Clinical Study Protocol **GE Healthcare**
GE-265-001

Title: A Descriptive, Comparative, Randomized, Crossover Study of Flurpiridaz (^{18}F) Injection for Positron Emission Tomography (PET) Imaging for Assessment of Myocardial Perfusion Imaging Quality using High Performance Liquid Chromatography (HPLC) and Solid Phase Extraction (SPE) Manufacturing Processes

REVISED TO INCORPORATE AMENDMENT A01

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GE Healthcare Confidentiality Statement

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature	Date

Print Name

1 SYNOPSIS

Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates

Name of Finished Product:
Flurpiridaz (^{18}F) Injection

Name of Active Ingredient:
[^{18}F]Flurpiridaz

Title of Study: A Descriptive, Comparative, Randomized, Crossover Study of Flurpiridaz (^{18}F) Injection for Positron Emission Tomography (PET) Imaging for Assessment of Myocardial Perfusion Imaging Quality using High Performance Liquid Chromatography (HPLC) and Solid Phase Extraction (SPE) Manufacturing Processes

Protocol Number: GE-265-001

Investigators and Study Centers: Approximately 4 centers in the United States (US)

Phase of Development: Phase 2

Objectives:

Primary Objective:

- Assess difference and variability between 2 sets of visually-based global rest scores resulting from 2 at-rest myocardial perfusion imaging (MPI) sessions using Flurpiridaz (^{18}F) Injection doses synthesized by the same or 2 different manufacturing processes

Secondary Objectives:

- Assess the intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses
- Assess the detection of myocardial segmental defect similarity from 2 sets of images acquired from doses synthesized by the same or 2 different manufacturing processes of Flurpiridaz (^{18}F) Injection PET for MPI at rest
- Assess the equivalence of 2 sets of [^{18}F]flurpiridaz time-activity curves (TACs) (blood, myocardium, lungs, liver) resulting from MPI using Flurpiridaz (^{18}F) Injection doses synthesized by the same or 2 different manufacturing processes
- Assess the safety of Flurpiridaz (^{18}F) Injection PET doses synthesized by 2 different manufacturing processes

Study Design:

This is a Phase 2 prospective, randomized, crossover study of Flurpiridaz (^{18}F) Injection for PET-MPI in subjects referred for evaluation of known coronary artery disease (CAD) or for suspected CAD with intermediate to high pre-test probability (PTP). Twenty-eight evaluable subjects will be enrolled in this study and will undergo 2 Flurpiridaz (^{18}F) Injection PET-MPI at rest. Each subject will attend a Screening Visit at least 2 days and up to 14 days prior to the first Flurpiridaz (^{18}F) Injection PET-MPI. The subjects will be randomized 1:1:1:1 to 4 possible sequences of receiving 2 doses of Flurpiridaz (^{18}F) Injection: 2 groups of 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by the same manufacturing processes (either HPLC or SPE) and 2 groups of 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by different manufacturing processes (1 dose by HPLC followed by 1 dose by SPE or 1 dose by SPE followed by 1 dose by HPLC). All subjects will be followed up by telephone for adverse events (AEs) and serious AEs (SAEs) at 24 (+8) hours following each Flurpiridaz (^{18}F) Injection administration.

Selection of Subjects:
Twenty-eight evaluable subjects will be enrolled in this study. Assuming a 20% drop-out rate, approximately 34 subjects will need to be enrolled initially. At least 30% of subjects enrolled should have a documented history of myocardial infarction, defined by history of a fixed defect.

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

1) The subject is a man or woman ≥18 years of age.

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2) The subject is undergoing evaluation of known CAD or for suspected CAD with an intermediate to high PTP.
3) The subject has read, signed, and dated an informed consent form (ICF) prior to any study procedures being performed, and is willing to allow the study investigator to make the subject's medical records available to GE Healthcare.
4) The subject is male or is a nonpregnant, nonlactating female who is either surgically sterile (has a documented bilateral tubal ligation and oophorectomy and/or documented hysterectomy [bilateral tubal ligation alone is insufficient]) or is post-menopausal (cessation of menses for more than 1 year); enrollment in the study without a pregnancy test at Screening is allowed for these categories of female subjects. For women of childbearing potential, the results of either a urine or serum human chorionic gonadotropin pregnancy test (with the result known on the day of each radiopharmaceutical administration) must be negative. These subjects must be practicing appropriate birth control from the time of the screening to 30 days after the second radiopharmaceutical administration. Such methods include: hormonal contraception including oral contraceptives; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence; adequate barrier method with spermicide (e.g., diaphragm, condom).
5) The subject is able and willing to comply with all study procedures as described in the protocol.

Exclusion Criteria:
Subjects who meet any of the following criteria will be excluded from the study:

1) Subjects who are pregnant, may possibly be pregnant, or wish (including their partners) to become pregnant during the study period, or are lactating.
2) Subjects who are unable to undergo all of the imaging procedures.
3) Subjects with unstable cardiovascular condition, including but not limited to:
   a. Transient ischemic attack/stroke within 3 months of enrollment;
   b. Significant congenital heart disease;
   c. Uncontrolled hypertension;
   d. Uncontrolled tachyarrhythmia leading to symptoms or hemodynamic compromise.
4) Subjects requiring cardiac intervention (i.e., percutaneous coronary intervention or coronary artery bypass graft) before completing the study.
5) Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant.
6) Subjects with screening laboratory findings as follows:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times the upper limit of normal;
   b. Total bilirubin ≥2.0 mg/dL (34.2 µmol/L);
   c. Serum creatinine ≥3.0 mg/dL (265.2 µmol/L).
7) Subjects who present with any clinically active, serious, life-threatening disease, medical or psychiatric condition, and/or who have a life expectancy of <6 months, or for whom study participation may compromise their management; and subjects whom the investigator judges to be unsuitable for participation in the study for any reason.
8) Subjects undergoing evaluation for heart transplantation or with a history of heart transplantation.
9) Subjects enrolled in another clinical study within the 30 days before enrollment in this study.
10) Subjects previously enrolled in this study or any Flurpiridaz (^{18}F) Injection study.

Number of Subjects/Centers Planned: Twenty-eight evaluable subjects enrolled at approximately 4 centers in the US.

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Treatment of Subjects:

Investigational Medicinal Product:

Flurpiridaz (^{18}F) Injection is a novel PET-MPI agent labelled with the radioisotope fluorine-18 (^{18}F) and administered as an intravenous (IV) injection. All subjects will be randomized 1:1:1:1 to receive 2 doses of Flurpiridaz (^{18}F) Injection:

Group 1: 2 doses of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method

Group 2: 2 doses of Flurpiridaz (^{18}F) Injection manufactured by the SPE method

Group 3: 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method followed by 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the SPE method

Group 4: 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the SPE method followed by 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method.

All doses will be administered at rest by bolus IV injection in a large peripheral vein. The targeted dose to the body of Flurpiridaz (^{18}F) Injection will be in the range of 1.7 to 2.5 mCi (63 to 93 MBq) for each administration and will not exceed a total of 6 mCi (222 MBq) for an individual subject. The image acquisitions in a list-mode at a single bed position centered on the heart will start 10 seconds before Flurpiridaz (^{18}F) Injection and last 15 minutes. In an effort to avoid bias in image acquisition, the test product manufacturing status will not be specified on the syringe.

Duration of Treatment: Subjects will have 2 rest Flurpiridaz (^{18}F) Injection PET-MPI procedures performed no more than 2 weeks apart. To allow for adequate decay of the first dose, at least 24 hours must separate the 2 injections/imaging procedures. Subjects will have their last follow-up safety contact 24 (+8) hours after the second Flurpiridaz (^{18}F) Injection.

Efficacy and Safety Variables
Primary Efficacy Endpoint:

- Intra-reader correlation and difference between the summed perfusion rest scores (SRS) and summed rest percent (SR%) after 2 MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes

Secondary Efficacy Endpoints:

- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the SPE process
- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the HPLC process
- Intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses
- Difference between the perfusion rest scores for each of the 17 segments and each reader using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes
- Difference in the standard uptake value (SUV) TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection synthesized by 2 different manufacturing processes
- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the HPLC process
- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses

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of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the SPE process • Intra-reader agreement of the image quality score between the 2 sets of PET images acquired after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection **Safety Endpoints:** Subjects will be closely monitored for safety until completion of all study procedures. Safety monitoring will include AEs, medication errors, treatment-emergent AEs (TEAEs), and SAE assessments, vital signs, electrocardiograms (ECGs), hematology, clinical chemistry laboratory tests, and urinalysis.
Statistical Methods and Planned Analysis: **General Considerations** All statistical analyses will be performed with SAS® software (Version 9.3 or higher). Subject data listings and tabular presentations of results will be provided. Presentation of summary statistics for continuous variables will include n, mean, median, and standard deviation (SD), as well as the minimum and maximum values. For categorical variables, the number and percent of each category within a parameter for non-missing data will be calculated. Further details of the criteria and conduct of the statistical analyses will be included in the Statistical Analysis Plan (SAP) for this study. **Analysis Populations** **Intent-to-Treat (ITT) Population:** The ITT population will consist of all subjects randomized to receive ≥1 dose of Flurpiridaz (^{18}F) Injection in the study. **Modified ITT (MITT) Population:** The MITT population will include all ITT subjects who have completed the 2 rest Flurpiridaz (^{18}F) Injection PET-MPI procedures. The MITT population will be the primary analysis set for the primary efficacy endpoint. **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 summarized for the Safety Population. **Efficacy Endpoints**: **Primary Efficacy Variable** **Myocardial Perfusion Imaging Evaluations:** Three qualified readers (independent from the study) will perform independent reads of all MPI images, inclusive of standard 17-segment polar-maps of perfusion defects. Each reader will score the perfusion pattern in each segment (17 segments) using a 5-point scale scoring: - Normal 0, - Minimal, mild impairment of perfusion, ambiguous image 1, - Moderate impairment of perfusion 2, - Significant impairment of perfusion 3, - No perfusion 4. The summed score of the 17 segments SRS, as well as the SR%, will be used as the primary endpoint, and summarized as a continuous variable by reader and using the median of the results of the 3 readers. The primary analysis for the primary endpoint will be based on the mixed-effects model for repeated measures (MMRM). The model will include the median SRS in each dosing period as the dependent variable, with manufacturing process, period and dosing sequence as fixed effects, and subject nested within sequence as the random effect. The estimated mean SRS difference and 90% CI will be provided from the MMRM analysis. Similarity will be established if the 90% CI of the difference is within a margin of (-0.75, 0.75). The margin size is defined as 0.75 to allow the difference of, at most, 43% of the mean SRS score (mean PET SRS score is 1.75 based on empirical data [Berman et al. 2013]).

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The correlation analysis will be stratified by the following 3 groups: 1) subjects who have received 2 doses of product manufactured by 2 different processes; 2) subjects who have received 2 doses of product both manufactured by the SPE process; and 3) subjects who have received 2 doses of product both manufactured by the HPLC process. The intra-reader (within-subject) correlation between the 2 manufacturing processes will be assessed by Pearson's correlation, Kendall's τ and Bland-Altman difference for the summed score stratified by the above 3 groups. The mean of paired difference between the 2 manufacturing processes, t-statistics based 95% confidence interval (CI), the median difference and 95% CI based on Hodges-Lehman method, and p-value obtained by Wilcoxon signed rank test will also be provided for descriptive purpose for the summed score of 17 segments among subjects who have received 2 doses of product manufactured by 2 different processes.

Sensitivity analyses will be performed to assess the impact of missing data on the primary analysis results (i.e., subjects in the ITT population with incomplete PET-MPI scans) using similar MMRM analysis for primary analysis. Details will be provided in the SAP.

Secondary Efficacy Variables

The intra-reader variability of the SRS will be estimated by the SD of the paired difference divided by $\sqrt{2}$, for subjects receiving 2 doses of the product both manufactured by the SPE process and separately for subjects receiving 2 doses of the product both manufactured by the HPLC process.

