Clinical Study Protocol **GE Healthcare**
GE Healthcare Protocol GE-265-303

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

REVISED TO INCORPORATE AMENDMENT A03

Sponsor

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "Sponsor")

EudraCT Number: 2017-005011-14

IND Number: 75,307

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Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

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	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use Only)**

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

Protocol Number: GE-265-303

Investigators and Study Centres: Approximately 60 centres in Europe and North America (United States and Canada)

Phase of Development: Phase 3

Objectives:

Primary Objective:

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

Secondary Objectives:

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

Exploratory Objectives:

[redacted]

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[redacted]

Study Design:

This is a Phase 3, prospective, open-label, international, multicentre study of Flurpiridaz (^{18}F) Injection for PET MPI in patients referred for ICA because of suspected CAD. Five hundred and fifty-two (552) evaluable subjects will be enrolled in this study, and will undergo SPECT MPI and Flurpiridaz (^{18}F) Injection PET MPI, prior to ICA.

Patients can be considered for enrolment if:

- They are being scheduled via written documentation at the time of enrolment to undergo ICA, and
- They have undergone a clinically indicated SPECT study which meets all study-specified imaging and stress testing (Section 9.3) criteria, or are willing to undergo SPECT MPI for the purposes of the clinical study.

Study Population:

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

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

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 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 (including clinically indicated SPECT studies occurring prior to the signing of the ICF as stipulated in inclusion criteria #4).
3) At the time of enrolment, the subject has been scheduled via written documentation to undergo an ICA for the assessment of CAD.
4) The subject has undergone a clinically indicated SPECT which meets all study-specific imaging and stress testing (Section 9.3) criteria and conforms to local guidelines (such as American Society of Nuclear Cardiology or European Association of Nuclear Medicine), OR the patient is willing to undergo SPECT MPI for the purposes of the clinical study.
5) 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); enrolment in the study without a pregnancy test at Screening is allowed for these categories of

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female patients. 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 radiopharmaceutical administration) must be negative; these subjects must be practicing appropriate birth control from the time of the screening to 30 days after the radiopharmaceutical administration.

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

Exclusion Criteria:

Patients who meet the following criteria will be excluded from the study:

1) Patients who are pregnant, may possibly be pregnant, or wish (including their partners) to become pregnant during the study period, or are lactating.
2) Patients who are unable to undergo all of the imaging procedures.
3) Patients who have an established diagnosis of CAD as confirmed by any of the following:
   a. Previous myocardial infarction (MI);
   b. Previous cardiac catheter angiography showing ≥50% stenosis;
   c. Previous coronary revascularisation, such as percutaneous coronary intervention (PCI), thrombolysis or coronary artery bypass graft (CABG) placement.
4) Patients incapable of undergoing either exercise or pharmacological cardiac stress testing
5) Patients who have a current illness or pathology that, in the opinion of the investigator, would pose a significant safety risk for the patient during cardiac stress testing.
6) For patients for whom pharmacological stress testing is being considered, the following additional exclusion criteria will apply:
   a. Known hypersensitivity to adenosine, regadenoson, dipyridamole, or aminophylline;
   b. Use of a caffeinated substance, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to vasodilator administration;
   c. Bronchoconstrictive or bronchospastic disease that in the opinion of the investigator poses a significant safety risk for the patient;
   d. Second- or third-degree atrioventricular block or sinus node dysfunction without functioning artificial pacemaker;
   e. Any additional contraindication to the pharmacological stress agent listed in the product's package insert/summary of product characteristics (SmPCs).
7) Patients with unstable cardiovascular condition, including but not limited to:
   a. Unstable angina, acute coronary syndrome within 6 months of enrolment;
   b. Transient ischaemic attack/stroke within 3 months of enrolment;
   c. Significant congenital heart disease;
   d. Uncontrolled hypertension;
   e. Uncontrolled tachyarrhythmia leading to symptoms or haemodynamic compromise.
8) Documented history of heart failure and/or cardiomyopathy (including nonischaemic cardiomyopathy, hypertrophic obstructive cardiomyopathy, or infiltrative cardiomyopathy).
9) Primary haemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant.

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10) Patients scheduled for or planning to undergo any cardiac interventional procedures between enrolment and ICA.
11) Patients 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).
12) Patients 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 patients whom the investigator judges to be unsuitable for participation in the study for any reason.
13) Patients undergoing evaluation for heart transplantation or with history of heart transplantation.
14) Patients enrolled in another clinical study within the 30 days prior to being enrolled in this study or scheduled to participate in another clinical study during the 17-day follow-up period of this study.
15) Patients previously enrolled in this study or any Flurpiridaz (^{18}F) Injection study.

Test Product, Dose, and Mode of Administration:

Flurpiridaz (^{18}F) Injection is a novel PET MPI agent labelled with the radioisotope fluorine-18 and administered as an intravenous (IV) injection. All subjects will receive 2 IV boluses of Flurpiridaz (^{18}F) Injection in a large peripheral vein: 1 at rest and 1 during stress. The dosages of Flurpiridaz (^{18}F) Injection administered at rest and during stress conditions will not exceed a total of 14 mCi (520 MBq) for an individual subject.

Other Products Administered, Dose, and Mode of Administration:

SPECT agents utilised for the purposes of this clinical study will be administered as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. For each subject, the same stress type (pharmacologic or exercise) should be used for the SPECT and Flurpiridaz (^{18}F) Injection PET MPI. Also, if pharmacological stress is used, the same agent and the same dose of pharmacological stress agent should be used for both types of imaging for the same subject.

Pharmacological stress agents utilised for the purposes of this clinical study will be administered according to the respective Package Insert (as applicable) or American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect according to the respective Package Insert (as applicable) of each stressor.

Duration of Study

All screening assessments will occur within 60 days prior to ICA. Flurpiridaz (^{18}F) Injection PET MPI test and SPECT MPI (including SPECT exams preceding informed consent) must precede the ICA and occur within 60 days prior to the ICA. Subjects will have Flurpiridaz (^{18}F) Injection rest and stress PET MPI performed on the same day. Subjects will have their last follow-up safety contact at approximately 2 weeks (14 to 17 days) following Flurpiridaz (^{18}F) Injection or at the time of their ICA, whichever occurs later.

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Efficacy Assessments:

Primary Efficacy Endpoints:

- The sensitivity and specificity of Flurpiridaz (^{18}F) Injection PET MPI in the detection of significant CAD as defined by cardiac catheterisation (ICA).

Secondary Efficacy Endpoints:

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

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

Exploratory Efficacy Endpoints:

[redacted]

Standard of Truth: Subjects will be considered to have CAD if quantitative coronary angiography (QCA) reveals ≥50% stenosis of ≥1 major coronary artery or major branch. Three qualified independent readers will perform a blinded assessment of each subject's PET image pair (rest and stress images) and each subject's SPECT image pair.

One blinded reviewer will perform QCA for all ICA images.

Safety Assessments:

Subjects will be closely monitored for safety until completion of all study procedures. Safety monitoring will include adverse events (AEs), medication errors, treatment-emergent adverse events (TEAEs), and

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serious adverse events (SAE) assessments, vital signs, electrocardiograms (ECGs), haematology, clinical chemistry laboratory tests, and urinalysis. All subjects will be followed up by telephone assessments for AEs within 2 days (+24 hours) following Flurpiridaz (^{18}F) Injection administration, and for AEs and SAEs at approximately 2 weeks (14 to 17 days) following the last Flurpiridaz (^{18}F) Injection dose administration and at the time of their ICA. For subjects undergoing SPECT for the purposes of this clinical study, their safety will be monitored as per institutional standards.

Statistical Methods:

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 nonmissing 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 enrolled subjects who received ≥1 dose of Flurpiridaz (^{18}F) Injection in the study.

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

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

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

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

Efficacy Endpoints:

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

Myocardial Perfusion Imaging Evaluations: Three qualified readers (independent from the study) will perform independent reads of all MPI images. The PET MPI and SPECT MPI reads will be performed by the same set of readers in cross-over sessions independent of one another. In each session, PET and SPECT images will be displayed in a randomised order, nonsequentially, with PET and SPECT MPI exams corresponding to individual subjects randomly allotted into reading session batches. For each modality, perfusion and gated acquisitions of rest and stress images will be rated for image quality and reviewed. After the results of each individual MPI (PET or SPECT) are locked as the "blinded" read,

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then clinical information will be provided. The reader will then be given the opportunity to submit a revised assessment of the existence of any perfusion defects as an "unblinded" read.

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

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

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

Sensitivity and specificity are defined as follows:

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

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

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

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

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

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

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

Therefore, the test of hypotheses will be as follows:

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

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

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

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

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

The above summary will be provided for each modality separately and for the following subgroups:

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

Secondary Efficacy Endpoints:

- The diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (^{18}F) Injection PET MPI compared to SPECT MPI in the detection of CAD, as defined by ICA, in the following sets of subjects:
  - All subjects (key secondary endpoint)
  - Female subjects

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- Subjects with BMI ≥30 kg/m^2
- Diabetic subjects

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

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

Let s_1 = sensitivity in Flurpiridaz (^{18}F) Injection PET MPI, and s_2 = sensitivity in SPECT MPI;

Let p_1 =specificity in Flurpiridaz (^{18}F) Injection PET MPI, and p_2 = specificity in SPECT MPI.

Therefore, the test of hypotheses will be as follows:

H_{01}: $s_1 - s_2 \leq 0$, H_{02}: $p_1 - p_2 \leq -0.1$

H_{a1}: $s_1 - s_2 > 0$, H_{a2}: $p_1 - p_2 > -0.1$

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

The tests of comparisons are based on paired responses, as the Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed on a within-subject basis, and the images will be read by the same readers in a cross-over design. The test of sensitivity comparison between Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a 1-sided McNemar's test at $\alpha = 0.025$. Similarly, the test of specificity noninferiority between Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a paired test for noninferiority [Liu et al 2002] at a 1-sided $\alpha = 0.025$. The criterion for the demonstration of diagnostic efficacy for the secondary endpoints will be meeting the tests of hypotheses for both sensitivity and specificity for the same 2 of the 3 readers for whom the null hypotheses was rejected in the analysis of the primary endpoint.

A minimal performance for SPECT in the targeted population for comparison to Flurpiridaz PET will be specified in the SAP.

Exploratory Endpoints:

[redacted]

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

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACLS	Advanced cardiac life support
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APMHR	Age-predicted maximum heart rate
BMI	Body mass index
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case report form
CRO	Contract research organisation
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CTECS	Clinical Trial Emergency Contact Service
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Effective dose
EEG	Electroencephalogram
FDA	Food and Drug Administration
FFR	Fractional flow reserve
FN	False negative(s)
FP	False positive(s)
GCP	Good Clinical Practice
IB	Investigator’s brochure
ICA	Invasive coronary angiography
ICF	Informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
ICL	Imaging core laboratory
IV	Intravenous
IVUS	Intravascular Ultrasound
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MITT	Modified intent-to-treat
MPI	Myocardial perfusion imaging
NHANES	National Health and Nutrition Examination Survey
NPV	Negative predictive value
PCI	Percutaneous Coronary Intervention
PET	Positron emission tomography
PPV	Positive predictive value
QCA	Quantitative coronary angiography
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Summed difference score
SMITT	Secondary modified intent-to-treat
SmPC	Summary of product characteristics
SOPs	Standard operating procedures
SPECT	Single photon emission computed tomography
SRS	Summed rest score
SSS	Summed stress score
TEAE	Treatment-emergent adverse event
TN	True negative(s)
TP	True positive(s)
US	United States

4 BACKGROUND INFORMATION

Coronary artery disease (CAD) is a major cause of death in modern industrialised countries. CAD is the single largest cause of death in the United States (US) [Roger et al 2012]. According to data from the US National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014, the prevalence of CAD in all adults >20 years of age was 6.3% (16.5 million Americans); and in 2014, mortality from CAD accounted for 1 in every 7 deaths (364,593 directly related to coronary heart disease [CHD], and there were 530,989 deaths where CHD was mentioned). In 2017, an estimated 695,000 Americans will have a new CHD event (defined as hospitalisation for myocardial infarction [MI] or CHD death) and 325,000 will have a recurrent event. Not only is CHD morbid, it strains healthcare resources. In 2011, hospital care associated with MI cost the US healthcare system $11.5 billion and CHD cost $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 [Benjamin et al 2017].

Invasive coronary angiography (ICA) is the definitive procedure for diagnosis of obstructive CAD. It is an invasive examination that involves catheterisation of the heart, allowing an anatomical evaluation that defines the presence, location, and severity of stenoses in the coronary arteries. However, limitations exist to the sensitivity and specificity of ICA for defining myocardial perfusion. ICA does not determine whether a stenosis causes ischemia. ICA is restricted to the assessment of large vessels, providing no visualisation of arterioles and capillaries. Fractional flow reserve (FFR) assessment, a measure of the decrease in perfusion pressure across a stenotic vessel under hyperaemic conditions, better defines the haemodynamic consequence of a stenosis. However, FFR analysis does not account for the presence of scar, collateral flow, or microvascular dysfunction of the area subtended by the vessel; these limitations may affect clinical interpretation of FFR analysis [Hussain et al 2016]. Despite guideline recommendations for its use to define the haemodynamic significance of intermediate stenoses, FFR is performed in only 27% of the cases where it is indicated [Toth et al 2014]. Cardiac catheterisation, including FFR analysis, is not without risk. Estimates of the incidence of periprocedural stroke range from 0.18% to 0.44%, while the incidence of coronary artery perforation ranges from 0.5% to 3%. The overall risk of periangiographic death in patients undergoing catheterisation without intervention is about 0.08% [Tavakol et al 2012].

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 haemodynamic significance of CAD. However, the greatest strength of MPI 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 ICA, without significant differences in clinical outcomes [Shaw et al 1999]. 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.

In nuclear cardiology, assessments of regional myocardial blood flow are performed in patients under rest and stress conditions with a radiolabelled MPI agent by using SPECT MPI (using tracers labelled with thallium-201 [^{201}Tl] or technetium-99m [^{99m}Tc]) or PET MPI (using tracers labelled with rubidium-82 [^{82}Rb] or nitrogen-13 [^{13}N] ammonia). The continued success of nuclear cardiology demands ongoing re-evaluation of imaging practices to optimise patient care. An important challenge is choosing the proper imaging procedure for the individual patient. Tailoring imaging to the patient is critical for providing accurate and clinically meaningful information to the physician.

There are several integral components to a successful patient-centred imaging approach. Patient safety is of paramount importance when one is contemplating any diagnostic and/or therapeutic medical option. For MPI, this approach includes not only the risk of the stress protocol but also the "risk" of performing unnecessary additional procedures or administering inappropriate therapy because of a suboptimally performed test. High-quality imaging limits the latter through improved diagnostic sensitivity and specificity, enhanced risk stratification, and less intra- and inter-observer variability when interpreting clinically significant changes in serial images.

Another 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 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 efficacy, including:

- Higher photon penetration combined with routinely measured (depth-dependent) attenuation correction because the high energy of the annihilation photons and the "coincidence detection" technique of PET imaging systems result in significant advantages in image quality.

- High spatial and contrast resolution that allows for improved detection of small perfusion defects.

- High temporal resolution that allows fast dynamic imaging of tracer kinetics.

