



Clinical trial results:

A Phase 3, Open-Label, Multicentre Study of Flurpiridaz (18F) 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

Summary

EudraCT number	2017-005011-14
Trial protocol	FI NL DE FR
Global end of trial date	05 May 2022

Results information

Result version number	v1
This version publication date	28 May 2023
First version publication date	28 May 2023

Trial information

Trial identification

Sponsor protocol code	GE-265-303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03354273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GE Healthcare Ltd.
Sponsor organisation address	Pollards Wood, Nightingales Lane , Chalfont St Giles, Buckinghamshire, United Kingdom, HP8 4SP
Public contact	Medical Director - Francois Tranquart, GE Healthcare Ltd, Francois.tranquart@ge.com
Scientific contact	Medical Director - Francois Tranquart, GE Healthcare Ltd, Francois.tranquart@ge.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the diagnostic efficacy (sensitivity and specificity) of Flurpiridaz (18F) Injection positron emission tomography (PET) myocardial perfusion imaging (MPI) in the detection of significant coronary artery disease (CAD), as defined by invasive coronary angiography (ICA), in subjects with suspected CAD.

Protection of trial subjects:

This study was conducted in full accordance with the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH), and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 79
Country: Number of subjects enrolled	Finland: 36
Country: Number of subjects enrolled	France: 71
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Canada: 129
Country: Number of subjects enrolled	United States: 412
Worldwide total number of subjects	730
EEA total number of subjects	189

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	372
From 65 to 84 years	354
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 48 centers in Finland, France, Germany, Netherlands, United States and Canada from 05 June 2018 to 05 May 2022.

Pre-assignment

Screening details:

A total 730 subjects signed informed consent and were enrolled, of these, 604 subjects received greater than or equal to ($\geq$) 1 dose of Flurpiridaz (18F) Injection in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Flurpiridaz (18F): All Subjects
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Arm description:

Subjects received 2 IV boluses of Flurpiridaz (18F) Injection in large peripheral vein: 1 at rest then 1 during stress on same day within 60 days prior to ICA. Flurpiridaz(18F) Injection administered were not to exceed total of 14 mCi (520 MBq). Flurpiridaz was administered on Day 1. SPECT agents 99mTc-based myocardial tracers e.g. [99mTc]tetrofosmin or [99mTc]sestamibi were administered per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. Same stress type (pharmacologic or exercise) was used for SPECT and Flurpiridaz(18F) Injection PETMPI. Also, if pharmacological stress was used, same agent, dose of pharmacological stress agent was used for both types of imaging for same subject. Pharmacological stress agents administered according to respective Package Insert or American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location.

Arm type	Experimental
Investigational medicinal product name	Flurpiridaz (18F)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Flurpiridaz (18F) Injection administered as an intravenous (IV) injection in large peripheral vein 1 at rest then 1 during stress at dose not to exceed a total of 14 mCi (520 MBq) for an individual subject.

Number of subjects in period 1	Flurpiridaz (18F): All Subjects
Started	730
Completed	578
Not completed	152
COVID-19 Restrictions	9
Consent withdrawn by subject	34
Physician decision	3
Issues With Performing ICA	20

Adverse event, non-fatal	5
Technical Problems	30
Investigational Medicinal Product Supply Issues	21
Screen failure	21
Unspecified	5
Lost to follow-up	4

Baseline characteristics

Reporting groups

Reporting group title	Flurpiridaz (18F): All Subjects
Reporting group description:	
Subjects received 2 IV boluses of Flurpiridaz (18F) Injection in large peripheral vein:1 at rest then 1 during stress on same day within 60 days prior to ICA. Flurpiridaz(18F) Injection administered were not to exceed total of 14 mCi (520 MBq). Flurpiridaz was administered on Day 1. SPECT agents 99mTc-based myocardial tracers e.g. [99mTc]tetrofosmin or [99mTc]sestamibi were administered per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. Same stress type (pharmacologic or exercise) was used for SPECT and Flurpiridaz(18F) Injection PETMPI. Also, if pharmacological stress was used, same agent, dose of pharmacological stress agent was used for both types of imaging for same subject. Pharmacological stress agents administered according to respective Package Insert or American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location.	

Reporting group values	Flurpiridaz (18F): All Subjects	Total	
Number of subjects	730	730	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 9.26	-	
Gender categorical			
Units: Subjects			
Female	235	235	
Male	495	495	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	98	98	
Not Hispanic or Latino	512	512	
Unknown or Not Reported	120	120	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	10	10	
Native Hawaiian or Other Pacific Islander	3	3	
Black or African American	55	55	