For the individual scores of 17 segments, the mean of paired difference between the 2 manufacturing processes, t-statistics based 95% CI, the median difference and 95% CI based on Hodges-Lehman method, and p-value obtained by Wilcoxon signed rank test will also be provided for descriptive purpose among subjects who have received 2 doses of product manufactured by 2 different processes.

The PET-MPI reads will be performed by the same set of readers. In each session, PET images will be displayed in a randomized order, non-sequentially, with PET-MPI exams corresponding to individual subjects randomly allotted into reading session batches. The intra-reader agreement of the detection of ischemic defect on PET-MPI will be assessed by percent agreement and Cohen's kappa value stratified by the 3 groups as used in the primary analysis.

Perfusion and gated acquisitions of rest images will be rated for image quality (excellent, good, fair, poor or non-diagnostic). The image quality score will be summarized descriptively for the 3 groups of data sets and the intra-reader agreement will be assessed between the 2 acquisitions stratified by the 3 groups as used in the primary analysis.

Within left ventricle, myocardium, lungs and liver regions of interest (ROIs), a TAC (in SUV units) will be generated for the dynamic scan during the 15-minute acquisition period. The SUV for each ROI will be generated using the following formula:

SUV= Decay Corrected Uptake (kBq/cc) / (Injected Dose (MBq) / Weight (kg))

There will be a descriptive statistical analysis only. The relative difference D in the SUV expressed as D = 100 (SUV1-SUV2)/[0.5 * (SUV1 + SUV2)] between the 2 processes will be summarized descriptively for each region among subjects who have received 2 doses of product. The mean absolute percentage difference (MAPD) will be determined as the mean of the absolute value of D over all subjects.

Safety Endpoints: 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.

Sample Size Estimates

The sample size for this clinical investigation has been determined a priori to be 28 subjects to assess the clinical imaging similarity and safety profiles of Flurpiridaz (^{18}F) Injection synthesized by 2 different manufacturing processes in subjects with suspected or established CAD. To account for 20% dropout, approximately 34 subjects will be randomized in a 1:1:1:1 ratio to each of the 4 treatment sequences.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACLS	Advanced cardiac life support
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
ECG	Electrocardiogram
ED	Effective dose
^{18}F	Fluorine-18
GCP	Good Clinical Practice
HPLC	High performance liquid chromatography
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
ITT	Intent-to-treat
IV	Intravenous
IxRS	Interactive web/voice response system
MAPD	Mean absolute percentage difference
MI	Myocardial infarction
MITT	Modified intent-to-treat
MMRM	Mixed-effects model for repeated measures
MPI	Myocardial perfusion imaging
^{13}N	Nitrogen-13

PET	Positron emission tomography
PTP	Pre-test probability
^{82}Rb	Rubidium-82
ROI	Region of interest
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
SPE	Solid phase extraction
SPECT	Single photon emission computed tomography
SR%	Summed Rest Percent
SRS	Summed Perfusion Rest Score(s)
SUV	Standard uptake value
TAC	Time-activity curve
TEAE	Treatment-emergent adverse event
US	United States

4 BACKGROUND INFORMATION

Coronary artery disease (CAD) is a major cause of death in modern industrialized countries. CAD is the single largest cause of death in the United States (US) [Benjamin et al 2017]. CAD is also the single most common cause of death in Europe: accounting for 1.92 million deaths in Europe each year. Over 1 in 5 women (22%) and over 1 in 5 men (21%) die from the disease according to data from "European Cardiovascular Disease statistics – 2008" [Allender et al. 2008]. Prevention, early diagnosis, and treatment of CAD are essential to reduce mortality. Not only is CAD morbid, but also it strains health care resources. In 2011, hospital care associated with myocardial infarction (MI) cost the US healthcare system $11.5 billion and care associated with coronary heart disease cost the US healthcare system $10.4 billion representing 2 of the 10 most expensive hospital principal discharge diagnoses. These costs are projected to double between 2013 and 2030. Therefore, prevention, early diagnosis, and treatment of CAD are essential to reduce mortality.

Radionuclide myocardial perfusion imaging (MPI) is the most mature cardiovascular imaging technique, with advanced quantitative tools and a vast evidence base in over 100,000 patients [Shaw and Iskandrian 2004]. Stress MPI with single photon emission computed tomography (SPECT-MPI) and positron emission tomography (PET-MPI) are widely used to identify the hemodynamic significance of CAD. These imaging modalities are non-invasive and widely used in patients with suspected CAD and in Europe almost 90% of perfusion studies are performed using SPECT. The prognostic value of rest and stress SPECT-MPI using ^{201}Thallium or ^{99m}Technetium-labelled tracers in individuals with suspected CAD has been well established in millions of patients [Ritchie et al. 1995] [Clark and Beller 2005]. The greatest strength of MPI, however, is its established value for risk assessment [Shaw et al 2012]. The extent and severity of ischemia and scarring on SPECT-MPI and PET-MPI are powerful predictors of future cardiovascular events [Shaw et al 2012]. MPI is cost effective for the management of CAD. In patients with stable angina pectoris, a noninvasive SPECT-MPI–guided management strategy has been shown to be economically superior to an anatomic approach guided by invasive coronary angiography, without significant differences in clinical outcomes [Shaw et al 1999]. More recently, radionuclide imaging of myocardial blood flow has been shown to be an indispensable tool for the evaluation and management of CAD [Murthy et al 2011] [Naya et al 2014]. With these unique capabilities, the clinical benefits of an appropriately performed MPI study are indisputable.

Patient safety is of paramount importance when contemplating any diagnostic and/or therapeutic medical option. One safety consideration is the risk from radiation exposure, which should be weighed in each individual case prior to initiating a study. Consequently, a major factor influencing the choice of MPI protocol is the radiopharmaceutical and its dose. This issue is particularly relevant to younger patients and in women of childbearing potential. However, even in older individuals and in those in whom the risk/benefit ratio is low, radiation exposure should be limited to that dose required to obtain a diagnostic study.

Like SPECT-MPI, PET-MPI can provide diagnostic and prognostic information in patients with CAD. PET has several technical advantages over SPECT that account for improved image quality and therefore improved image interpretation and lower radiation dose to patients, including: higher photon penetration combined with depth-dependent attenuation correction,

high spatial, contrast and temporal resolution, and high efficiency allowing for lower administered radioactivity.

A clear advantage of PET imaging is its use of attenuation correction in all PET systems. Initial dedicated PET imaging systems used rotating line-sources (cesium-137, germanium-68/gallium-68) to generate a transmission attenuation map, whereas currently manufactured PET systems use x-ray CT technology for attenuation correction resulting in an improved image quality and quantification opportunity. Unlike SPECT, cardiac PET allows acquisition of gated ‘‘stress’’ data during peak hyperemic blood flow with calculation of a peak stress left ventricular ejection fraction. This may improve identification of high-risk patients or those with multi-vessel CAD [Dorbala et al 2009]. Furthermore, recent software solutions allow for absolute quantification of regional myocardial blood flow from dynamically acquired rubidium-82 (^{82}Rb) and nitrogen-13 (^{13}N) ammonia cardiac PET studies, [Klein et al. 2010] [El Fakhri et al 2009] and this may be particularly important and useful in evaluating multi-vessel and small vessel coronary disease, responses to medical therapy, and transplant vasculopathy. Finally, due to the low dose from PET tracers, PET-MPI offers a significantly lower effective radiation dose than SPECT-MPI.

Despite the obvious clinical value of current generation SPECT-MPI and PET-MPI agents in patients with known or suspected CAD, there is a well-recognized need for the development of a new perfusion imaging agent with more ideal properties. Both ^{82}Rb chloride and ^{13}N ammonia are approved by the US Food and Drug Administration for use in PET-MPI. ^{82}Rb offers the advantage of being generator-produced on site, with a strong dependency upon strontium supply, as opposed to ^{13}N ammonia, whose potential use is limited by the requirement for an on-site cyclotron.

The ‘ideal’ MPI agent should have a very high first-pass extraction fraction and would track regional myocardial blood flow over a wider range, permitting accurate estimation of absolute blood flow particularly under conditions of either physical or pharmacologic stress. The agent should exhibit excellent target-to-nontarget uptake ratios, with high uptake in the myocardium and low uptake or rapid clearance from adjacent organs [Glover and Gropler 2007]. The opportunity exists for developing a new PET imaging agent using fluorine-18 (^{18}F) that exhibits high extraction fraction. Such an agent as [^{18}F]flurpiridaz would take advantage of the high resolution, quantitative power, resistance to attenuation artefacts, and logistical simplicity of unit dosing of ^{18}F PET, and would be expected to exhibit improved sensitivity overall and specifically in detecting multi-vessel disease. It also has the potential to reduce diagnostic uncertainty and reduce radiation dose compared with studies using SPECT agents.

Clinical studies conducted with Flurpiridaz (^{18}F) Injection include safety, dosimetry, and radiokinetic studies in healthy subjects, as well as 1 Phase 2 study and 1 Phase 3 study in subjects with known or suspected CAD. In the clinical studies completed to date, a total of 996 subjects have received Flurpiridaz (^{18}F) Injection. An additional 7 subjects have received [^{3}H]flurpiridaz. The results of these studies are detailed in the Flurpiridaz (^{18}F) Injection Investigator’s Brochure (IB). Overall, Flurpiridaz (^{18}F) Injection was well-tolerated, and no clinically significant safety concerns were noted.

Two consecutive Phase 1 studies administering Flurpiridaz (^{18}F) Injection to healthy subjects were conducted to assess safety, dosimetry, and radiokinetics. Safety assessments in both studies included adverse events (AEs), serious AEs (SAEs), vital signs, electrocardiograms (ECGs), electroencephalograms, laboratory values, and physical and neurological examinations.

The primary dosimetry endpoints in single-center, single-dose Study BMS747158-101 conducted in 12 healthy subjects were the estimated radiation dose delivered to the standard target organs, the salivary glands, and the total body and the effective dose (ED) - all for subjects at rest. This study demonstrated that good cardiac uptake can be achieved in humans. The organ that showed the largest uptake was the liver (with 19.1% of the injected activity), followed by the kidneys and the brain (with approximately 9.4% and 8.3%, respectively, of the injected activity). Therefore, the maximum injected Flurpiridaz (^{18}F) Injection dose that may be administered at rest without exceeding 5 rem to the critical organ is 21 mCi (760 MBq), and the mean ED for Flurpiridaz (^{18}F) Injection is 0.071 rem/mCi (0.019 mSv/MBq). The maximum injected dose that may be administered without exceeding l rem ED was estimated to be 14 mCi (520 MBq).

Study BMS747158-102 was a Phase 1, nonrandomized, 2-dose, open-label study conducted at 2 medical centers in the US to assess radiation exposure from Flurpiridaz (^{18}F) Injection to patients following stress. A total of 12 healthy subjects were enrolled in 2 cohorts. Six subjects (Cohort l) underwent 2-day rest and exercise treadmill stress PET imaging using a Bruce protocol, and 6 subjects (Cohort 2) underwent 2-day rest and pharmacologic stress PET imaging using adenosine as the stress agent. Doses of Flurpiridaz (^{18}F) Injection were administered at rest on the first day (Day l) and during stress on the second day (Day 2).

From the exposure data, the critical organ for Flurpiridaz (^{18}F) Injection following exercise stress was determined to be the heart wall, with a mean estimated dose of 0.15 rem/mCi (0.039 mSv/MBq). The critical organ for Flurpiridaz (^{18}F) Injection following pharmacologic stress was also determined to be the heart wall, with a mean estimated dose of 0.33 rem/mCi (0.090 mSv/MBq). Consequently, the maximum injected dose of the compound that may be administered following exercise stress without exceeding 5 rem to the critical organ was determined to be 35 mCi (1276 MBq). The maximum injected dose of the compound that may be administered following pharmacologic stress without exceeding 5 rem to the critical organ was determined to be 15 mCi (554 MBq).