- High efficiency resulting in lower administered radioactivity and therefore lower radiation dose to patients.

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 (caesium-137, germanium-

68/gallium-68) to generate a transmission attenuation map, whereas currently manufactured PET systems use x-ray computed tomography (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 hyperaemic blood flow, with calculation of a peak stress left ventricular ejection fraction (LVEF). This may improve identification of high-risk patients or those with multivessel CAD [Dorbala et al 2009]. Furthermore, software solutions allow for absolute quantification of regional myocardial blood flow from dynamically acquired ^{82}Rb and ^{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 multivessel and small vessel coronary disease, responses to medical therapy, and transplant vasculopathy. When combined with the low dose from PET tracers, PET MPI offers a significantly lower radiation dose than does 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-recognised need for the development of a new perfusion imaging agent with more nearly ideal properties. Both rubidium-82 (^{82}Rb) and nitrogen-13 ammonia (^{13}N ammonia) are approved by the US Food and Drug Administration (FDA) 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].

Most PET-MPI studies are performed with pharmacologic stress. Exercise PET-MPI is possible but is challenging because of the short half-lives of the radiotracers. In addition, a PET-MPI agent that could be used with both exercise and pharmacologic stress will find more universal application, as compared to agents limited to pharmacologic stress. Thus, the opportunity exists for a new PET imaging agent using Fluorine-18 (^{18}F) that exhibits high extraction fraction. Such an agent 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 multivessel CAD. It also has the potential to reduce diagnostic uncertainty and reduce radiation dose when compared with studies using SPECT agents.

The objective of using PET tracers such as Flurpiridaz (^{18}F) is to take advantage of the high extraction of this radiotracer, leading to a substantial difference in tracer uptake in normal vs underperfused regions. Therefore, the uptake ratio of this tracer between an underperfused region and a normal region is expected to be higher than is observed with other tracers, which have either a low extraction rate or a roll-off phenomenon. This increased ratio could possibly lead to an improved diagnostic efficacy. Whereas the current SPECT guidelines tend to propose performing stress MPI first, for identifying patients with very low likelihood of CAD presenting with normal stress perfusion images, a rest-stress acquisition sequence is

recommended for PET MPI. Giving the patient the highest PET radiotracer dose at peak stress could enhance the induced perfusion defects.

Clinical studies conducted with Flurpiridaz (^{18}F) Injection include safety, dosimetry, and radiokinetics studies in healthy subjects, as well as 1 Phase 2 study and 1 Phase 3 study in subjects with known or suspected CAD. Through the course of these studies, a total of 1003 patients have received Flurpiridaz (^{18}F) Injection. 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 (EEGs), laboratory values, and physical and neurological examinations.

The primary dosimetry endpoints in single-centre, 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).

BMS747158-102 was a Phase 1, nonrandomised, 2-dose, open-label study conducted at 2 medical centres 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 I single-centre study (BMS747l58-103) 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 faecal 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 metabolised, with no unchanged drug detected in urine or faeces. The major identified radiolabelled 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.

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 patients 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 optimised 1-day rest/stress protocol was subsequently adopted for the second cohort to assess efficacy in patients with a broad spectrum of pre-test likelihood of CAD.

In the first cohort, 33 patients 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 16-48 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 patients 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%.

Phase 3 Study BMS747158-301 was an open-label, international multicentre study for the assessment of CAD using Flurpiridaz (^{18}F) Injection PET MPI compared with SPECT MPI in patients with suspected or known CAD who were referred for ICA. Patients 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 catheterisation or a documented history of MI.

A total of 795 received ≥1 dose of Flurpiridaz (^{18}F) Injection (the safety population), and 764 patients completed the trial. The modified intent-to-treat (MITT) population comprised the 755 patients 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 patients 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 patients 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 patient 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 ($P \leq .001$). 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 patient 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%.

5 STUDY OBJECTIVES AND PURPOSE

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

Primary Objective

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

Secondary Objectives

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

Exploratory Objectives

[redacted]

[redacted]

6 STUDY DESIGN

6.1 Overall Study Design and Plan

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

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

The procedure order will not be randomised but will be dependent upon the presentation of the patient at the site; however, in all cases SPECT and Flurpiridaz (^{18}F) PET MPI must be performed within 60 days prior to ICA. Included in these 60 days are clinically indicated SPECT exams that may precede screening, which otherwise meet all study-specific imaging and stress testing (Section 9.3) criteria (hereby called "Off-study" SPECT exams) (see Study Diagram, Figure 1).

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

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

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

Patients can be considered for enrolment if:

- They are being scheduled via written documentation at the time of enrolment to undergo ICA, and
- They have undergone a clinically indicated SPECT study which meets all study-specified imaging and stress testing (Section 9.3) criteria, or are willing to undergo SPECT MPI for the purposes of the clinical study.

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

Study Population:

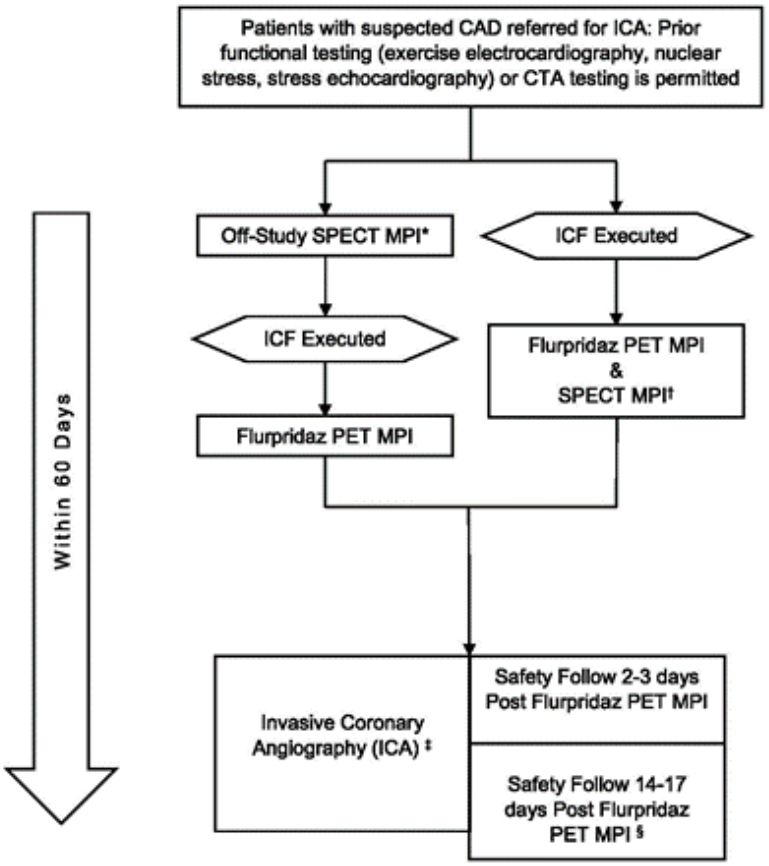
Five hundred and fifty-two (552) evaluable subjects will be enrolled in this study. Assuming a 15% dropout rate, 650 subjects will need to be enrolled initially.

While enrolment will not be formally stratified, enrolment will be monitored and the recruitment plan may be adjusted during the course of the study to ensure adequate representation of subjects aged ≥65 years of age and that at least one third of the enrolled

subjects will be diabetic, one third but no more than one half will have BMI ≥30 kg/m^2, and one third will be women.

An overview of study procedures is presented in Figure 1.

Figure 1 Study Diagram



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

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

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

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

6.2 Study Rationale

PET MPI may be particularly beneficial for patients whose SPECT MPI images are likely to be degraded by artefacts due to photon attenuation by soft tissue. This includes women, whose SPECT MPI images can be degraded by breast shadow artefacts, and obese patients. CAD remains one of the most important causes of morbidity and mortality among women [Mosca 2007]. Although overall cardiac mortality has declined on average 3% per year, with rates in men having decreased substantially, little change has been reported in women [Mieres 2005]. Even though women reportedly have a lower frequency of clinically significant CAD (>70% stenosis in 1 or more coronary arteries; adjusted odds ratio for women vs men, 0.34; *P*<.0001) and a lower rate of sudden cardiac death from coronary events (37% for women vs 56% for men), the prevalence of angina and mortality associated with ischaemic heart disease is higher in women than in men. Mortality 1 year after MI remains greater than 1 in 5 for women [Benjamin et al 2017]. Emerging evidence suggests that coronary microvascular disease, with or without obstructive CAD, contributes to the pathophysiology of ischaemic disease in women [Tailor et al 2017]. In women, attenuation of the SPECT MPI signal by breast tissue can create artefacts that can be mistaken for a fixed or reversible perfusion defect, thus leading to decreased specificity of SPECT MPI. Given inherent attenuation correction with PET MPI, Flurpiridaz (^{18}F) PET imaging may offer improved diagnostic accuracy when compared to SPECT MPI.

PET MPI may also be less subject than SPECT MPI to obesity-related signal attenuation. The prevalence of obesity has been increasing markedly over the past several decades, with more than 78 million adults in the United States (~35% of the adult population) being assessed as obese in 2009-2010. Once considered a problem only in high-income nations, the obesity epidemic is now global, with a dramatic rise in low- and middle-income countries, particularly in urban settings, even replacing more traditional problems such as undernutrition. Obesity is associated with numerous comorbidities such as cardiovascular diseases, type 2 diabetes, hypertension, the metabolic syndrome, heart failure with preserved ejection fraction, non-alcoholic steatohepatitis, certain cancers, and sleep apnoea/sleep-disordered breathing.

Obesity is an independent risk factor for cardiovascular disease and cardiac mortality [Jensen et al 2014]. As obesity is a major risk factor for cardiovascular disease, assessing ischemia in obese patients is clinically important. The cardiovascular clinical evaluation of obese patients is limited by several factors: rest ECG is influenced by adipose tissue and stress ECG by an impaired maximal exercise testing capacity. Imaging modalities may therefore be of interest in the evaluation of ischemia for obese patients. SPECT is frequently suboptimal, with artefactual myocardial perfusion defects resulting from the marked photon attenuation by soft tissue [DePuey 1994] [DePuey and Garcia 1989], even with more recent equipment such as cadmium-zinc-telluride cameras [Fiechter et al 2012].

Since the Framingham study report, an increased burden of CVD has been observed in patients with type 2 diabetes. The increase in the risk of CVD and mortality from diabetes represents an important decrease in life expectancy and in CVD-free life expectancy, given that diabetes is still associated with approximately an overall 2- to 3-fold increased risk of CVD mortality. On top of that, the prevalence of obesity has been reported to be dramatically higher among individuals with diabetes than among those without diabetes [Fox et al 2004]. When diabetic

patients are compared with patients with other medical conditions, the diabetic patients' first ischaemic events are more frequently silent and more likely to involve the small vessels, as opposed to large vessels. These findings highlight the need for high sensitivity, to accurately detect ischaemic lesions at an early stage, to improve secondary prevention.

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits a comparison of the safety variables in each subject at Baseline and after administration of investigational medicinal product (IMP).
- The design of the safety plan allows a comparison of this study's safety data set with those from other related studies.
- Consideration of a 2-week safety monitoring follow-up 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 proposed trial will last from [redacted].

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

6.4 Risks and Benefits to Subjects

A total of 1003 patients have received Flurpiridaz (^{18}F) Injection in Phase I through Phase III clinical studies: BMS-747158-101, BMS-747158-102, BMS-747158-103, BMS-747158-201, and BMS-747158-301.

In 3 Phase I clinical studies of healthy volunteers, there were no adverse events related to Flurpiridaz (^{18}F) Injection. In the most recent study (BMS-747158-201), 2 separate groups of patients (Cohort 1 [n=33] and Cohort 2 [n=143]) with known or suspected CAD were studied while having a stress test. Five patients (2 in Cohort 1 and 3 in Cohort 2) reported a total of 10 AEs; none of these adverse events were reported by another study patient, 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%), diarrhoea (1; 0.6%), nausea (1; 0.6%), electrocardiogram 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 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 treatment-emergent AEs (TEAEs). In 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%) patients experienced TEAEs deemed to be related to Flurpiridaz (^{18}F) Injection. Of these, 41 (5.2%) were subcategorised 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%), diarrhoea (0.5%), dyspnoea (0.5%), flushing (0.5%), and nausea (0.5%).

Therefore, we do not expect a significant risk for the subjects enrolled in the present Phase 3 study. The risk is mainly related to the need to induce a stress for increasing the myocardial blood flow to detect reversible or non-reversible perfusion defects. The expected diagnostic potential of Flurpiridaz (^{18}F) Injection should offset this limited risk by offering the opportunity for improving the detection of ischaemic 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.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrolment

Patients will be considered for enrolment if they have been scheduled via written documentation provided by a cardiologist to undergo an ICA for the assessment of CAD because of medical history and/or symptoms calling for this assessment.

The population will include patients with intermediate and high pre-test probability of CAD, reflecting the spectrum of patients who would be expected to undergo nuclear imaging tests. However, enrolment will not be based on pre-test likelihood of CAD. 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 enrolment is permitted. Recent intracoronary angiography (within the last 6 months) prior to enrolment is not permitted.

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 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 (including clinically indicated SPECT studies occurring prior to the signing of the ICF as stipulated in inclusion criteria #4).

3) At the time of enrolment, the subject has been scheduled via written documentation to undergo an ICA for the assessment of CAD.

4) The subject has undergone a clinically indicated SPECT which meets all study-specific imaging and stress testing (Section 9.3) criteria and conforms to local guidelines (such as American Society of Nuclear Cardiology or European Association of Nuclear Medicine), OR the patient is willing to undergo SPECT MPI for the purposes of the clinical study.

5) 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); enrolment in the study without a pregnancy test at screening is allowed for these categories of female patients. 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 radiopharmaceutical administration) must be negative; these subjects must be practicing appropriate birth control from the time of the screening to 30 days after the radiopharmaceutical administration.

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

7.3 Exclusion Criteria

Patients who meet the following criteria will be excluded from the study:

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

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

3) Patients who have an established diagnosis of CAD as confirmed by any of the following:

   a. Previous myocardial infarction (MI);

   b. Previous cardiac catheter angiography showing ≥50% stenosis;

   c. Previous coronary revascularisation, such as percutaneous coronary intervention (PCI), thrombolysis or coronary artery bypass graft (CABG) placement.

4) Patients incapable of undergoing either exercise or pharmacological cardiac stress testing.

5) Patients who have a current illness or pathology that, in the opinion of the investigator, would pose a significant safety risk for the patient during cardiac stress testing.

6) For patients for whom pharmacological stress testing is being considered, the following additional exclusion criteria will apply:

   a. Known hypersensitivity to adenosine, regadenoson, dipyridamole, or aminophylline;

   b. Use of a caffeinated substance, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to vasodilator administration;

   c. Bronchoconstrictive or bronchospastic disease that, in the opinion of the investigator, poses a significant safety risk for the patient;

   d. Second- or third-degree atrioventricular block or sinus node dysfunction without functioning artificial pacemaker;

   e. Any additional contraindication to the pharmacological stress agent listed in the product's package insert/summary of product characteristics (SmPCs).

7) Patients with unstable cardiovascular condition, including but not limited to:

   a. Unstable angina, acute coronary syndrome within 6 months of enrolment;

b. Transient ischaemic attack/stroke within 3 months of enrolment;

c. Significant congenital heart disease;

d. Uncontrolled hypertension;

e. Uncontrolled tachyarrhythmia leading to symptoms or haemodynamic compromise.

