creatinine		Urobilinogen
Gamma-glutamyltransferase		
Glucose		
Hemoglobin A1c		
Lactate dehydrogenase		
Potassium		
Protein (total)		
Sodium		
Urea nitrogen		

6.7.3 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline. There are two vital sign baselines, REST and STRESS. However, if the STRESS baseline value is not recorded (missing), the STRESS baseline value will be imputed using the REST post-administration value. For each vital-sign variable and each time point, the following safety endpoints will be summarised by counts and percentages by additional/other characteristics deemed necessary by the study team:

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than a pre-specified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats per minute for heart rate, 1.5 C for body temperature, 10 breaths per minute for respiration rate.

- The occurrence of post-administration values outside the normal limits (Table 5). Shift tables based on the normal range will be prepared.

Table 5 Criteria for Normal Limits for Vital Signs

	Normal Limits	
Vital Signs Parameter	**Low**	**High**
Systolic BP, mm Hg	85	139
Diastolic BP, mm Hg	60	89
Heart rate, beats/min	60	100
Respiration rate, breaths/min	12	22
Body temperature	36.4°C 97.5°F	37.7°C 99.5°F
Oxygen saturation, %	93	100
Body weight, kg [a]	41	113
Body mass index (BMI), kg/m^2 [b]	18.5	24.9

Changes in body weight are evaluated by the investigator (without taking height into account), since BMI is not collected on the CRF.
BMI is calculated and analysed retrospectively by the Sponsor, at which time height is taken into account.

6.7.4 Electrocardiograms

A standard 12-lead ECG will be obtained at Screening and during Flurpiridaz (^{18}F) MPI rest imaging. The Screening ECG can be obtained on any local ECG machine and will be interpreted by the investigator or a designee at the investigative site.

Before the administration of the Flurpiridaz (^{18}F) Injection for the rest examination, three 12-lead ECGs, separated by at least 5 minutes, will be obtained with equipment provided by the ECG Core Laboratory. ECG clocks should be synchronised with imaging equipment. Note: pre-dose ECGs should be obtained within 20 minutes before the transmission scan, and the patient should rest for 5 minutes prior to the first measurement. Three additional ECGs (each separated by 30-60 seconds) will be obtained starting at 2 minutes (± 30-60 seconds) after the administration of the Flurpiridaz (^{18}F) injection for the rest examination. Single ECGs

will also be obtained at 10 and 30 minutes post injection. These 8 ECGs will be submitted to the ECG Core Laboratory for analysis.

Baseline value is defined as the average for all values measured prior to first injection time and on the same date of first injection. For summary purposes, the result for 2 minutes post injection is defined as the average value for all values that are recorded as 2 minutes post injection and the assessment time is after first injection time.

Therefore, EDC data will be analyzed by the following 2 approaches:

- The overall interpretation

Shift analysis from Screening to each time point of post-IMP will be performed using the overall interpretation of the ECG that were interpreted by the investigator or a designee at the investigative site.

- 12-lead ECGs measurements

Descriptive statistics will be displayed for the observed values and changes from baseline for the ECG intervals.

For each ECG variable and each time-point, the following safety endpoints will be summarized by counts and percentages or by additional/other characteristics deemed necessary by study team:

- The occurrence of post-administration values outside the normal limits in the PR, QTc, QRS or RR interval (Table 6).

QTc-specific analyses:

Two correction formulae will be employed in analysing QTc data in an attempt to reduce the bias resulting from over- or under-correction:

Bazett's: $QTcB = QT/\sqrt{RR}$
Fridericia's: $QTcF = QT/\sqrt[3]{RR}$

The following analyses will employ both methods of correction:

- Changes from baseline in the QTc interval will be displayed according to Committee for Medicinal Products for Human Use (CHMP) criteria (absolute QTc interval prolongation, of >450, >480, >500 ms and change from baseline in QTc interval >30 and >60 ms).

- Number and percentage of subjects with absolute QTc values above the upper limit of normal will be provided. Shift tables based on the normal range will be prepared.

Table 6 Criteria for Normal Limits for ECGs

ECG Variable	Normal Limits (ms)	
	Low	**High**
PR interval	120	200
QRS interval	50	100
RR interval	600	1000
QT interval (sex not specified)	—	≤440
QTc interval[a] (sex not specified)	—	≤440

[a] No lower boundary set for QTc.

6.7.5 Physical Examination

The number and percentage of subjects with changes in physical examination status from normal at Baseline to abnormal at each post-administration time point (and vice versa) will be presented. Shift tables based on the normal range will be prepared.

6.7.6 Injection Site Monitoring

Findings of injection site monitoring will be summarized by time points. All monitoring information including date/time, reasons for not done will be listed in a listing.

7 REFERENCES

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