The mean ED for Flurpiridaz (^{18}F) Injection following exercise stress was 0.054 rem/mCi (0.015 mSv/MBq). The mean ED for Flurpiridaz (^{18}F) Injection following pharmacologic stress was 0.069 rem/mCi (0.019 mSv/MBq). Consequently, the maximum injected dose that may be administered during exercise stress without exceeding 1 rem ED was determined to be 19 mCi (685 MBq). The maximum injected dose that may be administered during pharmacologic stress without exceeding 1 rem ED was determined to be 15 mCi (539 MBq).

Flurpiridaz (^{18}F) Injection was rapidly cleared from the blood within the first few minutes. Afterward, there was a modest rise in blood radioactivity, which remained at low levels (3% to 5% of the injected dose per estimated whole-body blood volume over the next few hours. Subjects undergoing exercise stress exhibited significantly lower ^{18}F blood concentrations after

the first few minutes when compared to subjects undergoing pharmacologic stress. Overall, the kinetics of ^{18}F radioactivity in blood after Flurpiridaz (^{18}F) Injection were found to provide an acceptably low background activity for PET cardiac imaging.

A third Phase 1 single-center study (BMS747158-103) was conducted in 7 healthy adult male subjects who were administered a targeted intravenous (IV) dose of 100 ± 20 μCi (targeted at 2.98 μg) of [^{3}H]BMS747158, a tritiated preparation of BMS-747158-01 (the ^{19}F analogue of the active component in Flurpiridaz [^{18}F] Injection). The assessed metabolic disposition parameters comprised blood and plasma radioactivity, plasma pharmacokinetics of parent compound, mass balance (urinary and fecal radioactivity excretion), and metabolite assessments in the various matrices. The mean dose was 89.45 ± 0.68 μCi, corresponding to 2.88 ± 0.02 μg of BMS747158 drug substance. BMS747158 was extensively metabolized, with no unchanged drug detected in urine or feces. The major identified radiolabeled metabolite (M1) was a benzoic acid derivative, which appears to be formed by O-dealkylation of the fluroethoxy side chain. The product was considered safe and well-tolerated.

The Phase 2 study, BMS747158-201, consisting of 2 cohorts, was conducted to develop and subsequently to evaluate the diagnostic efficacy of 1-day rest/stress PET imaging protocols in subjects with known or suspected CAD. An initial cohort was used to identify the appropriate dose and timing of Flurpiridaz (^{18}F) Injection dose administration for a 1-day rest/stress protocol that identified the minimum acceptable rest dose and the minimum stress dose that ensured that residual activity from the rest dose did not contaminate the stress image. An optimized 1-day rest/stress protocol was subsequently adopted for the second cohort to assess efficacy in subjects with a broad spectrum of pre-test likelihood of CAD.

In the first cohort, 33 subjects presenting with reversible perfusion defects of varying severity as identified by prior rest/stress SPECT-MPI studies were enrolled and 32 completed the study, with 1 subject withdrawing voluntarily. All subjects underwent a 1-day rest/stress, Flurpiridaz (^{18}F) Injection PET-MPI protocol (Day 1) with a dosing interval of either 60 minutes or 120 minutes between rest and stress injections of Flurpiridaz (^{18}F) Injection, followed by a second stress Flurpiridaz (^{18}F) Injection PET-MPI study within 16 to 48 hours of the Day 1 rest dose. Subjects were enrolled in Arm A (pharmacologic stress, with adenosine as the pharmacologic stressor) or Arm B (exercise stress) on the basis of the stressor used in their qualifying SPECT study. Acquired PET-MPI data were modelled to assess adequate rest/stress Flurpiridaz (^{18}F) Injection PET-MPI doses and dosing intervals between rest and stress Flurpiridaz (^{18}F) Injection dose administrations as well as PET imaging parameters for 1-day rest/stress protocols. Dose and acquisition duration for reading perfusion imaging parameters were identified for 1-day rest/stress PET-MPI (4.66 ± 2.119 mCi of BMS747158).

In the second cohort, 143 subjects presenting with a broad spectrum of pre-test likelihood of CAD were enrolled to evaluate the sensitivity, specificity, and accuracy of Flurpiridaz (^{18}F) Injection in a 1-day rest/stress protocol; coronary angiography or 3-month follow-up for cardiac events was used as the truth standard. Of the 143 subjects enrolled, 125 were evaluable for efficacy. PET-MPI sensitivity was 76.9% for all readers, and specificity ranged from 74.0% to 87.7%. SPECT-MPI sensitivity ranged from 59.6% to 71.2%, and specificity ranged from 76.7% to 89.0%.

The Phase 3 Study BMS747158-301 was an open-label, international multicenter study for the assessment of CAD using Flurpiridaz (^{18}F) Injection PET-MPI compared with SPECT-MPI in subjects with suspected or known CAD who were referred for invasive coronary angiography. Subjects underwent a 1-day rest/stress protocol with coronary angiography as the truth standard. The primary objective was to assess the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET-MPI compared to SPECT-MPI in the detection of significant CAD, as defined by cardiac catheterization or a documented history of MI.

A total of 795 received ≥1 dose of Flurpiridaz (^{18}F) Injection (the safety population), and 764 subjects completed the trial; 31 subjects (3.9%) did not complete the study. The majority of cases of discontinuation were due to inability to perform all study mandated procedures (single photon emission computed tomography [SPECT] or coronary angiography). Only 4 (0.5%) discontinuations were due to treatment emergent AEs (TEAEs). Overall, TEAEs were reported in 555 subjects (69.8%), the majority being associated with either exercise or pharmacological stress testing or the underlying disease. Forty-four subjects (5.5%) experienced TEAEs deemed to be related to Flurpiridaz (^{18}F) Injection. Of these, 41 (5.2%) were sub-categorized as "possibly related" and 3 (0.4%) as "related". The most common (≥0.5%) related TEAEs reported were; headache (0.9%), angina pectoris (0.6%), dysgeusia (0.6%), diarrhea (0.5%), dyspnea (0.5%), flushing (0.5%), and nausea (0.5%). The modified intent-to-treat (MITT) population comprised the 755 subjects who had rest and stress SPECT-MPI and Flurpiridaz (^{18}F) Injection PET-MPI procedures resulting in evaluable data and had evaluable truth-standard data. In the safety population, the mean (standard deviation [SD]) decay-corrected total dose was 9.35 (1.28) mCi, with a range of 6.69 to 12.27 mCi. The mean (SD) decay-corrected dose for subjects who underwent pharmacologic stress was 8.59 (0.46) mCi, with a range of 6.69 to 12.01 mCi. The mean (SD) decay-corrected dose of subjects who underwent exercise stress was 11.20 (0.54) mCi, with a range of 8.28 to 12.27 mCi.

In a majority-rule assessment of the overall dataset of subject qualitative diagnosis, Flurpiridaz (^{18}F) Injection PET-MPI had a sensitivity of 71.9%. Sensitivity results for readers 1, 2, and 3 were 73.3%, 62.4%, and 76.7%, respectively. Statistically significant superiority in sensitivity was demonstrated for Flurpiridaz (^{18}F) Injection PET-MPI over SPECT-MPI across readers ($P \leq 0.001$). However, the endpoint that was intended to demonstrate the noninferiority of Flurpiridaz (^{18}F) Injection PET-MPI to SPECT-MPI in specificity was not met. The overall dataset of subject qualitative diagnosis (when majority rule was used) provided a Flurpiridaz (^{18}F) Injection PET-MPI specificity of 76.2%, compared to SPECT specificity of 86.8%.

Doses of Flurpiridaz (^{18}F) Injection used in the nonclinical and clinical studies performed by Lantheus Medical Imaging were manufactured using high performance liquid chromatography (HPLC) purification. This process is also being used to manufacture doses of Flurpiridaz (^{18}F) Injection for the current GE Healthcare clinical study (GE-265-303). The HPLC method is not ideal for future routine manufacturing of [^{18}F]fluorine tracers. GE Healthcare has, therefore, developed the manufacturing process for Flurpiridaz (^{18}F) Injection on the FASTlab synthesis module, a current and supported synthesis platform. This process enables the production of Flurpiridaz (^{18}F) Injection batches with approximately 4 times the product radioactivity compared to the HPLC process. This will significantly improve the availability of Flurpiridaz (^{18}F) Injection. In addition, the solid phase extraction (SPE) manufacturing process on

FASTlab is expected to enhance control, consistency and production reliability because it eliminates the manual cut required for HPLC purification. Also, it uses single-use commercially available cartridges, reagents and other disposable materials supplied in a pre-assembled cassette that is assembled, controlled and released by GE Healthcare under current Good Manufacturing Practice. The drug product from the SPE manufacturing process will have improved compatibility with dispensing equipment at manufacturing sites and pharmacy syringes. The latter is important for hospitals to use their standard radiation protection equipment to ensure low radiation dose for hospital staff. It is also important to avoid errors in dosing with use of non-compatible syringes.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary and secondary objectives of the study are as follows:

Primary:

- Assess difference and variability between 2 sets of visually-based global rest scores resulting from 2 at-rest MPI sessions using Flurpiridaz (^{18}F) Injection doses synthesized by the same or 2 different manufacturing processes

Secondary:

- Assess the intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses
- Assess the detection of myocardial segmental defect similarity from 2 sets of images acquired from doses synthesized by the same or 2 different manufacturing processes of Flurpiridaz (^{18}F) Injection PET for MPI at rest
- Assess the equivalence of 2 sets of [^{18}F]flurpiridaz time-activity curves (TACs) (blood, myocardium, lungs, liver) resulting from MPI using Flurpiridaz (^{18}F) Injection doses synthesized by the same or 2 different manufacturing processes
- Assess the safety of Flurpiridaz (^{18}F) Injection PET doses synthesized by 2 different manufacturing processes

5.2 Study Endpoints

5.2.1 Primary Efficacy Endpoint

- Intra-reader correlation and difference between the summed perfusion rest scores (SRS) and summed rest percent (SR%) after 2 MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes

5.2.2 Secondary Efficacy Endpoints

- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the SPE process
- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the HPLC process

- Intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses

- Difference between the perfusion rest scores for each of the 17 segments and each reader using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes

- Difference in the standard uptake value (SUV) TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection synthesized by 2 different manufacturing processes

- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the HPLC process

- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the SPE process

- Intra-reader agreement of the image quality score between the 2 sets of PET images acquired after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection

5.3 Safety Endpoints

- Subjects will be closely monitored for safety until completion of all study procedures. Safety monitoring will include AEs, medication errors, TEAEs, and SAE assessments, vital signs, ECGs, hematology, clinical chemistry laboratory tests, and urinalysis.

6 STUDY DESIGN

6.1 Overall Study Design and Plan

This is a Phase 2 prospective, randomized, crossover study of Flurpiridaz (^{18}F) Injection for PET-MPI in subjects referred for evaluation of known CAD or for suspected CAD with intermediate to high pre-test probability (PTP).

This study will be conducted at approximately 4 centers in the US. Twenty-eight evaluable subjects will be enrolled. Assuming a 20% drop-out rate, approximately 34 subjects will need to be enrolled initially. At least 30% of subjects enrolled should have a documented history of MI, defined by history of a fixed defect.

Each subject will attend a Screening Visit at least 2 days and up to 14 days prior to the first Flurpiridaz (^{18}F) Injection PET-MPI (PET-MPI Visit 1). 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.

Subjects will undergo 2 Flurpiridaz (^{18}F) Injection PET-MPI procedures at rest performed no more than 2 weeks apart. To allow for adequate decay of the first dose, at least 24 hours must separate the 2 injections/imaging procedures. The subjects will be randomized 1:1:1:1 to 4 possible sequences of receiving 2 doses of Flurpiridaz (^{18}F) Injection: 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by the same HPLC manufacturing process, 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by the same SPE manufacturing process, and 14 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by 2 different manufacturing processes (7 subjects will receive 1 dose manufactured by HPLC followed by 1 dose manufactured by SPE and 7 subjects will receive 1 dose manufactured by SPE followed by 1 dose manufactured by HPLC). All doses will be administered at rest by bolus IV injection in a large peripheral vein.