8) Documented history of heart failure and/or cardiomyopathy (including nonischaemic cardiomyopathy, hypertrophic obstructive cardiomyopathy, or infiltrative cardiomyopathy).

9) Primary haemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant.

10) Patients scheduled for or planning to undergo any cardiac interventional procedures between enrolment and ICA.

11) Patients 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).

12) Patients 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 patients whom the investigator judges to be unsuitable for participation in the study for any reason.

13) Patients undergoing evaluation for heart transplantation or with history of heart transplantation.

14) Patients enrolled in another clinical study within the 30 days prior to being enrolled in this study or scheduled to participate in another clinical study during the 17-day follow-up period of this study.

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

7.3.1 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, adverse events (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 the IMP(s), 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 once the subject has received ≥1 Flurpiridaz (^{18}F) Injection.

The reason for withdrawal must be noted in the case report form (CRF). If the reason for withdrawal is an 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 for AEs and SAEs for approximately 2 weeks (14 to 17 days) following the last Flurpiridaz (^{18}F) Injection dose administration.

Withdrawn subjects will not be replaced.

7.3.2 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 centre at which no patients have been enrolled within 3 months of initiation or in case of safety concerns or major protocol violations.

8 TREATMENT OF SUBJECTS

8.1 Description of Medicinal Products

8.1.1 Investigational Medicinal Product: Flurpiridaz (^{18}F) Injection

Flurpiridaz (^{18}F) Injection, the IMP in this study, is a novel PET MPI agent labelled with the radioisotope fluorine-18. Flurpiridaz (^{18}F) 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 in a large peripheral vein: 1 at rest and 1 during stress. The dosages of Flurpiridaz (^{18}F) Injection administered at rest and during stress conditions will not exceed a total of 14 mCi (520 MBq) for an individual subject.

- **Appearance**: Clear, colourless, and free of visible particulate matter
- **Strength/concentration:** [^{18}F]Flurpiridaz ≥70 mCi in a nominal volume of 10 mL
- **Storage and handling conditions:** Flurpiridaz is stable upon storage at 15°C to 25°C up to a maximum of 12 hours. The exact expiry time of each dose will be included on the label.

8.1.2 Other Medicinal Products (Non-IMP)

8.1.2.1 SPECT Agents

SPECT imaging must use ^{99m}Tc-based myocardial tracers, e.g., [^{99m}Tc]tetrofosmin or [^{99m}Tc]sestamibi. SPECT agents utilised for the purposes of this clinical study will be administered as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards, where applicable, and recorded in the subject's CRF.

8.1.2.2 Pharmacological Stress Agents

The Flurpiridaz (^{18}F) Injection PET MPI study must use the same stress type (pharmacological or exercise) as used for SPECT MPI in the same subject. Also, if pharmacological stress is used, the same agent and the same dose of pharmacological stress agent should be used for both types of studies in the same subject and recorded.

Pharmacologic stress agents will be restricted to the following 3 agents, as permitted by local marketing authorisations and availability: adenosine, dipyridamole, and regadenoson. Instructions regarding their administration are available in their respective Package Inserts.

Pharmacological stress agents utilised for the purposes of this clinical study will be administered as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards and drug labelling as per package insert; the administration will be through an IV line. During pharmacologic stress, the radiopharmaceutical will be administered during the peak vasodilatory effect according to the respective Package Insert (if applicable) of each stressor. If a pharmacologic stress is performed using adenosine, the Flurpiridaz (^{18}F) Injection and the adenosine must be administered via separate lines or via separate ports on the same IV line.

8.1.3 Medicinal Product Accountability

Each investigator is responsible for ensuring that deliveries of IMP, other medicinal products (specified above), 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 containers (opened, unopened, or empty) must be destroyed on site after its scheduled use in accordance with site policies. See IMP handling procedures 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.

8.1.4 Registration of Investigational Medicinal Product(s) Complaints

In the event of an IMP complaint (e.g., breakage, leakage, particulate matter, discoloration), 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). This should be promptly forwarded to the person indicated on the shipping documentation. Once the complaint is received, the Clinical Supplies Manager will register the complaint and determine, per Sponsor procedures, if the complaint is minor or significant. All complaints will be followed up and the appropriate action will be implemented, per Sponsor procedures.

8.2 Method of Numbering Subjects and Assigning Subjects to Treatment Groups

Each subject will be given a unique identification number. The identification number will be assigned to the subject during the Screening Visit, after the informed consent document has been signed and dated. Once an identification number has been assigned, it cannot be reassigned, even if the subject is deemed ineligible or withdraws consent. 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 to discuss the subject's eligibility.

Each subject's identification number will consist of a 3-digit site code plus a 4-digit consecutive number. For example, site "999" will assign the number "999-0001" to its first subject, "999-0002" to its second subject, and so on. To preserve the integrity of the study, it is crucial that these numbers be assigned in consecutive numerical order.

All subjects will receive the same treatment. Therefore, there will be no assignment to treatment groups.

8.3 Selection of Doses and Timing

Duration of Study

All screening assessments will occur within 60 days prior to ICA. Flurpiridaz (^{18}F) Injection PET MPI test and SPECT MPI (including SPECT exams preceding informed consent) must precede the ICA and occur within 60 days prior to the ICA. Subjects will have Flurpiridaz (^{18}F) Injection rest and stress PET MPI performed on the same day (dose specified in Section 9.4). Subjects will have their last follow-up safety contact at approximately 2 weeks (14 to 17 days) following Flurpiridaz (^{18}F) Injection or at the time of their ICA, whichever occurs later.

8.4 Blinding

This is a Phase 3, open-label study.

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

8.5 Prior and Concurrent Medications

Any medications taken by the subject within 12 hours before the screening (or 12 hours before the SPECT stress test if the SPECT stress tests precede screening) at the time of ICA and up to study completion will be recorded in the CRF, along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/contract research organisation (CRO)

will encode all therapy and medication per a current well-recognised dictionary of medical codes.

8.6 Contraception and Pregnancy Avoidance Procedure

Women of childbearing potential who are sexually active with a non-sterilized male partner and males who are sexually active with a partner of childbearing potential must use adequate contraception from Screening until 30 days after the Flurpiridaz (^{18}F) Injection. A woman NOT of childbearing potential is defined as surgically sterile (has a documented bilateral tubal ligation or oophorectomy and/or documented hysterectomy) or postmenopausal (cessation of menses for more than 1 year).

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate based on those methods identified in the Clinical Trial Facilitation Group (CTFG) document for clarification of effective contraception [CTFG Guidance 2014]. Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device[2]
- intrauterine hormone-releasing system[2]
- bilateral tubal occlusion[2]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of CTFG guidance are considered to have low user dependency.

- vasectomized partner[2,3]
- sexual abstinence[4]

Patients will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of childbearing 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 Sections 9.4 and 13.4, and Table 2).

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of CTFG guidance, sexual abstinence is considered a highly effective method only if defined as refraining 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.

9 STUDY PROCEDURES

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

Table 1 Study Schedule of Events

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

Table 1 Study Schedule of Events

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

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

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

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

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

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

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

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

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

h If any neurologic abnormalities are noted during physical examination.

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

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

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

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

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

9.1 Screening Visit

All screening assessments will occur within 30 days prior to Baseline Visit. The Screening and Baseline Visits can be combined with the SPECT MPI Visit. The investigator must be mindful of the 60-day window between screening and ICA procedures. The following will be done during the screening period:

- Signed and dated ICF must be obtained from all subjects prior to their entering the study. Study informed consent must be obtained from each subject prior to the initiation of any study-related procedures. Rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., "off-study" SPECT) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study.
- 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 (ESC) guidelines on the management of stable CAD [Montalescot et al 2013] (see Appendix 15.4). In addition, a Seattle Angina Questionnaire [Spertus et al 1995] (see Appendix 15.5) will be administered.
- Prior and concurrent medications.
- Demographic information will be recorded.
- Blood and urine samples will be collected for assessing haematology, abnormal glucose metabolism, liver and renal insufficiency. If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above).
- All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.
- 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 Flurpiridaz (^{18}F) Injection) must be negative; these subjects must be instructed to practice appropriate birth control from time of the screening to 30 days after the 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).
- 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).

- For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to PET and SPECT stress test.

- All AEs and SAEs that occur after informed consent will be recorded (see Table 1 for scheduled AE query points in time, and Sections 10.2.6, 10.2.7, and 10.2.8).

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 Baseline Visit (≤30 Days After Screening)

The Baseline Visit will take place between Screening and either of the SPECT or Flurpiridaz PET MPI imaging visits. The Baseline Visit can be combined with the Screening and SPECT MPI imaging visit. Investigators must be mindful of the maximum 60-day window between Screening or "off-study" SPECT and ICA.

At the Baseline Visit, the following will be performed:

- Physical examination will comprise a full examination with a specific focus on neurological and cardiovascular signs.

- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed.

- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]).

- Concurrent medications will be recorded.

- Vital signs will be recorded during the Baseline Visit. If the Baseline Visit is combined with the Rest and Stress SPECT MPI Visit, vital signs should be recorded up to 20 minutes before administration of the rest dose.

- Pulse oximetry will be recorded.

- AEs and SAEs will be recorded.

9.3 Rest and Stress SPECT MPI Visit

The Rest and Stress SPECT MPI Visit can be combined with the Screening or Baseline Visit. Results of rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., an "off-study" SPECT MPI) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already

been validated for use in the study. The "off-study" SPECT MPI must also achieve the minimal quality standard specified by the imaging core lab (ICL) in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study. Depending on the institution's standard practices, the rest and stress SPECT MPI procedures can take place on the same day or on 2 days (either consecutive or non-consecutive). The Rest and Stress SPECT MPI Visit may take place before or after the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit. The investigator must be mindful of the 60-day window between SPECT MPI and ICA procedures.

Subjects who are scheduled to undergo a pharmacologic stress test must not drink or eat caffeinated substances or take any dipyridamole-containing medication or methylxanthine-containing medication within 12 hours prior to vasodilator administration for SPECT MPI. In addition, it is recommended that patients who are scheduled to undergo exercise stress refrain from consuming any caffeinated substances, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to the exercise stress test, to allow for the use of a pharmacologic stressor in the event that the subject does not reach the protocol-required minimum 85% of age-predicted maximum heart rate (APMHR) or does not develop ischaemic symptoms during the exercise stress.

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to the SPECT MPI

If the SPECT MPI Visit is combined with the Screening or Baseline Visits, all of the following elements that were scheduled for the Screening or Baseline Visit will be performed during the SPECT MPI Visit:

- Informed consent will be obtained (Screening).
- Entry criteria will be evaluated and recorded (Screening).
- Medical/surgical history will be recorded (Screening).
- 12-lead ECG recording will be performed (Screening Visit). (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).
- Blood samples for laboratory testing will be collected. If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above) (Screening).

- Urine samples for laboratory testing will be collected (Screening).
- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]; Screening/Baseline).
- Demographic information will be recorded (Screening).
- Concurrent medications will be recorded (Baseline Visit).
- Vital signs will be recorded (Baseline Visit). If the Baseline Visit is combined with the Rest and Stress SPECT MPI Visit, vital signs should be recorded up to 20 minutes before administration of the rest dose.
- Pulse oximetry will be recorded (Baseline Visit).
- A physical examination will be performed (Baseline Visit).
- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed (Baseline Visit).

At the Rest and Stress SPECT MPI Visit, the following will be performed for all subjects:

- Concurrent medications will be recorded.
- Vital signs will be recorded. For rest SPECT-MPI, vital signs will be collected up to 20 minutes prior to dose and 30 (±5) minutes post-dose. For stress SPECT-MPI, vital signs will be collected up to 20 minutes prior to dose (if >60 minutes between rest and stress injections) and 30 (±5) minutes post-dose.
- Pulse oximetry will be recorded.
- Rest SPECT MPI will be performed, per the as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.
- After the rest SPECT MPI, stress SPECT MPI will be performed, per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.
    - If the subject has already undergone stress Flurpiridaz (^{18}F) PET MPI, the same type of stress (pharmacologic or exercise) should be used in the stress SPECT MPI, including the same dose of the same pharmacologic stressor, unless otherwise clinically indicated. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.

- If the subject has already undergone exercise stress Flurpiridaz (^{18}F) PET MPI, the same exercise protocol should be used for the stress SPECT MPI, unless otherwise clinically indicated.

- During exercise stress, the radiopharmaceutical for SPECT should be administered during peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.

- The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association (AHA) [Myers et al 2009]

- AEs and SAEs will be recorded.

- The images acquired during these procedures will be stored for the secondary blinded review, as specified in the Imaging Manual.

9.4 Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit

The Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit may take place before or after the Rest and Stress SPECT MPI Visit.

Subjects who are scheduled for pharmacologic stress must not drink or eat caffeinated substances or take dipyridamole-containing medication or methylxanthine-containing medication within 12 hours prior to vasodilator administration for Flurpiridaz (^{18}F) PET MPI. In addition, it is recommended that patients who are scheduled to undergo exercise stress refrain from consuming any caffeinated substances, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to the exercise stress test, to allow for the use of a pharmacologic stressor in the event that the patient does not reach the protocol-required minimum 85% of APMHR or does not develop ischaemic symptoms.

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to

the PET MPI. A focused clinical screen for new or worsening symptoms indicative of unstable coronary artery disease will be conducted prior to performing any procedures at the Flurpiridaz (^{18}F) PET visit. If the clinical status screening is positive, the Flurpiridaz (^{18}F) PET visit can either be rescheduled (up to 1 time) after symptoms stabilize or the subject can be discontinued from the study.

During the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit, the following will be performed:

- Blood samples for laboratory testing will be collected prior to the PET MPI and 1 hour after the last PET-MPI injection. If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above).

- 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]).

- Concurrent medications will be recorded.

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

- Pulse oximetry will be recorded.

- Eight 12-lead ECG recordings will be performed (See Section 10.2.3).

- A physical examination will be performed.

- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed.

- During the rest test, all subjects will receive an IV bolus injection of Flurpiridaz (^{18}F) Injection in a large peripheral vein. The dose (volume and radioactivity) will be recorded in the CRF.

- A stress test (exercise or pharmacologic) will be performed after the rest test, and on the same day.

    - The type of stress (exercise or pharmacologic) will be the same type used for that subject for the SPECT MPI test.

- For subjects who received a pharmacologic stressor during the stress SPECT MPI, the same agent and dose will be used during the stress Flurpiridaz (^{18}F) PET-MPI test. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.

    - If adenosine is used as a pharmacologic stressor, the Flurpiridaz (^{18}F) Injection and the adenosine must be administered through separate lines or through separate ports of the same IV line. Note: Central lines should NOT be used for the administration of Flurpiridaz (^{18}F) Injection. The Flurpiridaz (^{18}F) Injection will be administered after the administration of the pharmacologic stressor. The administration of Flurpiridaz (^{18}F) Injection will be timed to coincide with maximal coronary vasodilation, which depends on the vasodilatory agent used.

- For a subject who underwent exercise stress for SPECT MPI, the investigator is required to use the same exercise stress protocol for the Flurpiridaz (^{18}F) Injection PET that was used for the SPECT MPI, unless otherwise clinically indicated.

- During exercise stress, the radiopharmaceutical for both SPECT and PET should be administered at peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.

- The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the AHA [Myers et al 2009]

- At 1 hour after administration of Flurpiridaz (^{18}F) Injection for the stress exam, a physical examination will be performed.

- If any neurologic abnormalities are noted during the physical examination, a full neurologic examination will be performed.

- Injection-site monitoring (immediately prior to the first injection, immediately after the first injection of IMP for the rest exam, then immediately after the second injection of IMP for the stress exam, and ultimately at 1 hour after the last injection of IMP).

- The images acquired during the rest and stress Flurpiridaz (^{18}F) PET MPI will be stored for the secondary blinded review.

- AEs and SAEs will be recorded.

The dose and dosing interval protocol that has been adopted is presented in Table 2.

Table 2 GE-265-303: Flurpiridaz (^{18}F) Injection Doses for Exercise and Pharmacologic Stress

	Rest	Pharmacologic Stress	Exercise Stress
Dose in the syringe at time of assay (in mCi) [a]	2.5-3.0 mCi	6.0-6.5 mCi [b]	9.0-9.5 mCi [a]
Dose in the syringe at time of assay (in MBq) [a]	95-120 MBq	230-250 MBq	340-360 MBq
Targeted dose in the body	1.7 -3.0 mCi (62.9-111 MBq)	Minimum rest:stress ratio of 1:2	Minimum rest:stress of 1:3

a The dose in the syringe at the time of assay is presented in both mCi and MBq units for the convenience of the sites. Sites will record dose measurement units (mCi or MBq) in keeping with their standard institutional practice.
b The total dose that individual subjects receive (rest plus stress) must not exceed 14 mCi (520 MBq).

Each of the PET acquisitions (rest and stress) consists of a dynamic series for quantitative analysis, with an extended final frame for semiquantitative analysis with and without cardiac gating. Full details of the image protocol are presented in the GE-265-303 PET Imaging Manual.

9.5 Safety Follow-up 2 Days (+24 hours) After Flurpiridaz (^{18}F) PET MPI

All subjects will be followed up by telephone assessments for AEs and SAEs within 2 days (+24 hours) following administration of Flurpiridaz (^{18}F) Injection. During the assessment, the following will be recorded:

- Concurrent medications

- AEs and SAEs.

9.6 Safety Follow-up 14 to 17 Days After Flurpiridaz (^{18}F) PET MPI

All subjects will be followed up by telephone assessments for AEs and SAEs within 14 to 17 days following administration of Flurpiridaz (^{18}F) Injection. During the assessment, the following will be recorded:

- Concurrent medications

- AEs and SAEs.

9.7 ICA Visit (≤60 Days of Screening)

Within 60 days after the Screening Visit or "off-study" SPECT, the subject will undergo ICA, according to the institution's standard practices. At the ICA Visit, the following will be performed:

- Concurrent medications will be recorded.
- Preprocedure vital signs will be recorded (from the clinical record).
- Preprocedure pulse oximetry will be recorded (from the clinical record).
- Events since PET MPI acquisition (and prior to the ICA visit) will be recorded.
- Coronary angiography will be performed in accordance with investigational site institutional practice. The site will communicate imaging parameters via a Data Transmission Form sent with each set of images to the ICA Core Laboratory; in these communications, the site will follow the Angiography Imaging Guidelines and Transmission Procedures for GE-265-303. Ventriculograms, when performed for clinical reasons, will also be included. Doppler flow or pressure-wire measurements or intravascular ultrasound (IVUS) may also be performed at the time of the ICA. If a Doppler flow or pressure wire is used, the measurements will be collected on the electronic case report form (eCRF).
- AEs and SAEs will be recorded.

See Section 10.2 and the Study Schedule of Events Table (Table 1) for further details.

9.8 Clinical Pharmacology

Selected sites may participate in a separate substudy focused on obtaining pharmacokinetic and/or pharmacodynamic data that will assess the role of potential adjustments of the dose of Flurpiridaz (^{18}F) Injection for subsets of patients, including those with atypical demographic characteristics.

10 EFFICACY AND SAFETY

10.1 Efficacy Assessments

10.1.1 Primary Efficacy Endpoints

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

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

10.1.2 Secondary Efficacy Endpoints

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

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

10.1.3 Exploratory Efficacy Endpoints

[redacted]

[redacted]

10.1.4 Image Acquisition

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

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

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

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

Doppler flow or pressure-wire measurements and/or IVUS may also be performed at the time of the ICA. If a Doppler flow or pressure wire is used, the measurements will be collected on the electronic CRF (eCRF).

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

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

10.1.5 Image Interpretation and Correlation with Standard of Truth

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

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

10.2 Safety Assessments

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

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

- Clinical laboratory parameters: serum biochemistry, haematology, and urinalysis (Table 3)
- Vital signs: systolic/diastolic blood pressure, heart rate, pulse oximetry, and intermittent respiration rate and body temperature
- Continuous ECG monitoring
- Lead II rhythm strip and 12-lead ECG
- Physical examination
- Injection site monitoring
- Post-treatment events (AEs and SAEs)

Prespecified 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 3.

Table 3 Clinical Laboratory Parameters

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

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

Blood samples will be obtained for assessment of serum biochemistry and haematology 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 analysed at a central laboratory (for parameters, see Table 3). 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 analysed 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 various pre-treatment time point ranges described in Table 1. The time of void will be documented on the CRF. Urine voided will be analysed for parameters listed in Table 3. 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. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition (e.g., ordering a WBC differential to help characterise a high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit).

10.2.2 Vital Signs

Vital signs (pulse oximetry, blood pressure, heart rate, respiratory rate, temperature) will be monitored at Baseline (prior to IMP administration) and during the in- and out-patient follow-up periods, 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 contralateral to the site of IMP administration whenever possible.

10.2.3 Electrocardiograms

A standard 12-lead ECG will be obtained at Screening and during Flurpiridaz (^{18}F) MPI rest imaging. The Screening ECG can be obtained on any local ECG machine and will be interpreted by the investigator or a designee at the investigative site. 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 eCRF but not submitted to the ECG Core Laboratory for analysis.

Before the administration of the Flurpiridaz (^{18}F) Injection for the rest examination, three 12-lead ECGs, separated by at least 5 minutes, will be obtained with equipment provided by the ECG Core Laboratory. ECG clocks should be synchronised with imaging equipment. Note: pre-dose ECGs should be obtained within 20 minutes before the transmission scan, and the patient should rest for 5 minutes prior to the first measurement. Three additional ECGs (each separated by 30-60 seconds) will be obtained starting at 2 minutes (± 30-60 seconds) after the administration of the Flurpiridaz (^{18}F) injection for the rest examination. Single ECGs will also be obtained at 10 and 30 minutes post injection. These 8 ECGs will be submitted to the ECG Core Laboratory for analysis. The investigator will be asked to provide a determination of clinical significance on the eCRF only for the 3 ECGs obtained at 2, 10, and 30 minutes after injection of Flurpiridaz (^{18}F). If the investigator determines that there are any clinically significant changes from the 3 ECGs obtained before Flurpiridaz (^{18}F) injection, those changes will be reported as AEs.

No additional ECGs are required for this study. However, sites should perform stress testing with ECG monitoring as required by the site's institutional standards for stress testing. ECGs acquired in association with the stress test will not be collected by the Sponsor unless one or more become relevant to a reported TEAE. Reports generated during stress testing, including ECG analysis and interpretation, will be collected by the Sponsor.

10.2.3.1 Investigational Site Responsibilities

Each 12-lead ECG will be evaluated at US sites by a board-certified cardiologist or advanced cardiac life support (ACLS)-certified licensed physician. Each 12-lead ECG will be evaluated at European sites by a cardiologist. 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. During continuous ECG monitoring, the investigator or

appropriate delegate (concordant with local practice) will observe the real-time ECG findings and take note of any changes in intervals and/or waveforms. The continuous ECG monitoring need not be 12-lead.

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 will not be expected to calculate QTc intervals.

10.2.3.2 ECG Core Laboratory Responsibilities

The ECG data from all time points will be electronically transferred and independently read at an ECG core laboratory by a board-certified cardiologist or an internist who will measure the QTc interval. The core ECG laboratory cardiologist will review, interpret, and provide a written assessment of the ECGs, determining all intervals (e.g., PR, QRS, QT, and RR) and wave changes and calculating QTc intervals. The reports will be signed and dated. These data will be transmitted electronically directly to the Sponsor/CRO.

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 baseline time point, before the Flurpiridaz (^{18}F) Injection rest MPI exam and 1 hour after the Flurpiridaz (^{18}F) Injection stress MPI exam. 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 full neurological exam will be performed if neurologic abnormalities are observed during the physical neurological examination. It will include recording an assessment for the presence of abnormalities of the following: level of consciousness, motor function, sensory function, proprioception/position sense of extremities, reflexes (biceps, triceps, patellar, ankle), mood and affect, cognitive function, cerebellar, speech, orientation, memory, and gait.

In the event that *new* abnormal physical findings and *worsening* abnormal physical findings are encountered during the study, these terms are defined as follows: a new abnormal physical finding is defined as one that occurs when a subject's normal baseline physical examination becomes abnormal post-baseline. A worsening abnormal physical finding is defined as one that occurs when a subject's abnormal baseline physical examination becomes worse post-baseline. These new findings will be recorded as AEs.

10.2.5 Injection Site Monitoring

The injection site will be evaluated at the following time points: immediately prior to first injection of IMP, immediately after the first injection of IMP (for the rest exam) then

immediately after the second injection of IMP (for stress exam) and ultimately at 1 hour after the last injection.

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

10.2.6 Adverse Events

All AEs/SAEs that occur after informed consent shall be recorded in the AE/SAE report form (see the Study Schedule of Events, Table 1).

Study personnel must remain vigilant for the occurrence of AEs after administration of IMP (see Section 8.1), 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.

AE and TEAE Definition: An AE is defined as any untoward medical occurrence or an already present event that worsens either in intensity or frequency. A treatment-emergent adverse event (TEAE) is defined as an AE that starts on or after the time of the first injection of Flurpiridaz until the follow-up visit 14-17 days later. The TEAE does not necessarily have to have a causal relationship with exposure to the investigational agent. A TEAE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to the IMP, whether or not considered related to that product.

The 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 with non-leading questioning (e.g., “How do you feel?”). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Both the investigator(s) and Sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

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

Laboratory AE Evaluation

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the subject. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject’s condition (e.g., ordering a WBC differential to help characterise a

high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit); see also Section 10.2.8 (Other Significant Adverse Events).

10.2.7 Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that:

- Results in death.
- Is life threatening (requires that, in the view of either the investigator or Sponsor, the adverse event occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death).
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

*Other important medical events are those that may not result in death, be life threatening, or require hospitalisation, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical intervention to prevent one of the outcomes listed above.

For this Study, it is expected that the following may occur:

- Observations and findings (previously unknown) discovered during the ICA, and medically assessed as most likely pre-existing (e.g., coronary artery occlusions).
- Hospitalisations for greater than 24 hours for the ICA (without an AE) may be necessary for other reasons (non-AE) e.g., patient-convenience.
- Hospitalisations for post-ICA interventions deemed necessary following the ICA (without an AE) may occur (e.g., patient kept in hospital to undergo CABG for pre-existing coronary artery occlusions discovered during ICA).

For this study, these types of hospitalisations and/or imaging findings will not be considered AEs or SAEs and will not be reported as such in the CRFs.

10.2.8 Other Significant Adverse Events

Clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of

IMP, dose reduction or significant additional concomitant therapy), other than those reported as SAEs, will be reported and evaluated as other significant AEs.

10.2.9 Adverse Event and Serious Adverse Event Reporting

All AEs/SAEs shall be recorded in the AE/SAE report form using acceptable diagnoses, if possible. 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 myocardial infarction (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.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the IMP or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the Sponsor/CRO according to a well-recognised dictionary of medical codes, e.g., Medical Dictionary for Regulatory Activities (MedDRA).

All AEs/SAEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

Study centres are instructed to report all SAEs, together with a causality assessment, to the Sponsor (or a service provider/CRO acting on behalf of the Sponsor) within 24 hours. AEs and SAEs are reported in the AE form of the eCRF. Detailed information about management of AE information will be provided, e.g., in a Safety Management Plan.

Safety information from SAE reports will be submitted to local health authorities, IECs or IRBs and investigators as required by local regulations and applicable SOPs.

For any protocol or safety-related questions please contact the Medical Director:

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

Subjects enrolled at sites in the European Union will be provided with a Clinical Trial Participant card at the time of IMP administration. This card will list contact details for the investigator and for GE Healthcare medical emergency cover services (Clinical Trial Emergency Contact Service [CTECS]). The CTECS provides 24-hour, 7-day-a-week emergency cover service for Healthcare professionals to seek advice on trial–related medical questions or problems should a medical emergency arise and the investigator is not available.

10.2.10 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 trial subjects without prior IEC/IRB approval/favourable opinion.

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial 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.

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 IEC/IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the Sponsor/CRO by using the contact details listed in Section 10.2.9 within 24 hours of having to take such a measure(s). 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.

10.2.11 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or foetuses 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.

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.

When a trial subject reports a pregnancy (post-IMP administration) to the investigator, a pregnancy test should be arranged for the trial subject (or their partner) by the investigator within 7 days of the pregnancy being reported.

The investigator must inform the Sponsor/CRO within 24 hours of receiving positive pregnancy test results by using either a copy of the relevant CRF pages (demography, exposure to medicinal products, and/or AE) or via email. The investigator should include an estimated date of conception when communicating with the Sponsor/CRO.

10.3 Other Variables

10.3.1 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 enrolment will be calculated from the date of birth and the date of baseline. 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 eCRF or a partial date will be used in accordance with local practice.

10.3.2 Medical and Surgical History

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

10.3.3 Prior and Concurrent Medication

Any medications taken by the subject within 12 hours before the screening or the SPECT stress test if it precedes screening, at the time of ICA and up to study completion will be 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-recognised dictionary of medical codes.

10.4 Appropriateness of Measurements

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

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For electronic CRFs (eCRFs), 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 reason for the change, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

11.2 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.

11.3 Archiving

All study documentation at the investigator site and Sponsor site will be archived in accordance with ICH E6- GCP and the Sponsor/CRO's quality standards and SOPs.

All study documentation at the Investigator site and Sponsor site will be archived 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 analysed 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 centres in this protocol will be combined so that an adequate number of subjects will be available for analysis. The data will be summarised 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 with 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. The planning and reporting of statistical analysis will be carried out as described in the Sponsor/CRO's SOPs governing clinical studies. Further details of the criteria and conduct of the statistical analyses will be included in the Statistical Analysis Plan for this study.

12.2 Populations for Analysis

12.2.1 Intent-to-Treat Population

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

12.2.2 Modified Intent-to-Treat (MITT) Population

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

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

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

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

12.2.4 Determination of Safety Population

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

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, SMITT).
- 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 summarised by using descriptive statistics. Sex, ethnicity, and race will be summarised by counts and percentages.

Medical histories will be summarised by counts and percentages. Concurrent 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 and during stress conditions will be summarised by volume and radioactivity administered.