The targeted dose to the body of Flurpiridaz (^{18}F) Injection will be in the range of 1.7 to 2.5 mCi (63 to 93 MBq) for each administration and will not exceed a total of 6 mCi (222 MBq) for an individual subject. The image acquisitions in a list-mode at a single bed position centered on the heart will start 10 seconds before Flurpiridaz (^{18}F) Injection and last 15 minutes. In an effort to avoid bias in image acquisition, the test product manufacturing status will not be specified on the syringe.

All subjects will be followed up by telephone for AEs and SAEs at 24 (+8) hours following each Flurpiridaz (^{18}F) Injection administration.

Therefore, study subjects will participate in the study for up to 30 days.

A subject will be considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Study Schedule of Events (Table 1).

An overview of study procedures is presented in Figure 1.

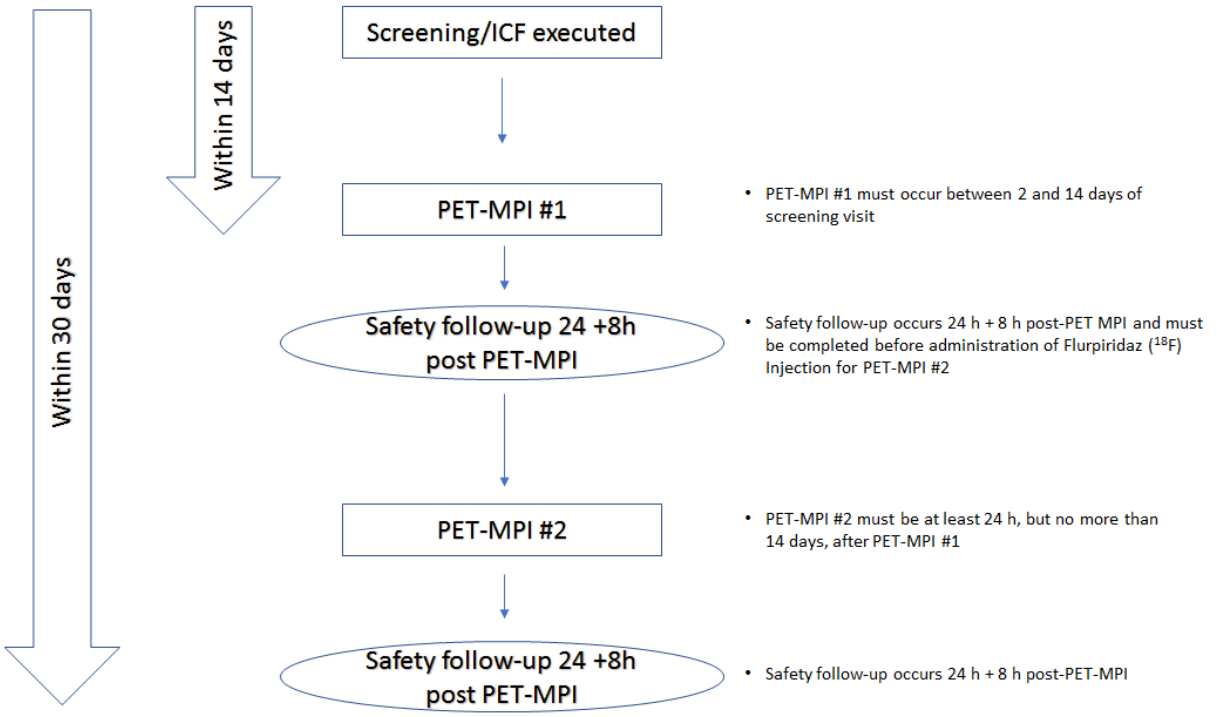

Figure 1 Study Diagram

6.2 Scientific Rationale for Study Design

GE Healthcare is currently conducting a clinical study titled "*A Phase 3, Open-Label, Multicenter 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 Phase 3 study (GE-265-303) is being conducted in North America and Europe to assess the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET-MPI in the detection of significant CAD, as defined by the standard of truth of invasive coronary angiography, in patients with suspected CAD. The first subject was enrolled on [redacted] The study is expected to be completed by [redacted].

Doses of Flurpiridaz (^{18}F) Injection produced for the GE-265-303 study are being manufactured with HPLC purification on synthesis platforms that are approaching their end of life. This is not sustainable for future commercial manufacturing of [^{18}F]fluorine tracers. GE Healthcare has, therefore, developed the manufacturing process for Flurpiridaz (^{18}F) Injection on the FASTlab synthesis module which is a current and supported synthesis platform.

The Chemistry, Manufacturing and Controls development of the SPE process has resulted in a product which is not significantly different to that produced with the HPLC process used so far in clinical development. Nonclinical studies have shown equivalent biodistribution in rats for the product manufactured by the 2 different processes.

GE Healthcare now plans to conduct a dedicated comparative study for a systematic and qualitative evaluation of any imaging differences. Clinical data will be collected to substantiate the clinical comparability of the products obtained with the 2 manufacturing processes in addition to a test-retest for each of the manufacturing processes to assess their respective reliability.

In reference to the guidelines on the investigation of bioequivalence, this study will be a prospective, randomized, crossover study of Flurpiridaz (^{18}F) Injection for PET-MPI in patients referred for evaluation of suspected or established CAD. This corresponds to the proposed indication of Flurpiridaz (^{18}F) Injection as it has been explored during the clinical development of Flurpiridaz (^{18}F) Injection. The sample size of 28 evaluable clinical subjects in a crossover study will be able to identify any important qualitative and quantitative signals of imaging discordance between Flurpiridaz (^{18}F) Injection manufactured by the SPE and HPLC processes.

Safety surveillance in this study is justifiable and adequate in view of the following:

- The design of the study permits a comparison of safety variables at baseline and post-investigational medicinal product (IMP) administration in the same subject.
- Consideration of a 24-hour safety monitoring follow-up after each administration of Flurpiridaz (^{18}F) Injection permits the evaluation of late appearing adverse effects that may emerge or progress after the administration of IMP.
- The measures used to assess safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of Flurpiridaz (^{18}F) Injection.

6.3 Study Timeframe

The study enrollment is expected to start in [redacted] and to be completed by [redacted].

Individual subjects will participate in the study for up to 30 days.

6.4 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the Study Schedule of Events (Table 1) for the last subject in the study globally.

6.5 Risks and Benefits to Subjects

A total of 996 subjects have received Flurpiridaz (^{18}F) Injection in Phase 1 through Phase 3 clinical studies completed to date: BMS-747158-101, BMS-747158-102, BMS-747158-201, and BMS-747158-301. An additional 7 subjects have received [^{3}H]flurpiridaz in a Phase 1 study: BMS747158-103.

In 3 Phase 1 clinical studies of healthy volunteers, there were no AEs related to Flurpiridaz (^{18}F) Injection or [^{3}H]flurpiridaz. In the Phase 2 study (BMS-747158-201), 2 separate groups of subjects (Cohort 1 [n=33] and Cohort 2 [n=143]) with known or suspected CAD were studied while having a stress test. Five subjects (2 in Cohort 1 and 3 in Cohort 2) reported a total of 10 AEs; none of these AEs were reported by another study subject, and all were judged by the investigator to be possibly or probably related to Flurpiridaz (^{18}F) Injection dose administration. The AEs in Cohort 1 included pain in extremity (1; 3%) and headache (1; 3%). The AEs in Cohort 2 included chest pressure (1; 0.6%), bradycardia (1; 0.6%), diarrhea (1; 0.6%), nausea (1; 0.6%), ECG ST-segment depression (1; 0.6%), metallic taste in mouth (1, 0.6%); cough (1; 0.6%), and high blood pressure (1; 0.6%). None of these events were considered serious, and all resolved in a short period of time without any complications.

In the most recent completed Phase 3 study, BMS747158-301, a total of 795 subjects received ≥1 dose of Flurpiridaz (^{18}F) Injection. Of these, 31 subjects (3.9%) did not complete the study. The majority of cases of discontinuation were due to inability to perform all study-mandated procedures (SPECT or coronary angiography). Only 4 (0.5%) discontinuations were due to TEAEs. In Study BMS747158-301, TEAEs were reported in 555 (69.8%) subjects; the majority of TEAEs were associated with either exercise or pharmacological stress testing or the underlying disease. Forty-four (5.5%) subjects experienced TEAEs deemed to be related to Flurpiridaz (^{18}F) Injection. Of these, 41 (5.2%) were subcategorized as "possibly related" and 3 (0.4%) as "related." The most common (≥0.5%) related TEAEs reported were headache (0.9%), angina pectoris (0.6%), dysgeusia (0.6%), diarrhea (0.5%), dyspnea (0.5%), flushing (0.5%), and nausea (0.5%).

In the ongoing GE-265-303 study, no safety signals have led the Data and Safety Monitoring Board to recommend to stop the study.

Therefore, we do not expect a significant risk for the subjects enrolled in this comparative study. The expected diagnostic potential of Flurpiridaz (^{18}F) Injection should offset this limited radiation risk by offering the opportunity for improving the detection of ischemic lesions in patients who are typically suffering from diagnostic limitations with SPECT techniques. Therefore, we consider the benefit-risk ratio as positive for conducting this trial.

Further information about the known and expected benefits and risks and reasonably expected AEs of Flurpiridaz (^{18}F) Injection may be found in the IB.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrollment

Subjects will be considered for enrollment if they are undergoing assessment for suspected or known CAD.

The population will include subjects with known CAD or suspected CAD with intermediate to high PTP, reflecting the spectrum of patients who would be expected to undergo nuclear imaging tests. The performance of other functional stress tests (such as stress echocardiography, exercise stress electrocardiography, nuclear stress tests including ^{82}Rb or ^{13}N-ammonia MPI imaging or SPECT-MPI) or coronary CT angiography prior to enrollment is permitted. At least 30% of subjects enrolled should have a documented history of MI, defined by history of a fixed defect.

7.2 Inclusion Criteria

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

(1) The subject is a man or woman ≥18 years of age.

(2) The subject is undergoing evaluation of known CAD or for suspected CAD with an intermediate to high PTP.

(3) The subject has read, signed, and dated an informed consent form (ICF) prior to any study procedures being performed, and is willing to allow the study investigator to make the subject's medical records available to GE Healthcare.

(4) The subject is male or is a nonpregnant, nonlactating female who is either surgically sterile (has a documented bilateral tubal ligation and oophorectomy and/or documented hysterectomy [bilateral tubal ligation alone is insufficient]) or is post-menopausal (cessation of menses for more than 1 year); enrollment in the study without a pregnancy test at Screening is allowed for these categories of female subjects. For women of childbearing potential, the results of either a urine or serum human chorionic gonadotropin pregnancy test (with the result known on the day of each radiopharmaceutical administration) must be negative. These subjects must be practicing appropriate birth control from the time of the screening to 30 days after the second radiopharmaceutical administration. Such methods include: hormonal contraception including oral contraceptives; intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence; adequate barrier method with spermicide (e.g., diaphragm, condom).

(5) The subject is able and willing to comply with all study procedures as described in the protocol.

7.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

(1) Subjects who are pregnant, may possibly be pregnant, or wish (including their partners) to become pregnant during the study period, or are lactating.

(2) Subjects who are unable to undergo all of the imaging procedures.

(3) Subjects with unstable cardiovascular condition, including but not limited to:

   a. Transient ischemic attack/stroke within 3 months of enrollment;

   b. Significant congenital heart disease;

   c. Uncontrolled hypertension;

   d. Uncontrolled tachyarrhythmia leading to symptoms or hemodynamic compromise.

(4) Subjects requiring cardiac intervention (i.e., percutaneous coronary intervention or coronary artery bypass graft) before completing the study.

(5) Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant.

(6) Subjects with screening laboratory findings as follows:

   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3 times the upper limit of normal;

   b. Total bilirubin ≥2.0 mg/dL (34.2 μmol/L);

   c. Serum creatinine ≥3.0 mg/dL (265.2 μmol/L).

(7) Subjects who present with any clinically active, serious, life-threatening disease, medical or psychiatric condition, and/or who have a life expectancy of <6 months, or for whom study participation may compromise their management; and subjects whom the investigator judges to be unsuitable for participation in the study for any reason.

(8) Subjects undergoing evaluation for heart transplantation or with a history of heart transplantation.

(9) Subjects enrolled in another clinical study within the 30 days before enrollment in this study.

(10) Subjects previously enrolled in this study or any Flurpiridaz (^{18}F) Injection study.

7.4 Screen Failures

Screen failures are subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7.5 Withdrawal and Termination Criteria

7.5.1 Subject Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the Sponsor will review the safety data for trends and signals that would indicate the need for withdrawal of a subject.

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of co-operation.

Should a subject decide to withdraw after administration of Flurpiridaz (^{18}F) Injection, or should the investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study. Safety data will be considered for any subject who has received ≥1 Flurpiridaz (^{18}F) Injection, however the imaging data will not be included in the blinded image evaluation if both Flurpiridaz (^{18}F) Injection PET-MPI scans are not completed.

The reason for withdrawal must be noted in the case report form (CRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the CRF. Depending on the time of their withdrawal, these subjects will be followed up by telephone for AEs and SAEs for 24 (+8) hours following each Flurpiridaz (^{18}F) Injection dose administration.

Withdrawn subjects will not be replaced.

7.5.2 Subject Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5.3 Study or Site Termination

The Sponsor reserves the right to terminate the study at any time.

The Sponsor also reserves the right to discontinue participation of a study center at which no subjects have been enrolled within 1 month of initiation or in case of safety concerns or major protocol violations.

8 TREATMENT OF SUBJECTS

8.1 Investigational Medicinal Product

8.1.1 Flurpiridaz (^{18}F) Injection

Flurpiridaz (^{18}F) Injection is a novel PET-MPI agent labelled with the radioisotope ^{18}F. Flurpiridaz (^{18}F) Injection is delivered as a sterile solution to be administered as an IV injection.

This agent is a structural analogue of pyridaben, a known mitochondrial complex 1 (MC-1) inhibitor. However, flurpiridaz does not inhibit cardiac mitochondrial function. Mitochondria constitute 20% to 30% of the myocardial intracellular volume. Consequently, molecules that target mitochondrial proteins may be enriched and retained selectively in the myocardium. The isotopic half-life of ^{18}F is 110 minutes.

All subjects will receive 2 IV boluses of Flurpiridaz (^{18}F) Injection obtained either by the same manufacturing process (both HPLC or both SPE) or by 2 different manufacturing processes (1 HPLC and 1 SPE), in a large peripheral vein at rest. The subjects will be randomized 1:1:1:1 to 4 possible sequences of receiving 2 Flurpiridaz (^{18}F) Injection. Seven subjects will receive 2 doses manufactured with the same HPLC process, 7 subjects will receive 2 doses manufactured with the same SPE process, and 2 groups of 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by different manufacturing processes (1 dose by HPLC followed by 1 dose by SPE or 1 dose by SPE followed by 1 dose by HPLC). The targeted dose to the body of Flurpiridaz (^{18}F) Injection will be in the range of 1.7 to 2.5 mCi (63 to 93 MBq) for each administration and will not exceed a total of 6 mCi (222 MBq) for an individual subject. Sites will record dose measurement units (mCi or MBq) in keeping with their standard institutional practices.

8.1.2 IMP Accountability

Each investigator is responsible for ensuring that deliveries of IMP, and other study materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol.

All IMP syringes (used, unused, or empty) must be destroyed on site after their scheduled use in accordance with site policies. See IMP handling procedures or similar document (e.g., Pharmacy Manual) for further details on receipt, recording, handling, and accountability procedures related to IMP. A list of IMP, other medicinal products, and other materials that were destroyed, must be prepared and signed by the principal investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

The site will be provided with the IB for the IMP.

8.1.3 Registration of Investigational Medicinal Product Complaints

In the event of an IMP complaint (e.g., breakage, leakage, particulate matter, discoloration, labelling mistakes), the investigator or recipient of the IMP is requested to report the problem on the IMP shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form) or through interactive web/voice response system (IxRS) (if possible). This should be indicated on the shipping documentation. The Responsible Person will register the complaint and determine if the complaint is minor or significant according to Sponsor procedures. All complaints will be followed-up and the appropriate action will be implemented according to Sponsor procedures.

8.2 Method of Numbering Subjects

A unique allocation number will be assigned to each subject at a center in successive order of entering the study after signing the ICF. No subject may enter the study more than once nor may a subject be re-screened for the study after having failed to meet the inclusion/exclusion criteria. If the investigator has any question about any subject's eligibility to participate in the study, the investigator or study personnel should contact the Sponsor or Sponsor representative to discuss the subject's eligibility.

The allocation number will be unique for each subject in the study and will consist of 7 numbers in total: 3 numbers for the center identification and 4 numbers for the subject identification at the center (e.g., 002-0001: first subject in center No. 2). Once a subject number has been assigned, it cannot be reassigned, even if the subject is deemed ineligible or withdraws consent. To preserve the scientific integrity of the study, numbers must be assigned in consecutive numerical order at each center.

Subjects will be randomized 1:1:1:1 to 4 possible sequences of receiving 2 Flurpiridaz (^{18}F) Injection. Seven subjects will receive 2 doses of the product manufactured with the same HPLC process, 7 subjects will receive 2 doses of the product manufactured with the same SPE process, and 2 groups of 7 subjects will receive 2 Flurpiridaz (^{18}F) Injection doses synthesized by different manufacturing processes (1 dose by HPLC followed by 1 dose by SPE or 1 dose by SPE followed by 1 dose by HPLC). Therefore, there will be assignment to specific treatment groups.

A subject who has given informed consent but does not fulfil the criteria to participate in the study will receive a subject number and will be logged as a screening failure within the IxRS. The subject will also be documented on the Screening Log by using the subject's initials (where permitted) and subject number.

8.3 Selection of Doses and Timing

All screening assessments will occur at least 2 days prior to the first Flurpiridaz (^{18}F) Injection PET-MPI visit (PET-MPI Visit 1). The Flurpiridaz (^{18}F) Injection PET-MPI procedure must occur within 14 days after screening. Subjects will have 2 rest Flurpiridaz (^{18}F) Injection PET-MPI performed no more than 2 weeks apart. To allow for adequate decay of the first dose, at

least 24 hours must separate the 2 injections/imaging procedures. Subjects must have completed the 24-hour safety follow-up after the PET-MPI Visit 1 prior to receiving the second Flurpiridaz (^{18}F) Injection. Subjects will have their last follow-up safety contact 24 (+8) hours after the second Flurpiridaz (^{18}F) Injection.

The dose of IMP to be administered has been selected on the basis of the previous clinical studies and is similar to the dose used in the ongoing GE-265-303 Phase 3 study.

8.4 Randomization and Blinding

Randomization

This is a randomized crossover study. Subjects will be randomized 1:1:1:1 into 4 treatment sequence groups:

Group 1: 2 doses of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method

Group 2: 2 doses of Flurpiridaz (^{18}F) Injection manufactured by the SPE method

Group 3: 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method followed by 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the SPE method

Group 4: 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the SPE method followed by 1 dose of Flurpiridaz (^{18}F) Injection manufactured by the HPLC method

Once subjects have completed the screening process they will be enrolled in the study and will be randomly assigned to one of the above 4 treatment sequences in accordance with a prespecified randomization list. Allocation to the enrollment groups, including randomization, will be performed centrally (via the IxRS) by the contract research organization (CRO).

No subject will be administered Flurpiridaz (^{18}F) Injection before it has been determined that he/she meets the study's inclusion criteria, does not meet the exclusion criteria and signed and dated informed consent has been obtained.

Blinding

This is a Phase 2, randomized study.

Subjects will be blinded to the manufacturing process used to obtain Flurpiridaz (^{18}F) Injection. In an effort to avoid bias in image acquisition, the test product manufacturing status will not be specified on the syringe.

The independent image readers will be blinded to subjects' medical history and the manufacturing process used to synthesize Flurpiridaz (^{18}F) Injection.

8.5 Prior and Concomitant Medications or Procedures

Any medications currently taken by the subject at the time of informed consent and through to their last follow-up will be recorded in the CRF, along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/CRO will encode all therapy and medication per a current well-recognized dictionary of medical codes.

8.6 Contraception and Pregnancy Avoidance Procedure

Women of child-bearing potential are "fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy" [CTFG Guidance 2014]. Post-menopausal means having had no menses for at least 12 months without an alternative medical cause.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy or vasectomized with confirmation of success.

Women of child-bearing potential who are sexually active with a non-sterile male partner and males who are sexually active with a female partner of childbearing potential must use an acceptable method of contraception (as defined below) from screening until 30 days after administration of the IMP.

Acceptable methods of contraception considered as highly effective are those with no higher than a 1% failure rate. Such methods include [CTFG Guidance 2014]:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, provided there is no concern about interaction with the IMP:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, provided there is no concern about interaction with the IMP:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system, provided there is no concern about interaction with the IMP
- Bilateral tubal occlusion

- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the women of child-bearing potential and that the vasectomized partner has received medical confirmation of the surgical success)
- Sexual abstinence (only if the subject refrains from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject).

Acceptable, but not highly effective, birth control methods that result in a failure rate of more than 1% per year include [CTFG Guidance 2014]:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of child-bearing potential must have a negative result for a urine or serum human chorionic gonadotropin pregnancy test at the time points detailed in Table 1.

8.7 Treatment Compliance

Subjects will receive the IMP under direct supervision of study personnel. Each radioactivity dose injected will be checked and the vial code and volume per administration will be recorded in each subject's CRF. Doses administered outside of specific dose requirements or defined range must be reported as protocol deviations (see Section 9.2 and 13.3).

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarized in the Study Schedule of Events (Table 1).

Table 1 Study Schedule of Events

Variables	Screening	PET-MPI Visit 1 (2 to 14 days after Screening)	Safety Follow-up (24 +8 hours after PET-MPI Visit 1)*	PET-MPI Visit 2 (≥24 hours and <2 weeks after PET-MPI Visit 1)	Safety Follow-up (24 + 8 hours after PET-MPI Visit 2)
Informed consent	X				
Entry criteria	X				
Pregnancy test [a]	X	X		X	
Demographic information	X				
Medical/surgical history	X				
Randomization	X				
Blood sampling	X	X[b]		X[b]	
Urine sampling	X	X[b]		X[b]	
Prior/concomitant medications	X	X	X	X	X
Vital signs and pulse oximetry	X	X[c]		X[c]	
12-lead ECG recording	X[d]	X[d]		X[d]	
Physical examination [e]		X[e]		X[e]	
Clinical screen for new/worsening symptoms		X[f]		X[f]	
Injection site monitoring		X[g]		X[g]	
IMP administration		X		X	
PET-MPI Image acquisition		X		X	
Adverse events (including AEs and SAEs)[h]	X	X	X	X	X

AE = adverse event; ECG = electrocardiogram; IMP = investigational medicinal product; MPI = myocardial perfusion imaging; PET = positron emission tomography; SAE = serious adverse event

* Safety follow-up after PET-MPI Visit 1 must be complete before administration of Flurpiridaz (^{18}F) Injection for PET-MPI Visit 2.

a) For women of childbearing potential, the results of either a urine or serum human chorionic gonadotropin pregnancy test (with the result known on the day of and before radiopharmaceutical administration) must be negative.
b) Before the IMP injection (blood and urine) and 1 hour after the IMP injection (blood).
c) Vital signs and pulse oximetry will be recorded up to 20 minutes pre-injection and at 30 (±5) minutes post-injection. In addition, heart rate only will be recorded at approximately 1 minute pre-injection and at 5, 10 and 15 minutes post-injection.
d) 12 lead ECG collected on local ECG machine and interpreted by the investigator or a designee at the investigative site. A clinically indicated ECG performed within 48 hours prior to screening, without intervening episodes of chest pain or instability, can be used as the Screening ECG, where available. At rest PET-MPI visits, 12-lead ECG will be recorded at pre-dose (within 20 minutes before transmission scan) and at 10 (±5) and 30 (±5) minutes post-injection.
e) Physical examination will comprise a full examination with a specific focus on cardiovascular signs. At rest PET-MPI visits, physical examination will be performed pre-injection and at 1 hour post-injection.
f) A clinical screen for new or worsening symptoms indicative of unstable CAD disease will be conducted prior to performing any procedures at the PET-MPI visits. If the clinical status screening is positive, the PET-MPI visits can either be rescheduled (up to 1 time and within the 2-week period specified) after symptoms stabilize or the subject can be discontinued from the study.
g) Immediately prior to injection, immediately after injection of IMP and 1 hour after injection of IMP.
h) 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.