Any other medications taken by the subject within 12 hours before and up to study completion 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 and SPECT MPI reads will be performed by the same set of

readers in cross-over sessions independent of one another. In each session, PET and SPECT images will be displayed in a randomised order, nonsequentially, with PET and SPECT MPI exams corresponding to individual subjects randomly allotted into reading session batches. For each modality, perfusion and gated acquisitions of rest and stress images will be rated for image quality and reviewed. After the results of each individual MPI (PET or SPECT) are locked as the "blinded" read, then clinical information will be provided. The reader will then be given the opportunity to submit a revised assessment of the existence of any perfusion defects as an "unblinded" read.

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

12.5.1.2 Coronary Angiography Evaluations

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

12.5.1.3 Image Quality

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

12.5.2 Primary Efficacy Endpoints

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

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

Sensitivity and specificity are defined as follows:

- True Positives (TP): Subjects with abnormal PET MPI and disease positive by the truth standard

- True Negatives (TN): Subjects with normal PET MPI and disease negative by the truth standard

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

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

12.5.3 Statistical Hypothesis, Model, and Method of Analysis

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

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

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

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

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

Therefore, the test of hypotheses will be as follows:

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

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

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

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

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

12.5.4 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 Statistical Analysis Plan (SAP).

12.5.5 Supportive Analyses

Sensitivity analyses will be performed to assess the impact of missing data on the primary analysis results (i.e., patients in the ITT population with incomplete PET MPI scans or missing truth standard). Details will be provided in the SAP.

The summary outlined in Section 12.5.3 will be provided for each modality separately and for the following subgroups:

- Age groups (<65 years and ≥65 years)
- BMI <30 kg/m^2 and BMI ≥30 kg/m^2
- Diabetic and nondiabetic
- Sex (male and female)
- Race (White, Black or African-American, other)
- Presence or absence of multivessel CAD (per the standard of truth)
- Presence or absence of renal impairment (i.e., serum creatinine level at predose evaluation is above normal range)

- Presence or absence of hepatic impairment (i.e., either ALT or AST value at predose evaluation is above normal range)

- Type of stress test (pharmacological, exercise)

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

12.5.6 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.

12.5.7 Reader Difference

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

12.6 Secondary Analyses

12.6.1 Secondary Efficacy Variables and Analyses

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

- All subjects (key secondary endpoint)

- Female subjects

- Subjects with BMI $\geq$30 kg/m^2

- Diabetic subjects

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

12.6.1.1 Hypothesis Testing for the Key Secondary Endpoint

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

Let s_1 = sensitivity in Flurpiridaz (^{18}F) Injection PET MPI, and s_2 = sensitivity in SPECT MPI.

Let p_1 =specificity in Flurpiridaz (^{18}F) Injection PET MPI, and p_2 = specificity in SPECT MPI.

Therefore, the test of hypotheses will be as follows:

$H_{01}: s_1 - s_2 \leq 0$, $H_{02}: p_1 - p_2 \leq -0.1$

$H_{a1}: s_1 - s_2 > 0$, $H_{a2}: p_1 - p_2 > -0.1$

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

The tests of comparisons are based on paired responses, as the Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed on a within-subject basis, and the images will be read by the same readers in a cross-over design. The test of sensitivity comparison between Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a 1-sided McNemar's test at $\alpha = 0.025$. Similarly, the test of specificity noninferiority between Flurpiridaz (^{18}F) Injection PET MPI and SPECT MPI will be performed with a paired test for noninferiority [Liu et al 2002] at a 1-sided $\alpha = 0.025$. The criterion for the demonstration of diagnostic efficacy for the secondary endpoints will be meeting the tests of hypotheses for both sensitivity and specificity for the same 2 of the 3 readers for whom the null hypotheses were rejected in the analysis of the primary endpoint.

A minimal performance for SPECT in the targeted population for comparison to Flurpiridaz PET will be specified in the SAP.

12.6.1.2 Hypothesis testing for other secondary endpoints

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

12.7 Exploratory Analyses

12.7.1 Exploratory Endpoints:

[redacted]

[redacted]

[redacted]

12.8 Safety Variables and Analyses

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

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

12.8.1 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 summarised by counts and percentages:

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

- The occurrence of post-administration values outside the normal limits (Section 15.3) (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.8.2 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital-sign variable and each time point (see Table 1), the following safety endpoints will be summarised by counts and percentages by additional/other characteristics deemed necessary by study team:

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

- The occurrence of post-administration values outside the normal limits (Section 15.3). Shift tables based on the normal range will be prepared.

12.8.3 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 summarised by counts and percentages or by additional/other characteristics deemed necessary by study team:

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

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

QTc-specific analyses:

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

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

The following analyses will employ both methods of correction:

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

(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.

12.8.4 Physical Examination

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

12.8.5 Adverse Events

AEs and SAEs will be coded by using a current version of MedDRA, and all reported events will be listed for the safety population. The number and percentage of patients 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 will also be presented for the safety population.

12.9 Interim Analysis

No formal interim analyses will be performed in this study.

12.10 Sample Size Calculation

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

12.11 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.

12.12 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 and ICA reads) 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.

12.13 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, Institutional and Ethical Review

Before the start of this study, the protocol (authorised by the Sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC/IRB. The study will not start before the IEC/IRB gives written approval or a favourable opinion in accordance with ICH E6 GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorised) protocol will be initiated without the IEC's/IRB's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Sponsor will authorise and the principal investigator(s) will sign the protocol amendment prior to submission to the IEC/IRB. Protocol amendments should be submitted to the IEC/IRB without delay.

13.2 Ethical Considerations

The subject will not benefit directly from the results of the proposed study since his or her treatment is not influenced by the results of the proposed PET MPI injection. However, the existing literature on PET MPI and the results from the previous phase 3 trials tend to indicate an increased diagnostic accuracy of PET MPI over SPECT MPI, this being more obvious for certain categories of patients. The risks from the proposed PET MPI are considered minimal based on the previously reported results. Therefore, the risk/benefit is considered as acceptable from a patient perspective.

13.3 Investigator's Responsibilities

13.3.1 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 centres participating in this study that cannot comply with these standards will be documented.

13.3.2 Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated ICF before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the

study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record; and the investigator will sign and date the ICF after the subject has signed and dated the ICF. The investigator(s) will keep the original consent forms, and copies will be given to the subjects.

13.3.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorised personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorised members of IECs/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.

13.3.4 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 examinations, e.g., PET, SPECT, and ICA imaging) 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 scrutinised for the purpose of verifying data recorded in the CRF. This may be done by the monitor(s), properly authorised persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.4 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.

13.5 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.

An independent data and safety monitoring board (DSMB) will be established to monitor the safety of patients participating in this clinical study. The DSMB will provide safety assessments including, but not limited to, review of study patient demographics, vital signs, diagnostic tests, laboratory tests, and adverse events. The DSMB will conduct reviews of the safety data and will make recommendations to the Sponsor based on conclusions reached after

careful consideration of the patient safety data. Complete details concerning the DSMB are contained in a separate DSMB Charter.

13.6 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.

13.7 Financial Disclosure

The Sponsor will cover all the expenses related to the present study, and no external contribution is considered for any of the aspects described in the present protocol.

13.8 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.

13.9 Publication Policy

The investigator and/or Institution shall have the right to publish the results of their work conducted under this protocol, subject to providing the Sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission.

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[Toth et al 2014]
Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. Circ Cardiovasc Interv. 2014;7(6):751-759.

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.

GE Healthcare marketed medicinal products like Myoview (^{99m}Tc based SPECT MPI agent) and Rapiscan (a pharmacological stress agent) may be used in this trial. Reference safety information for assessment of expectedness are company core safety information, and approved SmPC or US Package Insert in the country of occurrence.

No expectedness assessment will be performed for other medicinal products.

15.2 Equipment Parameters

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

15.3 Normal Limits for Vital Signs and ECG Intervals

Table 4 Criteria for Normal Limits for Vital Signs

	Normal Limits	
Vital Signs Parameter	**Low**	**High**
Systolic BP, mm Hg	85	139
Diastolic BP, mm Hg	60	89
Heart rate, beats/min	60	100
Respiration rate, breaths/min	12	22
Body temperature	36.4°C 97.5°F	37.7°C 99.5°F
Oxygen saturation, %	93	100
Body weight, kg [a]	41	113
Body mass index (BMI), kg/m² [b]	18.5	24.9

[a] Changes in body weight are evaluated by the investigator (without taking height into account), since BMI is not collected on the CRF.

[b] BMI is calculated and analysed retrospectively by the Sponsor, at which time height is taken into account.

Table 5 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 Patients with Stable Chest Pain Symptoms

Table 6 Clinical Pre-test Probabilities in Patients with Stable Chest Pain Symptoms [Montalescot et al 2013]

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.

[a] Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.

- Groups in white boxes have a PTP <15% and hence can be managed without further testing.
- Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
- Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
- In groups in dark red boxes the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

15.5 Seattle Angina Questionnaire

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks:**

Place an X in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, **or angina** when doing your **most strenuous** activities?

I have had **chest pain**, **chest tightness**, **or angina**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, **or angina**?

I have had **chest pain**, **chest tightness**, **or angina**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain**, **chest tightness**, **or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness or angina** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, **or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, **or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, **or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the <u>past 4 weeks</u>, how much has your **chest pain**, **chest tightness**, **or angina** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, **or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I can't stop thinking or worrying about it	**I often** think or worry about it	**I occasionally** think or worry about it	**I rarely** think or worry about it	**I never** think or worry about it
☐	☐	☐	☐	☐

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

- LVEF <50% has been removed from exclusion criterion (8). The purpose of exclusion criterion 8 is to eliminate known/confirmed heart failure. The inclusion of an EF lower limit to specify which patients should be included does not address this aim. Ejection fraction defines different heart failure phenotypes (e.g. heart failure with preserved, reduced or mid-range ejection fraction) and as such is not relevant to the aim of excluding those with a heart failure diagnosis as a whole. Even if the purpose was to exclude only patients with reduced EF, the EF of 50% corresponds to 'normal' EF when echocardiography is performed but does not correspond to the appropriate value to demark normal and abnormal ejection fractions for other modalities such as SPECT.

- Clarification of follow-up period for the study.

- Clarification of medicinal products in the study and update of storage and handling conditions for Flurpiridaz (^{18}F) Injection.

- Corrections to text to ensure recording of concurrent medications to study completion.

- Removal of requirement for drug and alcohol screening. Drug and alcohol abuse screening is useful to address: (1) unique safety concerns associated with potential interactions of IMP with illicit drugs, (2) concerns regarding confounding of an efficacy signal, and (3) concerns that follow-up would be compromised given occult substance abuse.
  GE Healthcare feels that these concerns are minimal, given: (1) There are no unique concerns regarding drug / illicit drug interactions. This is particularly the case given that Flurpiridaz is administered to subjects in one sitting (as opposed to repeatedly) at a tracer dose. (2) Concerns of confounding the correlation between the anatomical gold standard of the QCA and the PET MPI blinded reads are minimal. It is possible that toxic effects of illicit drugs (such as cocaine) could affect the microvascular function that in turn could lead to perfusion abnormalities as seen on MPI in the absence of significant epicardial coronary stenoses evidenced on QCA. GE Healthcare believes that these discrepancies are likely to be minimal and encountered infrequently.
  (3) Subjects are already screened for psychiatric conditions which could impair participation in all study visits (exclusion #12). Substance abuse is an axis II disorder and investigators are counselled to exclude patients with ongoing drug abuse that may lead to poor compliance in the manual of procedures. Given the short-term follow-up of this study, it is unlikely that occult substance abuse (missed as part of the medical history) would frequently impair patient follow up.
  Since we believe that active substance abuse is likely to be rare and to have minimal if any effect on efficacy, no effect on safety, and minimal if any effect on follow-up compliance, the collection of this sensitive health information is not justified.

- Guidance regarding use of beta-blocker therapy has been added. To ensure that the PET and SPECT MPI will be conducted according to guidelines and in accordance with standard clinical care, study sites are advised to withhold the beta-blocker when possible for at least 24 hours prior to the stress test. Evidence demonstrates that beta-blockade at the time of stress testing may reduce the sensitivity of MPI. GE Healthcare acknowledges that withholding the beta-blocker might not always be possible due to clinical concerns such as difficult to control hypertension or arrhythmia (as per the guidelines) [Dorbala et al. 2013]. In patients using beta blockers, the investigator must discuss with the treating physician the safety of withholding the beta-blocker. Subjects who require continued beta-blockade during MPI will not be eliminated.

- Clarification that an additional blood sample at screening may be analysed by the local lab to determine if the subject meets exclusion criteria. Dependence on central lab results for screening purposes will result in a delay from screening to the earliest performance of in study visits (including the PET or on-study SPECT) of at least 48 hours from the time of the lab draw (in most cases). This delay adds a significant hurdle to patient recruitment and retainment in a study where all study visits must occur prior to a prescheduled invasive coronary angiography. In most cases the window between screening and the clinical intracoronary angiography is expected to be less than 7 days. Permitting screening through the uses of local labs permits patients to be screened, enrolled and have a SPECT scan in a minimal amount of time (or even in the same day) with a PET scan following as closely after as doses are available. Central labs results may still be used for screening if local labs are not drawn. The determination of whether to draw local labs for this purpose rests with the investigator and will depend on the rapidity with which the study visits must occur (e.g. if the window between screening and ICA is brief, local labs are advised, if this window is more lengthy than local labs should not be drawn).
  Significant discordance between local and central lab results are unlikely since the central and local labs will be drawn in the same sitting at screening. If they do occur the local lab should take precedence for the screening purposes. The safety data set will use the exclusively the central labs to analyse changes in biochemistry, since all patients will systematically have labs analysed centrally at screening and pre- and post-scan timepoints. Listings and summary tables will describe the local lab data.

- Safety reporting for AEs and SAEs has been updated and clarified.

- Minor typographical errors have been corrected.