9.1 Screening Period

All screening assessments will be performed at least 2 days and within 14 days prior to Rest PET-MPI Visit 1. The following will be done during the screening period:

- Signed and dated informed consent must be obtained from all subjects prior to their entering the study and prior to the initiation of any study-related procedures.
- All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.
- Medical and surgical history will be checked and recorded. This medical history will include any significant past or present illnesses, by body system, as well as a complete cardiac history (including 5-year general medical history) and a pretest likelihood of CAD. The pretest likelihood of CAD will be derived from the European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes [Knuuti et al. 2020] (see Appendix 15.4).
- Prior and concomitant medications.
- Demographic information will be recorded.
- Blood and urine samples will be collected for assessing hematology, abnormal glucose metabolism, liver and renal insufficiency. If for scheduling reasons, the study PET-MPI must occur rapidly after the Screening Visit (e.g., within 48 hours), an additional blood sample may be analyzed by local labs specifically to determine if the subject meets exclusion criteria (i.e., serum creatinine, AST, ALT and total bilirubin). For all subjects, blood must be sent for central analysis of all protocol-specified laboratory parameters, whether or not blood is sent to a local lab for limited biochemical analysis for screening purposes.
- For women of childbearing potential, the results of either a urine or serum human chorionic gonadotropin pregnancy test (with the result known on the day of and prior to Flurpiridaz (^{18}F) Injection) must be negative; these subjects must be instructed to practice appropriate birth control from time of screening to 30 days after the last Flurpiridaz (^{18}F) Injection. A pregnancy test is not needed for women who are either surgically sterile (has a documented bilateral tubal ligation and oophorectomy and/or documented hysterectomy) or post-menopausal (cessation of menses for more than 1 year).
- Vital signs and pulse oximetry will be recorded.
- 12-lead ECG recording will be performed (a clinically indicated ECG performed within 48 hours prior to screening, without intervening episodes of chest pain or instability, can be used as the Screening ECG, where available).
- All AEs and SAEs that occur after informed consent will be recorded (see Table 1 for scheduled AE query time points).

- Subjects will be randomized to receive either 2 doses of Flurpiridaz (^{18}F) Injection manufactured by the same process (HPLC or SPE) or 2 doses of Flurpiridaz (^{18}F) Injection manufactured by different processes (1 dose by HPLC and 1 dose by SPE in a random order; see Section 8.4).

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances. Any exceptions to protocol-specified requirements will be considered as protocol deviations.

9.2 Flurpiridaz (^{18}F) Injection PET-MPI Visits 1 and 2

Subjects will have 2 rest Flurpiridaz (^{18}F) Injection PET-MPI visits performed no more than 2 weeks apart. To allow for adequate decay of the first dose, at least 24 hours must separate the 2 injections/imaging procedures. The first rest Flurpiridaz (^{18}F) Injection PET-MPI visit (PET-MPI Visit 1) must take place at least 2 days and within 14 days after screening. The 24-hour safety follow-up after PET-MPI Visit 1 must be completed before administration of Flurpiridaz (^{18}F) Injection for PET-MPI Visit 2.

A clinical screen for new or worsening symptoms indicative of unstable CAD disease will be conducted prior to performing any procedures at the Flurpiridaz (^{18}F) Injection PET-MPI visits. If the clinical status screening is positive, the Flurpiridaz (^{18}F) Injection PET-MPI visits can either be rescheduled (up to 1 time and within the 2-week period specified) after symptoms stabilize or the subject can be discontinued from the study.

During PET-MPI Visits 1 and 2, the following will be performed:

- Blood samples for laboratory testing will be collected prior to the PET-MPI and 1 hour after the PET-MPI injections. For all subjects, blood must be sent for central analysis of all protocol-specified laboratory parameters, whether or not blood is sent to a local lab for limited biochemical analysis for screening purposes.
- Urine samples for laboratory testing will be collected prior to the PET-MPI.
- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]).
- Concomitant medications will be recorded.
- Vital signs and pulse oximetry will be recorded up to 20 minutes pre-injection and at 30 (±5) minutes post-injection. In addition, heart rate only will be recorded at approximately 1 minute pre-injection and at 5, 10 and 15 minutes post-injection.
- 12-lead ECGs will be recorded pre-injection (within 20 minutes before transmission scan) and at 10 (±5) and 30 (±5) minutes post-injection (See Section 10.2.3).
- A physical examination will be performed pre-injection and at 1 hour post-injection.
- During the rest test, all subjects will receive an IV bolus injection of Flurpiridaz (^{18}F) Injection in a large peripheral vein (see Section 8.1.1). The dose (volume and radioactivity) will be recorded in the CRF.

- Injection-site monitoring (immediately prior to and immediately after the injection and 1 hour after injection of IMP)
- The images acquired during Flurpiridaz (^{18}F) Injection PET-MPI will be stored for the secondary blinded review.
- AEs and SAEs will be recorded.

9.3 24 (+8) hours Safety Follow-up (after Flurpiridaz (^{18}F) Injection PET-MPI Visits 1 and 2)

All subjects will be followed up by telephone for assessment of AEs and SAEs at 24 (+8) hours after each administration of Flurpiridaz (^{18}F) Injection, i.e., after PET-MPI Visits 1 and 2. The following will be recorded:

- Concomitant medications
- AEs and SAEs.

9.4 Unscheduled Visits

Unscheduled visits can be arranged at the discretion of the investigator. At a minimum, the date and reason for the visit will be captured. Any procedures performed will also be captured in the CRF.

10 EFFICACY AND SAFETY ASSESSMENTS

10.1 Efficacy Assessments

The efficacy endpoints will assess:

Primary endpoint:

- Intra-reader correlation and difference between the SRS and SR% after 2 MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes

Secondary endpoints:

- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the SPE process
- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the HPLC process
- Intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses
- Difference between the perfusion rest scores for each of the 17 segments and each reader using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes
- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection synthesized by 2 different manufacturing processes
- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the HPLC process
- Difference in the SUV TACs and the relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the subjects receiving 2 doses of the product manufactured by the SPE process
- Intra-reader agreement of the image quality score between the 2 sets of PET images acquired after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection

10.1.1 Image Acquisition

Imaging procedures include PET-MPI.

The image acquisitions in a list-mode at a single bed position centered on the heart will start 10 seconds before Flurpiridaz (^{18}F) Injection and last 15 minutes. Both PET images must be acquired on the same PET camera.

The PET list-mode acquisition will be reframed to produce a dynamic series for TAC analysis (0 to 15 minutes) and a static image (5 to 15 minutes) with and without cardiac gating for visual and semiquantitative analysis. Full details of the imaging protocol are presented in the GE-265-001 PET Imaging Manual.

Incidental findings are not likely.

10.1.2 Image Interpretation

Three qualified independent readers will perform a blinded assessment of each subject's PET image pair (with each injection images). Further details will be provided in the GE-265-001 PET Independent Review Charter.

Details of the TAC and SUV analysis will be provided in the GE-265-001 PET Image Processing Manual.

10.2 Safety Assessments

Subjects will be closely monitored for safety until completion of all study procedures. Safety monitoring will include AEs, medication errors, TEAEs, and SAE assessments, vital signs, ECGs, hematology, clinical chemistry laboratory tests, and urinalysis. All subjects will be followed up by telephone for AEs at 24 (+8) hours following each Flurpiridaz (^{18}F) Injection administration. The 24-hour safety follow-up after PET-MPI Visit 1 must be completed before administration of Flurpiridaz (^{18}F) Injection for PET-MPI Visit 2.

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, hematology and urinalysis (Table 2).
- Vital signs: systolic/diastolic blood pressure, heart rate, respiration rate, and pulse oximetry.
- 12-lead ECG.
- Physical examination.
- Injection site monitoring
- Post-treatment events (AEs and SAEs).

Pre-specified normal limits for vital signs and ECG intervals are provided in Section 15.3.

10.2.1 Clinical Laboratory Evaluation

Clinical laboratory parameters assessed in this study are displayed in Table 2.

Table 2 Clinical Laboratory Parameters

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

The signed and interpreted laboratory results will be kept together with the subject's CRF (paper or electronic) as supplemental pages, both centrally (in an electronic format only) and at the site.

Blood samples will be obtained for assessment of serum biochemistry and hematology at the various pre- and post-treatment time point ranges described in Table 1. It is anticipated that the maximum amount of blood taken will not be more than 50 mL for all the samples taken during the subject's study participation. Samples will be analyzed at a central laboratory (for parameters, see Table 2). All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed after completion of the study. For the purposes of screening, an additional blood sample may be analyzed by local labs specifically to determine if the subject meets exclusion criteria (i.e., serum creatinine, AST, ALT and total bilirubin).

Urine will be collected at the time points described in Table 1. The time of void will be documented on the CRF. Urine voided will be analyzed for parameters listed in Table 2.

Any abnormal laboratory findings that constitute an AE (e.g., any abnormal findings leading to an intervention other than repeating the laboratory test) should be reported as such and should be followed up until the outcome is known.

10.2.2 Vital Signs

Vital signs (pulse oximetry, blood pressure, heart rate, respiratory rate) will be monitored at Screening and at PET-MPI Visits 1 and 2, according to the study schedule of events (Table 1). Before vital signs are measured, the subject should rest for ≥5 minutes in a supine position (if possible). The same position will be used each time vital signs are measured for a given subject and blood pressure will be measured from the arm contra-lateral to the site of IMP administration whenever possible.

10.2.3 Electrocardiograms

A standard 12-lead ECG will be obtained at Screening and at PET-MPI Visits 1 and 2, according to the study schedule of events (Table 1). ECGs can be obtained on any local ECG machine and will be interpreted by the investigator or a designee at the investigative site. A clinically indicated ECG performed within 48 hours prior to screening, without intervening episodes of chest pain or instability, can be used as the Screening ECG. The results of this ECG will be captured in the CRF.

ECG clocks should be synchronized with imaging equipment. Note: pre-dose ECGs should be obtained within 20 minutes before the transmission scan, and the subject should rest for 5 minutes prior to this. Single ECGs will also be obtained at 10 (±5) and 30 (±5) minutes post-injection. The investigator will be asked to provide a determination of clinically significant changes on the CRF for the ECGs obtained at 10 and 30 minutes after administration of Flurpiridaz (^{18}F) Injection. If the investigator determines that there are any clinically significant changes from the ECG obtained before Flurpiridaz (^{18}F) injection, those changes will be reported as AEs.