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

Section 6.1, Overall Study Design and Plan, Third Paragraph

Previously read:

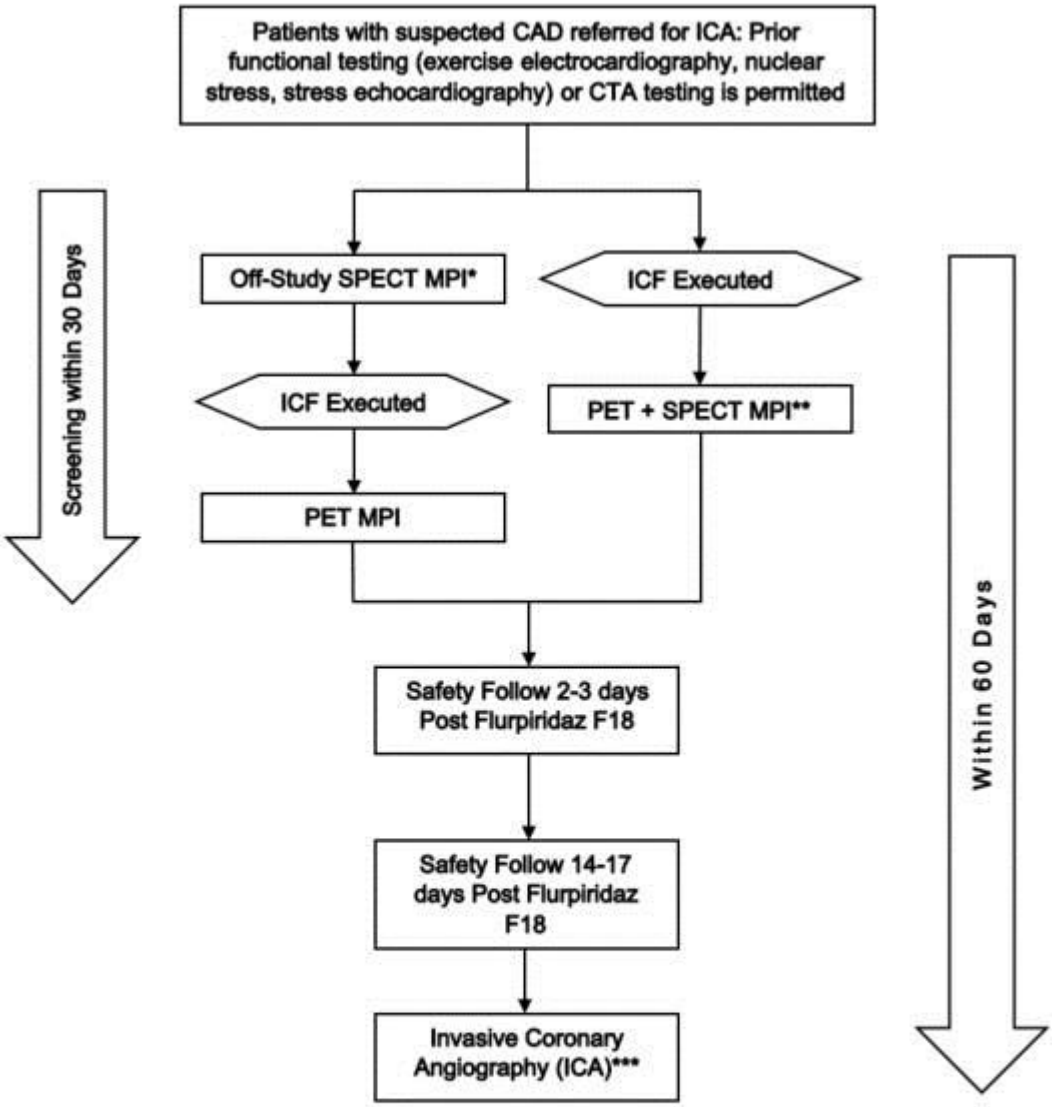
The procedure order will not be randomised but will be dependent upon the presentation of the patient at the site; however, in all cases SPECT and Flurpiridaz (^{18}F) PET MPI must be performed within 60 days prior to ICA. Included in this 60 days are clinically indicated SPECT exams that may precede screening, which otherwise meet all study-specific imaging and stress testing (Section 9.3) criteria (hereby called "Off-study" SPECT exams) (see Study Diagram, Figure 1).

Now reads:

The procedure order will not be randomised but will be dependent upon the presentation of the patient at the site; however, in all cases SPECT and Flurpiridaz (^{18}F) PET MPI must be performed within 60 days prior to ICA. Included in *these* 60 days are clinically indicated SPECT exams that may precede screening, which otherwise meet all study-specific imaging and stress testing (Section 9.3) criteria (hereby called "Off-study" SPECT exams) (see Study Diagram, Figure 1).

Section 6.1, Figure 1, Study Diagram

Previously read:

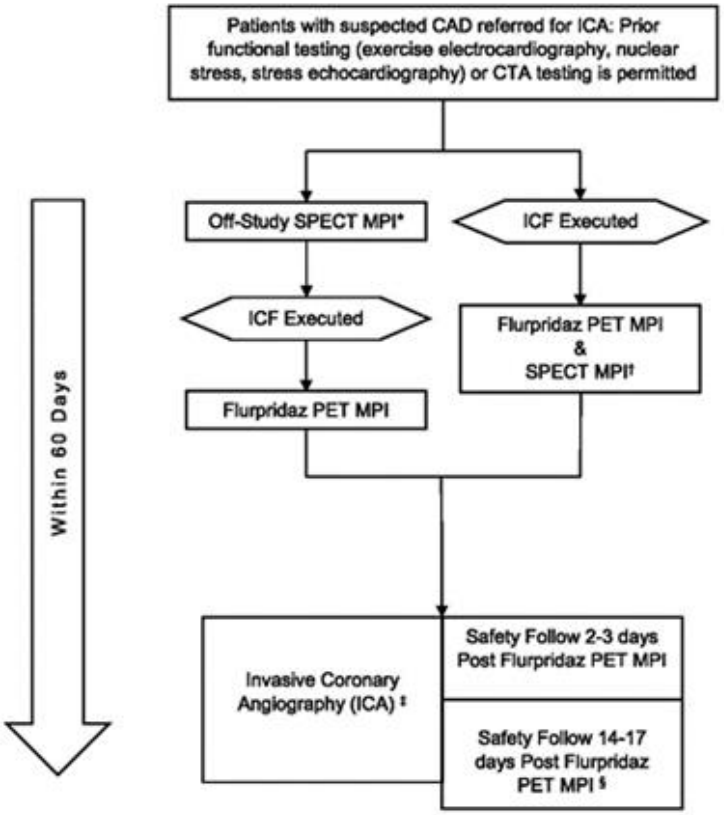


*Off-study SPECT MPI performed prior to signing of ICF, in accordance with procedures developed by ICL, and on a validated camera

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

*** ICA may occur during safety follow up post Flurpiridaz F18.

Now reads:



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

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

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

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

Section 6.4, Risks and Benefits to Subjects, Third Paragraph

Previously read:

In the most recent study, BMS747158-301, a total of 795 subjects received ≥1 dose of study drug. 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 treatment-emergent AEs (TEAEs). In 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%) patients experienced TEAEs deemed to be related to study drug. Of these, 41 (5.2%) were subcategorised 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%), diarrhoea (0.5%), dyspnoea (0.5%), flushing (0.5%), and nausea (0.5%).

Now reads:

In the most recent 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 treatment-emergent AEs (TEAEs). In 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%) patients experienced TEAEs deemed to be related to *Flurpiridaz (^{18}F) Injection*. Of these, 41 (5.2%) were subcategorised 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%), diarrhoea (0.5%), dyspnoea (0.5%), flushing (0.5%), and nausea (0.5%).

Section 7.1, Procedures for Enrolment, Second Paragraph

Previously read:

The population will include patients with intermediate and high pre-test probability of CAD, reflecting the spectrum of patients who would be expected to undergo nuclear imaging tests. However, enrolment will not be based on pre-test likelihood of CAD. The performance of other functional stress tests (such as stress echocardiography, exercise stress electrocardiography, nuclear stress tests including ^{82}Rb or ^{13}N MPI imaging or SPECT MPI) or coronary CT angiography prior to enrolment is permitted. Recent intracoronary angiography (within the last 6 months) prior to enrolment is not permitted.

Now reads:

The population will include patients with intermediate and high pre-test probability of CAD, reflecting the spectrum of patients who would be expected to undergo nuclear imaging tests. However, enrolment will not be based on pre-test likelihood of CAD. 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 enrolment is permitted. Recent intracoronary angiography (within the last 6 months) prior to enrolment is not permitted.

Section 7.3, Exclusion Criteria, Exclusion Criterion (8)

Previously read:

(8) Documented history of heart failure and/or cardiomyopathy (including nonischaemic cardiomyopathy, hypertrophic obstructive cardiomyopathy, or infiltrative cardiomyopathy) and/or prior LVEF <50%.

Now reads:

(8) Documented history of heart failure and/or cardiomyopathy (including nonischaemic cardiomyopathy, hypertrophic obstructive cardiomyopathy, or infiltrative cardiomyopathy).

Section 7.3, Exclusion Criteria, Exclusion Criterion (14)

Previously read:

(14) Patients enrolled in another clinical study within the 30 days prior to being enrolled in this study or scheduled to participate in another clinical study during the 7-day follow-up period of this study.

Now reads:

(14) Patients enrolled in another clinical study within the 30 days prior to being enrolled in this study or scheduled to participate in another clinical study during the *17*-day follow-up period of this study.

Section 7.3.1, Subject Withdrawal, Fourth Paragraph, First Sentence

Previously read:

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.

Now reads:

The reason for withdrawal must be noted in the case report form (CRF). If the reason for withdrawal is *an AE*, monitoring will continue until the outcome is evident.

Section 8.1, Title

Previously read:

Investigational Medicinal Product(s)

Now reads:

Description of Medicinal Products

Section 8.1.1, Investigational Medicinal Product: Flurpiridaz (^{18}F) Injection (previously Flurpiridaz (^{18}F) Injection)

Previously read:

Flurpiridaz (^{18}F) Injection is a novel PET MPI agent labelled with the radioisotope fluorine-18. Flurpiridaz (^{18}F) 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 in a large peripheral vein: 1 at rest and 1 during stress. The dosages of Flurpiridaz (^{18}F) Injection administered at rest and during stress conditions will not exceed a total of 14 mCi (520 MBq) for an individual subject.

- **Appearance**: Clear, colourless, and free of visible particulate matter
- **Strength/concentration:** [^{18}F]Flurpiridaz ≥ 70 mCi in a nominal volume of 10 mL
- **Storage and handling conditions:** Flurpiridaz is stable upon storage at 25°C/60% ***relative humidity*** over a 12-hour period.

Now reads:

Flurpiridaz (^{18}F) Injection*, the IMP in this study,* is a novel PET MPI agent labelled with the radioisotope fluorine-18. Flurpiridaz (^{18}F) 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 in a large peripheral vein: 1 at rest and 1 during stress. The dosages of Flurpiridaz (^{18}F) Injection administered at rest and during stress conditions will not exceed a total of 14 mCi (520 MBq) for an individual subject.

- **Appearance**: Clear, colourless, and free of visible particulate matter
- **Strength/concentration:** [^{18}F]Flurpiridaz ≥ 70 mCi in a nominal volume of 10 mL
- **Storage and handling conditions:** Flurpiridaz is stable upon storage at *15°C to 25°C up to a maximum of 12 hours. The exact expiry time of each dose will be included on the label*.

Section 8.1.2.2, Pharmacological Stress Agents, First Sentence

Previously read:

The Flurpiridaz (^{18}F) Injection PET MPI study should use the same stress type (pharmacological or exercise) as used for SPECT MPI in the same subject.

Now reads:

The Flurpiridaz (^{18}F) Injection PET MPI study *must* use the same stress type (pharmacological or exercise) as used for SPECT MPI in the same subject.

Section 8.1.2, Other Medicinal Products (Non-IMP)

New section heading introduced.

Section 8.1.2.1, SPECT Agents

Previously read:

SPECT imaging must use ^{99m}Tc-based myocardial tracers. SPECT agents utilised for the purposes of this clinical study will be administered as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards, where applicable, and recorded in the subject's CRF.

Now reads:

SPECT imaging must use ^{99m}Tc-based myocardial tracers*, e.g., [^{99m}Tc]tetrofosmin or [^{99m}Tc]sestamibi*. SPECT agents utilised for the purposes of this clinical study will be administered as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards, where applicable, and recorded in the subject's CRF.

Section 8.1.3, Medicinal Product Accountability (previously IMP Accountability)

Previously read:

Each investigator is responsible for ensuring that deliveries of IMP(s) 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 containers (opened, unopened, or empty) must be destroyed on site after its scheduled use in accordance with site policies. See IMP handling procedures for further details on receipt, recording, handling, and accountability procedures. A list of IMP(s) 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.

Package inserts, SmPCs, or other safety documents for IMPs will be supplied to the site by the Sponsor.

Now reads:

Each investigator is responsible for ensuring that deliveries of IMP*, other medicinal products (specified above)*, 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 containers (opened, unopened, or empty) must be destroyed on site after its scheduled use in accordance with site policies. See IMP handling procedures 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.

Section 8.5, Prior and Concurrent Medications (previously Prior and Concurrent Therapy)

Previously read:

Any medications taken by the subject within 12 hours before the screening (or 12 hours before the SPECT stress test if the SPECT stress tests precede screening) and up to the end of the observation period of 2 weeks after Flurpiridaz (^{18}F) Injection will be recorded in the CRF, along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/contract research organisation (CRO) will encode all therapy and medication per a current well-recognised dictionary of medical codes.

Now reads:

Any medications taken by the subject within 12 hours before the screening (or 12 hours before the SPECT stress test if the SPECT stress tests precede screening) *at the time of ICA* and up to *study completion* will be recorded in the CRF, along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/contract research organisation (CRO) will encode all therapy and medication per a current well-recognised dictionary of medical codes.

Section 9, Study Procedures, Table 1 Study Schedule of Events

Previously read:

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

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

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

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

c Before the first IMP injection and 1 hour after the last IMP 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 obtained up to 48 hours prior to Screening is acceptable.

e Physical examination will comprise a full examination with a specific focus on neurological and cardiovascular signs. During the Rest/Stress PET MPI Visit, a physical examination will be performed before and 1 hour after the administration of Flurpiridaz (^{18}F) Injection for the stress exam. Additionally, a focused clinical screen for new or worsening symptoms indicative of unstable coronary artery disease will be conducted prior to the Flurpiridaz (18F) PET stress MPI

f If any neurologic abnormalities are noted during physical examination.

g Immediately after the first and second IMP administration and at 1 hour after the last IMP injection.

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

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

j Events collected from the time of informed consent through study completion.

k Preprocedure vitals, pulse-oximetry and concomitant medications can be extracted from the clinical record

Now reads:

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

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

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

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

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

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

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 obtained up to 48 hours prior to Screening is acceptable.

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

f If any neurologic abnormalities are noted during physical examination.

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

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

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

j *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*.

k Preprocedure vitals, pulse-oximetry and concomitant medications can be extracted from the clinical record.

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

Section 9.1, Screening Visit

Previously read:

All screening assessments will occur within 30 days prior to Baseline Visit. The Screening and Baseline Visits can be combined with the SPECT MPI Visit. The investigator must be mindful of the 60-day window between screening and ICA procedures. The following will be done during the screening period:

- Signed and dated ICF must be obtained from all subjects prior to their entering the study. Study informed consent must be obtained from each subject prior to the initiation of any study-related procedures. Rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., "off-study" SPECT) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study.
- 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 (ESC) guidelines on the management of stable CAD [Montalescot et al 2013] (see Appendix 15.4). In addition, a Seattle Angina Questionnaire [Spertus et al 1995] (see Appendix 15.5) will be administered.
- Demographic information will be recorded.
- Subjects will be screened for current illicit drug and/or alcohol abuse.
- Blood and urine samples will be collected for assessing haematology, abnormal glucose metabolism, liver or renal insufficiency, and alcohol and drug screening.
- All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.
- 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 Flurpiridaz (^{18}F) Injection) must be negative; these subjects must be instructed to practice appropriate birth control from time of the screening to 30 days after the 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).
- 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).

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.