10.2.3.1 Investigational Site Responsibilities

Each 12-lead ECG will be evaluated by a board-certified cardiologist or advanced cardiac life support (ACLS)-certified licensed physician. An ACLS-certified licensed physician reading ECGs may make clinical management decisions as needed. However, the hardcopy ECG strips will be read on the same day or day after the ECG examination by a board-certified cardiologist at the site who signs off on the ECG interpretation.

Subject management decisions may be based on the 12-lead ECG findings.

Pre-specified normal limits and expanded normal limits for 12-lead ECG intervals are provided in Section 15.3. Each 12-lead ECG tracing must be signed and dated, and the assessment results collected in the CRF.

Each 12-lead ECG at each time point (all intervals, heart rate and interpretation, and identified with the subject's initials, subject's study number, and date and time of recording), will be retained in the investigator's study record for each subject. The investigator is expected to calculate QTc intervals.

10.2.4 Physical Examination

A qualified physician or a non-physician medically certified individual who is certified either by State/National law to perform physical examinations will conduct physical examinations at the PET-MPI visits before the Flurpiridaz (^{18}F) Injection rest MPI exam and 1 hour post-injection. Ideally, the same individual should conduct the physical examination at all required time points. The physical examination will include recording an assessment for the presence of abnormalities of the following: general appearance, skin, head, eyes, ears, nose, throat, lungs, cardiovascular system, back and spine, abdomen, extremities, injection site, lymph nodes, and neurological exam.

A *new* abnormal physical finding is one that occurs when a subject's normal baseline physical examination becomes abnormal post baseline. A *worsening* abnormal physical finding is one that occurs when a subject's abnormal baseline physical examination becomes worse post baseline.

10.2.5 Injection Site Monitoring

The injection site will be evaluated at the following time points: immediately prior to and immediately after each injection of IMP, and at 1 hour after each injection.

Abnormal injection site findings include, but are not limited to, radiopharmaceutical extravasation, bleeding, hematoma, redness, and infection. They will be recorded as AEs in the CRF.

10.3 Adverse Events and Serious Adverse Events

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for 1 hour after dosing. Treatment of SAEs should be primarily supportive of vital functions.

10.3.1 Definition of Adverse Event

AE Definition: An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have to have a causal relationship with their treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to that product. Only symptoms/signs that begin or worsen in severity and/or frequency after signing informed consent will be recorded as AEs.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- A new condition detected or diagnosed after IMP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Treatment-emergent AE: A treatment-emergent AE is defined as an AE that occurs from time of administration of IMP to the end of the follow-up period.

Adverse Reaction: An AE that is caused by the IMP.

Suspected Adverse Reaction: A reasonable possibility exists for causality between the IMP and the AE.

10.3.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that:

a) Results in death

b) Is life-threatening
   - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization
   - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Is another medically important event
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Subjects (or, when appropriate, a caregiver, surrogate, or the subject's legally authorized representative) will report AEs to the investigator and/or qualified designee.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that cause the subject to discontinue the study.

10.3.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last follow-up visit at the time points specified in the Schedule of Events (Table 1).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the Sponsor.

10.3.4 Adverse Event and Serious Adverse Event Recording and Evaluation

Adverse Event and Serious Adverse Event Recording:

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF and/or the SAE reporting form. If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if MI is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and MI was not diagnosed, then each event would be reported as an AE.

It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor/CRO in lieu of completion of the AE/SAE CRF page/reporting form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor/CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor/CRO.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 10.3.2), NOT when it is rated as severe.

Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events).

Assessment of Causality:

Causality should be assessed as Related or Not Related (Unrelated).

The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator will also consult the IB in his/her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor/CRO. However, it is very important

that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/CRO.

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Subjects will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period. Open-ended and non-leading verbal questioning of the subject (e.g., "How do you feel?") is the preferred method to inquire about AE occurrences. Subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

10.3.5 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.5.2).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor/CRO with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the Sponsor/CRO within 24 hours of receipt of the information.

10.3.6 Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met. **Study centers are instructed to report all SAEs to the Sponsor/CRO within 24 hours.**

Details of the procedures for notifying the Sponsor/CRO of SAEs and contact details for any protocol or safety-related questions are provided in a separate guidance document.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional/Independent Review Boards (IRBs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs or a MedWatch/Council for International Organizations of Medical Sciences [CIOMS]) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

10.3.7 Urgent Safety Measures

In accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Council for Harmonisation (ICH) E6, the investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB approval/favorable opinion.

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazards to their health or safety. However, the investigator must inform the Sponsor/CRO within 24 hours of having taken such measures. Such reports can be initiated by telephone but must be officially documented by the investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

The Sponsor in turn shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IRB of the measures taken and the circumstances giving rise to those measures.

10.3.8 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or fetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all subjects following exposure to IMP.

Female trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if she suspects she may be pregnant during 1 month after dosing.

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's confirmed pregnancy.

The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any female subject who becomes pregnant while participating in the study will discontinue IMP or be withdrawn from the study.

Male trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if they suspect their partner became pregnant after the subject was administered IMP during 1 month after dosing.

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive IMP.

After obtaining the necessary signed informed consent from the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's confirmed pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

When a study subject reports a pregnancy (post-IMP administration) to the investigator, a pregnancy test should be arranged for the study subject (or their partner) by the investigator if the pregnancy has not been confirmed by another physician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at ≤22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 10.3.6. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.4 Other Variables

10.4.1 Demographic Data

Subject demographic data (date of birth/age, race, ethnicity, sex, weight, and height) will be recorded at Screening. Subject age at the time of screening will be calculated from the date of birth and the date of screening. Body mass index (BMI) will be calculated from height and weight. If local regulations do not permit collection of specific demographic items (e.g., date of birth), either age will be entered on the CRF or a partial date will be used in accordance with local practice.

10.4.2 Medical and Surgical History

The subjects' relevant medical and surgical history will be recorded at Screening and will be summarized.

10.4.3 Prior and Concomitant Medication

Any medications currently taken by the subject at the time of informed consent, and through to their last follow-up will be recorded in the CRF, along with the indication and dosage. Either the generic or the trade name may be recorded. The CRO will encode all therapy and medication per a current well-recognized dictionary of medical codes.

10.5 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Clinical Data Management

The CRO will be responsible for the processing and quality control of the data. Data management will be carried out by the CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines. Full details of procedures for data handling will be documented in the Data Management Plan.

11.2 Completing and Signing Case Report Forms

For electronic CRFs, data will be entered by trained site personnel with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error and the reason for the correction. The appropriate electronic signature will be provided.

Any data recorded directly in the CRF, for which no other written or electronic record will be maintained in the subject's medical record, will be considered source data and should be signed by the investigator(s) (e.g., results of physical examinations, vital signs testing, or the IMP administration procedure).

11.3 Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or similar document.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records, including, but not limited to, the image data, may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4 Record Retention

All study documentation at the investigator site and Sponsor site will be retained in accordance with ICH E6-GCP and the Sponsor/CRO's quality standards and standard operating procedures (SOPs).

All study documentation at the Investigator site and Sponsor site will be retained for a minimum of 15 years following completion or discontinuation of the study, unless the site is notified otherwise by the Sponsor or a longer period is required by local legislation. The Investigator must request written agreement from the Sponsor before destruction of archived study documentation.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analyzed by the Sponsor and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to the Sponsor before publication or presentation.

Data from participating centers in this protocol will be combined so that an adequate number of subjects will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software, Version 9.3 or higher. Descriptive statistics for continuous data in summary tables will include the number of subjects in the analysis (n), mean, SD, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. The last observation prior to administration of IMP will be used as the baseline value for calculating changes from baseline after administration of IMP. All data obtained on the CRF and entered into the database will be provided in separate data listings showing individual subject values. All summary tables and data listings will be separated by treatment groups. The planning and reporting of statistical analysis will be carried out as described in the Sponsor/CRO's SOPs governing clinical studies and will be described in further detail in the Statistical Analysis Plan (SAP).

12.2 Populations for Analysis

12.2.1 Intent-to-Treat Population

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

12.2.2 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (MITT) population will include all ITT subjects who have completed the 2 rest Flurpiridaz (^{18}F) Injection PET-MPI procedures. The MITT population will be the primary analysis set for the primary efficacy endpoint.

12.2.3 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 summarized for the Safety Population.

12.3 Subject Demographics/Other Baseline Characteristics

A table will be provided with the following information:

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

Demographic information (age, height, weight and BMI) will be summarized by using descriptive statistics. Sex, ethnicity, and race will be summarized by counts and percentages.

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

12.4 Study Treatments

The dosages of Flurpiridaz (^{18}F) Injection administered at rest will be summarized by volume and radioactivity administered.

Any other medications taken by a subject at time of informed consent, and through to the last follow-up will be recorded in the CRF along with the indication and dosage. Either the generic or the trade name may be recorded. The CRO will encode all therapy and medication according to a current well-recognized dictionary of medical codes.

12.5 Primary Efficacy Analysis

12.5.1 Efficacy Variables

12.5.1.1 Myocardial Perfusion Imaging Evaluations

Three qualified readers (independent from the study) will perform independent reads of all MPI images. The PET-MPI reads will be performed by the same set of readers in crossover sessions independent of one another. In each session, PET images will be displayed in a randomized order, non-sequentially, with PET-MPI exams corresponding to individual subjects randomly allotted into reading session batches.

The independent reads of all MPI images will be based on standard 17-segment polar-maps of perfusion defects. Each reader will score the perfusion pattern in each segment (17 segments) using a 5-point scale scoring:

- Normal 0,
- Minimal, mild impairment of perfusion, ambiguous image 1,
- Moderate impairment of perfusion 2,
- Significant impairment of perfusion 3,
- No perfusion 4.

The summed score of the 17 segments SRS, as well as the SR%, will be used as the primary endpoint, and summarized as a continuous variable by reader and using the median of the results of the 3 readers.

12.5.2 Statistical Hypothesis, Model, and Method of Analysis

The SRS will be summarized as a continuous variable by reader and using the median of the results of the 3 readers.

The primary analysis for the primary endpoint will be based on the mixed-effects model for repeated measures (MMRM). The model will include the median SRS in each dosing period as the dependent variable, with manufacturing process, period and dosing sequence as fixed effects, and subject nested within sequence as the random effect. The estimated mean SRS difference and 90% CI will be provided from the MMRM analysis. Similarity will be established if the 90% CI of the difference is within a margin of (-0.75, 0.75). The margin size is defined as 0.75 to allow the difference of, at most, 43% of the mean SRS score (mean PET SRS score is 1.75 based on empirical data [Berman et al. 2013]).

The correlation analysis will be stratified by the following 3 groups: 1) subjects who have received 2 doses of product manufactured by 2 different processes; 2) subjects who have received 2 doses of product both manufactured by the SPE process; and 3) subjects who have received 2 doses of product both manufactured by the HPLC process. The intra-reader (within-subject) correlation between the 2 manufacturing processes will be assessed by Pearson's correlation, Kendall's τ and Bland-Altman difference for the summed score stratified by the above 3 groups. The mean of paired difference between the 2 manufacturing processes, t-statistics based 95% confidence interval (CI), the median difference and 95% CI based on Hodges-Lehman method, and p-value obtained by Wilcoxon signed rank test will also be provided for descriptive purpose for the summed score of 17 segments among subjects who have received 2 doses of product manufactured by 2 different processes.

12.5.3 Handling of Missing Values/Censoring/Discontinuations

Missing values will not be imputed, and only observed values will be used in data analyses and reports, unless otherwise specified in the SAP.

12.5.4 Supportive Analyses

Sensitivity analyses will be performed to assess the impact of missing data on the primary analysis results (i.e., subjects in the ITT population with incomplete PET-MPI scans) using similar MMRM analysis for primary analysis. Details will be provided in the SAP.

12.5.5 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.