Now reads:

All screening assessments will occur within 30 days prior to Baseline Visit. The Screening and Baseline Visits can be combined with the SPECT MPI Visit. The investigator must be mindful of the 60-day window between screening and ICA procedures. The following will be done during the screening period:

- Signed and dated ICF must be obtained from all subjects prior to their entering the study. Study informed consent must be obtained from each subject prior to the initiation of any study-related procedures. Rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., "off-study" SPECT) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study.
- 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 (ESC) guidelines on the management of stable CAD [Montalescot et al 2013] (see Appendix 15.4). In addition, a Seattle Angina Questionnaire [Spertus et al 1995] (see Appendix 15.5) will be administered.
- *Prior and concurrent medications.*
- Demographic information will be recorded.
- Blood and urine samples will be collected for assessing haematology, abnormal glucose metabolism, liver *and* renal insufficiency. *If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above).*
- All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.
- 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 Flurpiridaz (^{18}F) Injection) must be negative; these subjects must be instructed to practice appropriate birth control from time of the screening to 30 days after the 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).
- 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).

- *For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to PET and SPECT stress test.*

- *All AEs and SAEs that occur after informed consent will be recorded (see Table 1 for scheduled AE query points in time, and Sections 10.2.6, 10.2.7, and 10.2.8).*

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.

Section 9.2, Baseline Visit (≤30 Days After Screening), Start of Bulleted List

Previously read:

At the Baseline Visit, the following will be performed:

- Medical/surgical history will be recorded.

- Physical examination will comprise a full examination with a specific focus on neurological and cardiovascular signs.

……..

Now reads:

At the Baseline Visit, the following will be performed:

- Physical examination will comprise a full examination with a specific focus on neurological and cardiovascular signs.

…….

Section 9.3, Rest and Stress SPECT MPI Visit

Previously read:

The Rest and Stress SPECT MPI Visit can be combined with the Screening or Baseline Visit. Results of rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., an "off-study" SPECT MPI) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study. The "off-study" SPECT MPI must also achieve the

minimal quality standard specified by the imaging core lab (ICL) in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study. Depending on the institution's standard practices, the rest and stress SPECT MPI procedures can take place on the same day or on 2 consecutive days. The Rest and Stress SPECT MPI Visit may take place before or after the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit. The investigator must be mindful of the 60-day window between SPECT MPI and ICA procedures.

Subjects who are scheduled to undergo a pharmacologic stress test must not drink or eat caffeinated substances or take any dipyridamole-containing medication or methylxanthine-containing medication within 12 hours prior to vasodilator administration for SPECT MPI. In addition, it is recommended that patients who are scheduled to undergo exercise stress refrain from consuming any caffeinated substances, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to the exercise stress test, to allow for the use of a pharmacologic stressor in the event that the subject does not reach the protocol-required minimum 85% of age-predicted maximum heart rate (APMHR) or does not develop ischaemic symptoms during the exercise stress.

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

If the SPECT MPI Visit is combined with the Screening or Baseline Visits, all of the following elements that were scheduled for the Screening or Baseline Visit will be performed during the SPECT MPI Visit:

- Informed consent will be obtained (Screening).
- Entry criteria will be evaluated and recorded (Screening).
- Medical/surgical history will be recorded (Screening/Baseline).
- 12-lead ECG recording will be performed (Screening Visit). (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).
- Blood samples for laboratory testing will be collected (Screening).
- Urine samples for laboratory testing will be collected (Screening).
- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]; Screening/Baseline).
- Drug and alcohol screening will be performed (Screening).
- Demographic information will be recorded (Screening).
- Concurrent medications will be recorded (Baseline Visit).

- Vital signs will be recorded (Baseline Visit).
- Pulse oximetry will be recorded (Baseline Visit).
- A physical examination will be performed (Baseline Visit).
- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed (Baseline Visit).

At the Rest and Stress SPECT MPI Visit, the following will be performed for all subjects:

- Concurrent medications will be recorded.
- Vital signs will be recorded.
- Pulse oximetry will be recorded.
- Rest SPECT MPI will be performed, per the as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.
- After the rest SPECT MPI, stress SPECT MPI will be performed, per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.
    - If the subject has already undergone stress Flurpiridaz (^{18}F) PET MPI, the same type of stress (pharmacologic or exercise) should be used in the stress SPECT MPI, including the same dose of the same pharmacologic stressor, unless otherwise clinically indicated. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.
    - If the subject has already undergone exercise stress Flurpiridaz (^{18}F) PET MPI, the same exercise protocol should be used for the stress SPECT MPI, unless otherwise clinically indicated.
    - During exercise stress, the radiopharmaceutical for SPECT should be administered during peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.
    - The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by

experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association (AHA) [Myers et al 2009]

- Adverse events will be recorded per institution's standard practices.
- The images acquired during these procedures will be stored for the secondary blinded review, as specified in the Imaging Manual.

Now reads:

The Rest and Stress SPECT MPI Visit can be combined with the Screening or Baseline Visit. Results of rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., an "off-study" SPECT MPI) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study. The "off-study" SPECT MPI must also achieve the minimal quality standard specified by the imaging core lab (ICL) in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study. Depending on the institution's standard practices, the rest and stress SPECT MPI procedures can take place on the same day or on 2 consecutive days. The Rest and Stress SPECT MPI Visit may take place before or after the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit. The investigator must be mindful of the 60-day window between SPECT MPI and ICA procedures.

Subjects who are scheduled to undergo a pharmacologic stress test must not drink or eat caffeinated substances or take any dipyridamole-containing medication or methylxanthine-containing medication within 12 hours prior to vasodilator administration for SPECT MPI. In addition, it is recommended that patients who are scheduled to undergo exercise stress refrain from consuming any caffeinated substances, dipyridamole-containing medication, or methylxanthine-containing medication within 12 hours prior to the exercise stress test, to allow for the use of a pharmacologic stressor in the event that the subject does not reach the protocol-required minimum 85% of age-predicted maximum heart rate (APMHR) or does not develop ischaemic symptoms during the exercise stress.

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to the SPECT MPI.

If the SPECT MPI Visit is combined with the Screening or Baseline Visits, all of the following elements that were scheduled for the Screening or Baseline Visit will be performed during the SPECT MPI Visit:

- Informed consent will be obtained (Screening).
- Entry criteria will be evaluated and recorded (Screening).
- Medical/surgical history will be recorded (Screening).
- 12-lead ECG recording will be performed (Screening Visit). (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).
- Blood samples for laboratory testing will be collected. *If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above)* (Screening).
- Urine samples for laboratory testing will be collected (Screening).
- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]; Screening/Baseline).
- Demographic information will be recorded (Screening).
- Concurrent medications will be recorded (Baseline Visit).
- Vital signs will be recorded (Baseline Visit).
- Pulse oximetry will be recorded (Baseline Visit).
- A physical examination will be performed (Baseline Visit).
- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed (Baseline Visit).

At the Rest and Stress SPECT MPI Visit, the following will be performed for all subjects:

- Concurrent medications will be recorded.
- Vital signs will be recorded.
- Pulse oximetry will be recorded.

- Rest SPECT MPI will be performed, per the as per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.

- After the rest SPECT MPI, stress SPECT MPI will be performed, per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards.

    - If the subject has already undergone stress Flurpiridaz (^{18}F) PET MPI, the same type of stress (pharmacologic or exercise) should be used in the stress SPECT MPI, including the same dose of the same pharmacologic stressor, unless otherwise clinically indicated. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.

    - If the subject has already undergone exercise stress Flurpiridaz (^{18}F) PET MPI, the same exercise protocol should be used for the stress SPECT MPI, unless otherwise clinically indicated.

    - During exercise stress, the radiopharmaceutical for SPECT should be administered during peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.

    - The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association (AHA) [Myers et al 2009]

- *AEs and SAEs* will be recorded.

- The images acquired during these procedures will be stored for the secondary blinded review, as specified in the Imaging Manual.

Section 9.4, Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit

Previously read:

…….

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

A focused clinical screen for new or worsening symptoms indicative of unstable coronary artery disease will be conducted prior to the Flurpiridaz (^{18}F) PET stress MPI.

During the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit, the following will be performed:

- Blood samples for laboratory testing will be collected prior to the PET MPI and 1 hour after the last PET-MPI injection.
- Urine samples for laboratory testing will be collected prior to the PET MPI and 1 hour after the last PET-MPI injection.
- Pregnancy test, for women of child-bearing potential (see the Study Schedule of Events [Table 1]).
- Concurrent medications will be recorded.
- Vital signs will be recorded.
- Pulse oximetry will be recorded.
- Eight 12-lead ECG recordings will be performed (See Section 10.2.3).
- A physical examination will be performed.
- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed.
- During the rest test, all subjects will receive an IV bolus injection of Flurpiridaz (^{18}F) Injection in a large peripheral vein. The dose (volume and radioactivity) will be recorded in the CRF.
- A stress test (exercise or pharmacologic) will be performed after the rest test, and on the same day.
    - The type of stress (exercise or pharmacologic) will be the same type used for that subject for the SPECT MPI test.
    - For subjects who received a pharmacologic stressor during the stress SPECT MPI, the same agent and dose will be used during the stress Flurpiridaz (^{18}F) PET-MPI

test. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.

- If adenosine is used as a pharmacologic stressor, the Flurpiridaz (^{18}F) Injection and the adenosine must be administered through separate lines or through separate ports of the same IV line. Note: Central lines should NOT be used for the administration of Flurpiridaz (^{18}F) Injection. The Flurpiridaz (^{18}F) Injection will be administered after the administration of the pharmacologic stressor. The administration of Flurpiridaz (^{18}F) Injection will be timed to coincide with maximal coronary vasodilation, which depends on the vasodilatory agent used.

- For a subject who underwent exercise stress for SPECT MPI, the investigator is required to use the same exercise stress protocol for the Flurpiridaz (^{18}F) Injection PET that was used for the SPECT MPI, unless otherwise clinically indicated.

- During exercise stress, the radiopharmaceutical for both SPECT and PET should be administered at peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.

- The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the AHA [Myers et al 2009]

- At 1 hour after administration of Flurpiridaz (^{18}F) Injection for the stress exam, a physical examination will be performed.

- If any neurologic abnormalities are noted during the physical examination, a full neurologic examination will be performed.

- Injection-site monitoring (immediately after the first injection of IMP for the rest exam, then immediately after the second injection of IMP for the stress exam, and ultimately at 1 hour after the last injection of IMP).

…….

Now reads:

…….

No food will be allowed within 3 hours prior to either the pharmacologic stress or exercise stress.

For subjects on beta-blocker therapy, a determination should be made, in concert with their treating physician, if there are any conditions in which discontinuation of beta-blocker therapy could be contraindicated (e.g., tachyarrhythmias, uncontrolled or poorly controlled hypertension). If medically safe, beta-blocker therapy should be withheld for 24 hours prior to the PET MPI. A focused clinical screen for new or worsening symptoms indicative of unstable coronary artery disease will be conducted prior to *performing any procedures at* the Flurpiridaz (^{18}F) PET *visit. If the clinical status screening is positive, the Flurpiridaz (^{18}F) PET visit can either be rescheduled (up to 1 time) after symptoms stabilize or the subject can be discontinued from the study.*

During the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit, the following will be performed:

- Blood samples for laboratory testing will be collected prior to the PET MPI and 1 hour after the last PET-MPI injection. *If for scheduling reasons, the study SPECT or study PET MPI must occur rapidly after the screening visit (e.g. within 48 hours), an additional blood sample may be analysed 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 (as noted above).*

- 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]).

- Concurrent medications will be recorded.

- Vital signs will be recorded.

- Pulse oximetry will be recorded.

- Eight 12-lead ECG recordings will be performed (See Section 10.2.3).

- A physical examination will be performed.

- If neurologic abnormalities are found during the physical examination, a full neurologic examination will be performed.

- During the rest test, all subjects will receive an IV bolus injection of Flurpiridaz (^{18}F) Injection in a large peripheral vein. The dose (volume and radioactivity) will be recorded in the CRF.

- A stress test (exercise or pharmacologic) will be performed after the rest test, and on the same day.

    - The type of stress (exercise or pharmacologic) will be the same type used for that subject for the SPECT MPI test.

    - For subjects who received a pharmacologic stressor during the stress SPECT MPI, the same agent and dose will be used during the stress Flurpiridaz (^{18}F) PET-MPI test. During pharmacologic stress, radiopharmaceutical injection will be administered during the peak vasodilatory effect, according to the respective prescribing information or SmPC (as applicable) of each stressor. Acceptable pharmacologic stress agents are listed in Section 8.1.2.2.

        - If adenosine is used as a pharmacologic stressor, the Flurpiridaz (^{18}F) Injection and the adenosine must be administered through separate lines or through separate ports of the same IV line. Note: Central lines should NOT be used for the administration of Flurpiridaz (^{18}F) Injection. The Flurpiridaz (^{18}F) Injection will be administered after the administration of the pharmacologic stressor. The administration of Flurpiridaz (^{18}F) Injection will be timed to coincide with maximal coronary vasodilation, which depends on the vasodilatory agent used.

    - For a subject who underwent exercise stress for SPECT MPI, the investigator is required to use the same exercise stress protocol for the Flurpiridaz (^{18}F) Injection PET that was used for the SPECT MPI, unless otherwise clinically indicated.

    - During exercise stress, the radiopharmaceutical for both SPECT and PET should be administered at peak stress, defined as ≥85% of the APMHR or following the occurrence of typical cardiac ischaemic symptoms. Patients should continue to exercise for an additional 1 to 2 minutes, as clinically advisable, after the radiopharmaceutical injection. If a patient cannot reach the study-required minimum of 85% of the APMHR or does not develop ischaemic symptoms, the radiopharmaceutical should not be administered.

- The standard clinical practice should be used for determining early termination of exercise or pharmacologic stress testing in the presence of any absolute or relative indications, including the presence of ischaemic symptoms (i.e., angina, or angina equivalent) for early termination. The exercise stress test should be performed only by experienced site personnel with access to resuscitation equipment. Detailed recommendations for exercise testing performance must be followed as described in detail in the 2009 Recommendations for clinical exercise laboratories: a scientific statement from the AHA [Myers et al 2009]

- At 1 hour after administration of Flurpiridaz (^{18}F) Injection for the stress exam, a physical examination will be performed.

- If any neurologic abnormalities are noted during the physical examination, a full neurologic examination will be performed.

- Injection-site monitoring (*immediately prior to the first injection*, immediately after the first injection of IMP for the rest exam, then immediately after the second injection of IMP for the stress exam, and ultimately at 1 hour after the last injection of IMP).

…….

Section 9.6, Safety Follow-up 14 to 17 Days After Flurpiridaz (^{18}F) PET MPI, First Sentence

Previously read:

All subjects will be followed up by telephone assessments for AEs and SAEs within 2 days (+24 hours) following administration of Flurpiridaz (^{18}F) Injection.

Now reads:

All subjects will be followed up by telephone assessments for AEs and SAEs within *14 to 17* days following administration of Flurpiridaz (^{18}F) Injection.

Section 10.1.4, Image Acquisition, Second Paragraph

Previously read:

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

Now reads:

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

Section 10.1.5, Image Interpretation and Correlation with Standard of Truth

Previously read:

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

One blinded reviewer will perform QCA, according to the Imaging Manual, for all ICA images.

Now reads:

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

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

Section 10.2.1, Clinical Laboratory Evaluation, Table 3 and following paragraphs

Previously read:

Table 3 Clinical Laboratory Parameters

Serum Biochemistry	Haematology	Urinalysis
Alanine aminotransferase (ALT)	Haematocrit	Bilirubin
Albumin	Platelet count	Glucose
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Ketone
Bicarbonate		Occult blood
Bilirubin (total)		pH
Calcium		Protein
Chloride		Specific gravity
Creatinine		Urobilinogen
Gamma-glutamyltransferase		
Glucose		
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 and at the site.

Blood samples will be obtained for assessment of serum biochemistry and haematology 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 analysed at a central laboratory (for parameters, see Table 3). All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed after completion of the study.

…….

Now reads:

Table 3 Clinical Laboratory Parameters

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

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

Blood samples will be obtained for assessment of serum biochemistry and haematology 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 analysed at a central laboratory (for parameters, see Table 3). 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 analysed by local labs specifically to determine if the subject meets exclusion criteria (i.e., serum creatinine, AST, ALT and total bilirubin).*

…….

Section 10.2.2, Vital Signs, First Sentence

Previously read:

Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be monitored at Baseline (prior to IMP administration) and during the in- and outpatient follow-up periods, according to the Study Schedule of Events (Table 1).

Now reads:

Vital signs (*pulse oximetry,* blood pressure, heart rate, respiratory rate, temperature) will be monitored at Baseline (prior to IMP administration) and during the in- and outpatient follow-up periods, according to the Study Schedule of Events (Table 1).

Section 10.2.3.1, Investigational Site Responsibilities, Third and Fourth Paragraphs

Previously read:

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. During continuous ECG monitoring, the investigator will observe the real-time ECG findings and take note of any changes in intervals and/or waveforms. The continuous ECG monitoring need not be 12-lead.

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 will not be expected to calculate QTc intervals. A copy of the ECG strips will be provided to the Sponsor or the Sponsor's representative with the subject's CRF.

Now reads:

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. During continuous ECG monitoring, the investigator *or appropriate delegate (concordant with local practice)* will observe the real-time ECG findings and take note of any changes in intervals and/or waveforms. The continuous ECG monitoring need not be 12-lead.

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 will not be expected to calculate QTc intervals.

Section 10.2.4, Physical Examination, First Paragraph

Previously read:

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 baseline time point, 30 minutes prior to administration, and at the 1 hour post-treatment time point. 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, breasts and axillae, cardiovascular system, back and spine, abdomen, extremities, injection site, lymph nodes, and neurological exam.

Now reads:

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 baseline time point, *before the Flurpiridaz (^{18}F) Injection rest MPI exam and 1 hour after the Flurpiridaz (^{18}F) Injection stress MPI exam. 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.

Section 10.2.6, Adverse Events (previously Treatment-emergent Adverse Events)

Previously read:

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.

AE Definition: An AE is defined as any untoward medical occurrence or an already present event that worsens either in intensity or frequency. A treatment-emergent adverse event (TEAE) is an AE which occurs temporally following exposure to the investigational agent. A TEAE is defined as an AE that starts on or after the time of the first injection of Flurpiridaz until the follow-up visit 14-17 days later. The TEAE does not necessarily have to have a causal relationship with exposure to the investigational agent. A TEAE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to an IMP, whether or not considered related to that product.

The 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 with non-leading

questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Both the investigator(s) and Sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

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.

Laboratory AE Evaluation

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the subject. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition (e.g., ordering a WBC differential to help characterise a high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit).

Now reads:

All AEs/SAEs that occur after informed consent shall be recorded in the AE/SAE report form (see the Study Schedule of Events, Table 1).

Study personnel must remain vigilant for the occurrence of AEs *after administration of IMP (see Section 8.1)*, 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.

AE *and TEAE* Definition: An AE is defined as any untoward medical occurrence or an already present event that worsens either in intensity or frequency. A treatment-emergent adverse event (TEAE) is defined as an AE that starts on or after the time of the first injection of Flurpiridaz until the follow-up visit 14-17 days later. The TEAE does not necessarily have to have a causal relationship with exposure to the investigational agent. A TEAE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to *the* IMP, whether or not considered related to that product.

The 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 with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Both the investigator(s) and Sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

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

Laboratory AE Evaluation

Interpretation and follow-up of abnormal laboratory test results should be conducted in consideration of the clinical situation of the subject. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition (e.g., ordering a WBC differential to help characterise a high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit); *see also Section 10.2.8 (Other Significant Adverse Events)*.

Section 10.2.7, Serious Adverse Events, Final Paragraph

Previously read:

For this study, these types of hospitalisations and/or imaging findings will not be considered AEs or SAEs and will not be reported as such in the CRFs. However, these observations and hospitalisations will be reported elsewhere in the eCRF.

Now reads:

For this study, these types of hospitalisations and/or imaging findings will not be considered AEs or SAEs and will not be reported as such in the CRFs.

Section 10.2.9, Adverse Event and Serious Adverse Event Reporting

Previously read:

All AEs should be recorded using acceptable diagnoses, if possible. 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.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild: Tolerable.
Moderate: Interferes with normal activity.
Severe: Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the IMP or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the Sponsor/CRO according to a well-recognised dictionary of medical codes.

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

- After a subject first received an IMP and throughout the subject's follow-up period*, whether or not considered related to the IMP, and

- After the subject's follow-up period, and for which a causal relationship to the IMP cannot be ruled out.

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

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

Study centres are instructed to report all SAEs, together with a causality assessment, to the Sponsor (or a service provider acting on behalf of the Sponsor) within 24 hours. Detailed information will be provided in a Safety Management Plan.

……..

Now reads:

All AEs*/SAEs shall* be recorded *in the AE/SAE report form* using acceptable diagnoses, if possible. 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 *myocardial infarction* (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.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild: Tolerable.
Moderate: Interferes with normal activity.
Severe: Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the IMP or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the Sponsor/CRO according to a well-recognised dictionary of medical codes, *e.g., Medical Dictionary for Regulatory Activities (MedDRA)*.

All AEs/SAEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

Study centres are instructed to report all SAEs, together with a causality assessment, to the Sponsor (or a service provider*/CRO* acting on behalf of the Sponsor) within 24 hours. *AEs and SAEs are reported in the AE form of the eCRF.* Detailed information *about management of AE information* will be provided, *e.g.,* in a Safety Management Plan.

……..

Section 10.2.11, Pregnancy Reporting, Final Paragraph

Previously read:

The investigator must inform the Sponsor/CRO within 24 hours of receiving positive pregnancy test results by using either a copy of the relevant CRF page (demography or AE) or via email. The investigator should include an estimated date of conception when communicating with the Sponsor/CRO.

Now reads:

The investigator must inform the Sponsor/CRO within 24 hours of receiving positive pregnancy test results by using either a copy of the relevant CRF *pages* (demography, *exposure to medicinal products, and/*or AE) or via email. The investigator should include an estimated date of conception when communicating with the Sponsor/CRO.

Section 10.3.1, Demographic Data

Previously read:

Subject demographic data (date of birth, race, sex, weight, and height) will be recorded at Screening. Subject age at the time of randomisation will be calculated from the date of birth and the date of baseline. BMI will be calculated from height and weight. If local regulations do not permit collection of specific demographic items (e.g., date of birth), a dummy date will be used in accordance with local practice.

Now reads:

Subject demographic data (date of birth*/age*, race, *ethnicity,* sex, weight, and height) will be recorded at Screening. Subject age at the time of *enrolment* will be calculated from the date of birth and the date of baseline. 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 eCRF or a partial* date will be used in accordance with local practice.

Section 10.3.2, Medical and Surgical History

Previously read:

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

Now reads:

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

Section 10.3.3, Prior and Concurrent Medication

Previously read:

Any medications taken by the subject within 12 hours before the screening or the SPECT stress test if it precedes screening and up to the end of the observation period of 2 weeks after Flurpiridaz (^{18}F) Injection 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-recognised dictionary of medical codes.

Now reads:

Any medications taken by the subject within 12 hours before the screening or the SPECT stress test if it precedes screening*, at the time of ICA* and up to *study completion* will be 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-recognised dictionary of medical codes.

Section 10.3.4, Drug and Alcohol Screening

Section deleted.

Section 11.1, Completing and Signing Case Report Forms

Previously read:

For electronic CRFs (eCRFs), 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 reason for the change, the date and time of the correction, and the person correcting the error. 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).

Now reads:

For electronic CRFs (eCRFs), 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 reason for the change, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

Section 12.3, Subject Demographics/Other Baseline Characteristics, Second Paragraph

Previously read:

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

Now reads:

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

Section 12.4, Study Treatments, Second Paragraph

Previously read:

Any medications taken by the subject within 12 hours before and up to the end of the observation period (including the drug stressor) 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.

Now reads:

Any *other* medications taken by the subject within 12 hours before and up to *study completion* 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.

Section 12.5.6, Handling of Uninterpretable Images

Previously read:

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. To document when a diagnosis is forced, the reader will use the blinded read CRF to record which images are considered uninterpretable.

Now reads:

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.

Section 12.8.5, Adverse Events, First Sentence

Previously read:

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

Now reads:

AEs and SAEs will be coded by using *a current version of* MedDRA, and all reported events will be listed for the safety population.

Section 13.3.2, Subject Informed Consent

Previously read:

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be

documented in a signed and dated ICF before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record; and the investigator will sign, date, and time the ICF after the subject has signed, dated, and recorded the time. The investigator(s) will keep the original consent forms, and copies will be given to the subjects.

Now reads:

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated ICF before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record; and the investigator will sign *and* date the ICF after the subject has signed *and* dated *the ICF*. The investigator(s) will keep the original consent forms, and copies will be given to the subjects.

Section 15.1, Information on Investigational and Registered Products

Previously read:

The reference document for this study is the current Investigator's Brochure (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 applicable product information (e.g., the IB for an unapproved IMP).

Now reads:

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.

GE Healthcare marketed medicinal products like Myoview (^{99m}Tc based SPECT MPI agent) and Rapiscan (a pharmacological stress agent) may be used in this trial. Reference safety information for assessment of expectedness are company core safety information, and approved SmPC or US Package Insert in the country of occurrence.

No expectedness assessment will be performed for other medicinal products.

16.2 Amendment A02

16.2.1 Reasons for Amendment

- Clarification of time points for recording vital signs.
- Section 10.2.1 corrected to clarify urine will be collected at pre-treatment time points only, in line with the Schedule of Events.
- Medical Director details are updated following a change in personnel.

Where appropriate the changes are indicated in *italics*.

16.2.2 Description of Changes

Title Page, Medical Director Details

Previously read:

[redacted]
The Grove Centre, GC-18
White Lion Road
Bucks Amersham HP7 9LL
Phone: [redacted]
Mobile: [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 9, Study Procedures, Table 1 Study Schedule of Events

Previously read:

Table 1 Study Schedule of Events

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

Table 1 Study Schedule of Events

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

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

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

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

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

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 obtained up to 48 hours prior to Screening is acceptable.

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

f If any neurologic abnormalities are noted during physical examination.

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

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

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

j 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.

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

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

Now reads:

Table 1 Study Schedule of Events

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

Table 1 Study Schedule of Events

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

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

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

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

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

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

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

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

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

h If any neurologic abnormalities are noted during physical examination.

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

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

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

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

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

Section 9.2, Baseline Visit (≤30 Days After Screening), Bullet Point #5

Previously read:

Vital signs will be recorded.

Now reads:

Vital signs will be recorded *during the Baseline Visit. If the Baseline Visit is combined with the Rest and Stress SPECT MPI Visit, vital signs should be recorded up to 20 minutes before administration of the rest dose.*

Section 9.3, Rest and Stress SPECT MPI Visit, First Bulleted List, Bullet Point #10

Previously read:

Vital signs will be recorded (Baseline Visit).

Now reads:

Vital signs will be recorded (Baseline Visit). *If the Baseline Visit is combined with the Rest and Stress SPECT MPI Visit, vital signs should be recorded up to 20 minutes before administration of the rest dose.*

Section 9.3, Rest and Stress SPECT MPI Visit, Second Bulleted List, Bullet Point #2

Previously read:

Vital signs will be recorded.

Now reads:

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

Section 9.4, Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit, Bulleted List, Bullet Point #5

Previously read:

Vital signs will be recorded.

Now reads:

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

Section 10.2.1, Clinical Laboratory Evaluation, Final Paragraph, First Sentence

Previously read:

Urine will be collected at the various pre- and post-treatment time point ranges described in Table 1.

Now reads:

Urine will be collected at the various pre-treatment time point ranges described in Table 1.

Section 10.2.9, Adverse Event and Serious Adverse Event Reporting, Medical Director Details

Previously read:

For any protocol or safety-related questions please contact the Medical Director:

[redacted]
[redacted]
The Grove Centre, GC-18
White Lion Road
Bucks Amersham HP7 9LL
Office telephone: [redacted]
Mobile telephone: [redacted]
E-mail: [redacted]

In case of a medical emergency and none of the above persons can be reached, call [redacted]

Now reads:

For any protocol or safety-related questions please contact the Medical Director:

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

Section 12.8.2, Vital Signs, Second Sentence

Previously read:

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

Now reads:

For each vital-sign variable and each time point *(see Table 1)*, the following safety endpoints will be summarised by counts and percentages by additional/other characteristics deemed necessary by study team:

16.3 Amendment A03

16.3.1 Reasons for Amendment

- Editorial correction to clarify that rest and stress SPECT MPI procedures can take place on 2 separate days that do not have to be consecutive.

- Correction of typographical error in the description of the semi-quantitative read (exploratory analysis).

Where appropriate the changes are indicated in *italics*.

16.3.2 Description of Changes

Section 9.3, Rest and Stress SPECT MPI Visit, First Paragraph

Previously read:

The Rest and Stress SPECT MPI Visit can be combined with the Screening or Baseline Visit. Results of rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., an "off-study" SPECT MPI) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study. The "off-study" SPECT MPI must also achieve the minimal quality standard specified by the imaging core lab (ICL) in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study. Depending on the institution's standard practices, the rest and stress SPECT MPI procedures can take place on the same day or on 2 consecutive days. The Rest and Stress SPECT MPI Visit may take place before or after the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit. The investigator must be mindful of the 60-day window between SPECT MPI and ICA procedures.

Now reads:

The Rest and Stress SPECT MPI Visit can be combined with the Screening or Baseline Visit. Results of rest and stress SPECT MPI studies that were performed before the subject signed the ICF (i.e., an "off-study" SPECT MPI) can be used if the SPECT MPI was performed in accordance with the study imaging manual and was performed on a camera that had already been validated for use in the study. The "off-study" SPECT MPI must also achieve the minimal quality standard specified by the imaging core lab (ICL) in the same manner as a study SPECT MPI performed prospectively. If an "off-study" SPECT MPI does not achieve the minimal quality standards of the ICL, a repeat SPECT MPI can be performed and used as a study SPECT MPI if performed during the study. Depending on the institution's standard practices, the rest and stress SPECT MPI procedures can take place on the same day or on 2 days *(either consecutive or non-consecutive)*. The Rest and Stress SPECT MPI Visit may take place before or after the Rest and Stress Flurpiridaz (^{18}F) PET-MPI Visit. The investigator must be mindful of the 60-day window between SPECT MPI and ICA procedures.

Section 12.7.1, Exploratory Endpoints, First Paragraph after Bulleted List

Previously read:

[redacted]

Now reads:

[redacted]

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Date / Name	Justification / Role
Signed By: [redacted] Date of signature: 20-Jul-2021 14:05:16 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 20-Jul-2021 16:28:34 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 22-Jul-2021 16:06:15 GMT+0000	Justification: Approved Role: [redacted]