12.6 Secondary Analyses

12.6.1 Efficacy Variables and Analyses (Secondary)

Secondary efficacy endpoints include:

- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the SPE process
- Variability of the SRS after MPI sessions using 2 Flurpiridaz (^{18}F) Injection doses synthesized for the subjects receiving 2 doses of the product manufactured by the HPLC process
- Intra-reader agreement of the detection of ischemic defect on PET-MPI at rest between 2 MPI acquisitions using 2 Flurpiridaz (^{18}F) Injection doses
- Difference between the perfusion rest scores for each of the 17 segments and each reader using 2 Flurpiridaz (^{18}F) Injection doses synthesized using the same or 2 different manufacturing processes
- Difference in the SUV TACs and relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection synthesized by 2 different manufacturing processes
- Difference in the SUV TACs and relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the 7 subjects receiving 2 doses of the product manufactured by the HPLC process
- Difference in the SUV TACs and relative difference in SUV (5- to 15-minute perfusion image) in left ventricular cavity, myocardium, lungs and liver measured after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection for the 7 subjects receiving 2 doses of the product manufactured by the SPE process

- Intra-reader agreement of the image quality score between the 2 sets of PET images acquired after two [^{18}F]flurpiridaz injections using doses of Flurpiridaz (^{18}F) Injection.

The intra-reader variability of the SRS will be estimated by the SD of the paired difference divided by $\sqrt{2}$, for subjects receiving 2 doses of the product both manufactured by the SPE process and separately for subjects receiving 2 doses of the product both manufactured by the HPLC process.

For the individual scores of 17 segments, the mean of paired difference between the 2 manufacturing processes, t-statistics based 95% CI, the median difference and 95% CI based on Hodges-Lehman method, and p-value obtained by Wilcoxon signed rank test will also be provided for descriptive purpose among subjects who have received 2 doses of product manufactured by 2 different processes.

The PET-MPI reads will be performed by the same set of readers. In each session, PET images will be displayed in a randomized order, non-sequentially, with PET-MPI exams corresponding to individual subjects randomly allotted into reading session batches. The intra-reader agreement of the detection of ischemic defect on PET-MPI will be assessed by percent agreement and Cohen's kappa value stratified by the 3 groups as used in the primary analysis.

Perfusion and gated acquisitions of rest images will be rated for image quality (excellent, good, fair, poor or non-diagnostic). The image quality score will be summarized descriptively for the 3 groups of data sets and the intra-reader agreement will be assessed between the 2 acquisitions stratified by the 3 groups as used in the primary analysis.

Within left ventricle, myocardium, lungs and liver regions of interest (ROIs), a TAC (in SUV units) will be generated for the dynamic scan during the 15-minute acquisition period. The SUV for each ROI will be generated using the following formula:

SUV= Decay Corrected Uptake (kBq/cc) / (Injected Dose (MBq) / Weight (kg))

There will be a descriptive statistical analysis only. The relative difference D in the SUV expressed as D = 100 (SUV1-SUV2)/[0.5 * (SUV1 + SUV2)] between the 2 processes will be summarized descriptively for each region among subjects who have received 2 doses of product. The mean absolute percentage difference (MAPD) will be determined as the mean of the absolute value of D over all subjects.

12.6.2 Safety Variables and Analyses

Safety Endpoints: 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 summarized by mean, SD, minimum, and maximum at each time point.

12.6.2.1 Clinical Laboratory Evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline. In addition, for each clinical laboratory variable and each time point, the following safety endpoints will be summarized by counts and percentages for each manufacturing process:

- 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 (Section 15.3) (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.6.2.2 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital-sign variable and each time point, the following safety endpoints will be summarized by counts and percentages and by manufacturing process:

- 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, 10 breaths per minute for respiration rate).
- The occurrence of post-administration values outside the normal limits (Section 15.3). Shift tables based on the normal range will be prepared.

12.6.2.3 Electrocardiograms

Descriptive statistics will be displayed for the observed values and changes from baseline. For each ECG variable and each time-point, the following safety endpoints will be summarized by counts and percentages and by manufacturing process:

- The occurrence of post-administration values outside the normal limits in the PR, QTc, QRS or RR interval (Section 15.3). Shift tables based on the normal range will be prepared.

ECGs for which the overall interpretation was abnormal will be summarized by counts and percentages at each post-administration time point or by additional/other characteristics deemed necessary by study team.

<u>QTc correction:</u>

The following correction formula will be employed in analyzing QTc data in an attempt to reduce the bias resulting from over- or under-correction:

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

The following analyses will employ this method of correction:

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

(2) 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.

12.6.2.4 Physical Examination

The number and percentage of subjects with changes in physical examination status from normal at pre-administration to abnormal at 1 hour post-administration (and vice versa) will be presented by manufacturing process. Shift tables based on the normal range will be prepared.

12.6.2.5 Adverse Events

AEs and SAEs will be coded using a current version of Medical Dictionary for Regulatory Activities and all reported events will be listed for the safety population. TEAEs are defined as AEs that occur from the time of IMP administration through the end of the follow-up period. The number and percentage of subjects with 1 or more TEAEs will be summarized by system organ class and preferred term. Summaries and listings will also be presented by AE intensity and judged relationship to IMP. Treatment-emergent SAEs are defined as SAEs that occur from the time of IMP administration through the end of the follow-up period. Treatment-emergent SAEs will also be presented for the safety population.

12.6.3 Reader Difference

Reader variability will be assessed by the reread of images. Further details can be found in the GE-265-001 Independent Review Charter.

12.6.4 Resource Utilization

The summed score of the 17 myocardial segments and the individual scores of 17 segments, the SUV values between the injection time-point and 15 minutes in left ventricular cavity, myocardium, lungs and liver will be analyzed.

12.7 Interim Analysis

No formal interim analyses will be performed in this study.

12.8 Sample Size Calculation

The sample size for this clinical investigation has been determined a priori to be 28 subjects to assess the clinical imaging similarity and safety profiles of Flurpiridaz (^{18}F) Injection

synthesized by 2 different manufacturing processes in subjects with suspected or established CAD. To account for 20% dropout, approximately 34 subjects will be randomized in a 1:1:1:1 ratio to each of the 4 treatment sequences.

12.9 Procedures for Missing, Unused and Spurious Data

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.

12.10 Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the analyses unless otherwise specified. The Sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. Such judgments should be made in a blinded fashion (with regards to the central MPI read) before database lock and before any analyses have been performed. If the subject has received any IMP, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

12.11 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

Before starting this study, the protocol, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB and reviewed and approved by the IRB. The protocol will also be submitted to regulatory bodies/local health authorities in accordance with local regulations as required. The study will not start before the IRB gives written approval or a favorable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favorable opinion as required.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects (see Section 10.3.7).

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

13.2 Investigator's Responsibilities

13.2.1 Overall Responsibilities

The investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centers participating in this study that cannot comply with these standards will be documented.

13.2.2 Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects. The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary and that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Subjects will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center. A subject's ICF must be obtained before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The investigator(s) will keep the original consent forms. A copy of the signed ICF(s) must be provided to the subject or the subject's legally authorized representative.

13.2.3 Source Data/Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported or entered on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The monitor(s), auditor(s), authorized personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorized members of IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

13.2.4 Confidentiality Regarding Study Subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In CRFs and other documents or image material (including materials from all PET examinations) submitted to the Sponsor/CRO, subjects will not be identified by their names, but by an identification code (e.g., study subject number).

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

13.2.5 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

13.2.6 Dissemination of Clinical Study Data

The sponsor will disclose clinical study reports, periodic safety reports, and clinical study summary reports after review by regulatory authorities.

The sponsor will post company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinTrials.gov and other publicly-accessible sites.

The sponsor will take appropriate measures to ensure that the results will be published in peer-reviewed journal, to warrant the scientific integrity and credibility of publication activities performed by or on behalf of the company. The sponsor will grant access to analyzable datasets from the clinical study through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.

13.3 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.

13.4 Study Monitoring

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

13.5 Audit and Inspection

According to ICH E6-GCP, the Sponsor or regulatory authorities may audit the investigational site. The Sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.6 Financial Disclosure

According to 21 CFR, Part 54, the Sponsor is required to completely and accurately disclose or certify information concerning the financial interests of a clinical investigator (or investigating institution) who is not a full-time or part-time employee to the FDA. Therefore, the investigator(s) (or investigating institution) must provide the Sponsor with sufficient, accurate financial certification that none of the following financial arrangements (further defined in 21CFR Part 54.2) exist with the Sponsor or fully disclose the nature of the arrangement. This financial disclosure also applies to any financial arrangements that exist between the Sponsor and the investigator's spouse(s) or dependent children:

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

13.7 Insurance

This study is covered under the Sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study Sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.8 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for the IMP in this study is the current IB. The reference document provides up-to-date information on the efficacy and safety of Flurpiridaz (^{18}F) Injection and is used for assessing expectedness of Serious Adverse Drug Reactions, in order to determine regulatory reportability. An unexpected adverse drug reaction is a reaction for which the nature, seriousness, severity or outcome is not consistent with the IB.

15.2 Equipment Parameters

Hardware and software functionality for PET acquisition are specified in the reference imaging manual.

15.3 Normal Limits for Vital Signs and ECG Intervals

Table 3 Criteria for Normal Limits for Vital Signs

Vital Signs Parameter	Normal Limits	
	Low	High
Systolic BP (mmHg)	85	139
Diastolic BP (mmHg)	60	89
Heart Rate (beats/min)	60	100
Respiration Rate (breaths/min)	12	22
Oxygen Saturation (%)	93	100
Body Weight (kg)[a]	41	113
Body Mass Index (kg/m²)[b]	18.5	24.9

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

Table 4 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.

15.4 Pre-test Probability of Obstructive Coronary Artery Disease in Symptomatic Patients

Table 5 Clinical Pre-test Probabilities of Obstructive Coronary Artery Disease in 15,815 Symptomatic Patients [Knuuti et al. 2020]

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

Pre-test probabilities of obstructive coronary artery disease in 15,815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis of contemporary data.
In addition to the classic Diamond and Forrester classes, 59 patients with dyspnoea only or dyspnoea as the primary symptom are included.
The regions shaded dark green denote the groups in which non-invasive testing is most beneficial (PTP >15%).
The regions shaded light green denote the groups with PTPs of CAD between 5–15%, in which testing for diagnosis may be considered after assessing the overall clinical likelihood based on the modifiers of PTPs presented in the 2019 ESC guidelines.

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

- Medical director details updated following a change in personnel.
- Number of centers in the study updated from ‘up to 4’ to ‘approximately 4’.
- Correction of minor typographical errors.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate, the changes are indicated in *italics*.

16.1.2 Description of Changes

Title Page, Medical Director Details

Previously read:

[redacted]
GE Healthcare
100 Results Way,
Marlborough, MA 01752,
United States
Phone [redacted]
Email: [redacted]

Now reads:

[redacted]
GE Healthcare
Pollards Wood, Nightingales Lane
Chalfont St Giles
Buckinghamshire HP8 4SP
United Kingdom
Phone [redacted]
Email: [redacted]

Section 6.1, Overall Study Design and Plan, Second Paragraph, First Sentence

Previously read:

This study will be conducted at up to 4 centers in the US.

Now reads:

This study will be conducted at *approximately* 4 centers in the US.

Section 8.4, Randomization and Blinding, Second Sentence

Previously read:

Thirty-two subjects will be randomized 1:1:1:1 into 4 treatment sequence groups:

Now reads:

Subjects will be randomized 1:1:1:1 into 4 treatment sequence groups:

Section 9, Study Procedures, Table 1 - Study Schedule of Events, Footnote b

Previously read:

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

Now reads:

b) Before the IMP injection (blood and urine) and 1 hour after the IMP injection (blood).

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: [redacted] Date of signature: [redacted]	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: [redacted]	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: [redacted]	Justification: Approved Role: [redacted]

This is a representation of an electronic record that was signed electronically in accordance with GxP guidelines and controls. The information above is a valid manifestation of the electronic signature(s) and is legally binding