White	579	579	
More than one race	0	0	
Unknown or Not Reported	82	82	

End points

End points reporting groups

Reporting group title	Flurpiridaz (18F): All Subjects
Reporting group description:	
Subjects received 2 IV boluses of Flurpiridaz (18F) Injection in large peripheral vein: 1 at rest then 1 during stress on same day within 60 days prior to ICA. Flurpiridaz(18F) Injection administered were not to exceed total of 14 mCi (520 MBq). Flurpiridaz was administered on Day 1. SPECT agents 99mTc-based myocardial tracers e.g. [99mTc]tetrofosmin or [99mTc]sestamibi were administered per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. Same stress type (pharmacologic or exercise) was used for SPECT and Flurpiridaz(18F) Injection PETMPI. Also, if pharmacological stress was used, same agent, dose of pharmacological stress agent was used for both types of imaging for same subject. Pharmacological stress agents administered according to respective Package Insert or American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location.	
Subject analysis set title	SPECT MPI
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
SPECT agents 99mTc-based myocardial tracers, example [99mTc]tetrofosmin or [99mTc]sestamibi were 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) was used for the SPECT and Flurpiridaz (18F) Injection PET MPI. Also, if pharmacological stress was used, the same agent and the same dose of pharmacological stress agent was used for both types of imaging for the same subject. Pharmacological stress agents were 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.	

Primary: Sensitivity and Specificity of Flurpiridaz (18F) Injection Positron Emission Tomography (PET) Myocardial Perfusion Imaging (MPI) in the Detection of Significant Coronary Artery Disease (CAD) as Defined by Cardiac Catheterization

End point title	Sensitivity and Specificity of Flurpiridaz (18F) Injection Positron Emission Tomography (PET) Myocardial Perfusion Imaging (MPI) in the Detection of Significant Coronary Artery Disease (CAD) as Defined by Cardiac Catheterization ^[1]
End point description:	
Sensitivity was defined as true positives (TP)/(TP+false negatives [FN]). TP was subjects with abnormal PET MPI and disease positive by truth standard and FN was subjects with normal PET MPI and disease positive by truth standard. Specificity defined as true negatives (TN)/(TN+ false positives [FP]). TN was subjects with normal PET MPI and disease negative by truth standard and FP was subjects with abnormal PET MPI and disease negative by truth standard. Truth standard was presence of CAD as evidenced by presence of stenosis of ≥ 50 percent (%) in ≥ 1 coronary artery or major branch of a coronary artery as determined by quantitative coronary angiography (QCA) analysis. Subjects were considered to have CAD if QCA revealed $\geq 50\%$ stenosis of ≥ 1 major coronary artery or major branch. Sensitivity and specificity were calculated for 3 readers and majority rule using each subject judgement (positive or negative) by at least 2 of 3 readers. MITT population.	
End point type	Primary
End point timeframe:	
Up to 60 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analyses was performed for 'Flurpiridaz (18F): All Subjects' arm only, and due to database limitation statistical analyses could not to be reported for single arm. Therefore, statistical analyses data for this endpoint is provided in PDF document.

End point values	Flurpiridaz (18F): All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	578			
Units: percent				
number (confidence interval 95%)				
Reader 1: Sensitivity	77.1 (71.9 to 82.3)			
Reader 1: Specificity	65.7 (60.5 to 70.8)			
Reader 2: Sensitivity	73.5 (68.0 to 79.0)			
Reader 2: Specificity	69.6 (64.6 to 74.6)			
Reader 3: Sensitivity	88.8 (84.8 to 92.7)			
Reader 3: Specificity	52.6 (47.2 to 58.0)			
Majority Rule: Sensitivity	80.3 (75.4 to 85.3)			
Majority Rule: Specificity	63.8 (58.6 to 69.0)			

Attachments (see zip file)	Statistical Data/Statistical data-Sensitivity and Specificity of
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Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for All Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth

End point title	Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for All Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth
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End point description:

Sensitivity: TP/(TP+FN). TP: subjects with abnormal PET MPI and disease positive by truth standard and FN: subjects with normal PET MPI and disease positive by truth standard. Specificity: TN/(TN+ FP). TN: subjects with normal PET MPI and disease negative by truth standard and FP: subjects with abnormal PET MPI and disease negative by truth standard. Truth standard was presence of CAD as evidenced by presence of stenosis of $\geq 50\%$ in ≥ 1 coronary artery or major branch of coronary artery as determined by QCA analysis. Subjects considered to have CAD if QCA revealed $\geq 50\%$ stenosis of ≥ 1 major coronary artery or major branch. Sensitivity, specificity was calculated for 3 readers and majority rule using each subject judgement (positive or negative) by at least 2 of 3 readers. SMITT population. Here, "number of subjects analyzed"= subjects who were analysed for a specific reader (combined sensitivity or specificity) and "n" = subjects who were evaluable for specified categories.

End point type	Secondary
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End point timeframe:

Up to 60 days

End point values	Flurpiridaz (18F): All Subjects	SPECT MPI		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	578	578		
Units: percent				
number (confidence interval 95%)				
Reader 1: Sensitivity (n=249, 249)	77.1 (71.9 to 82.3)	62.7 (56.6 to 68.7)		
Reader 1: Specificity (n=329, 329)	65.7 (60.5 to 70.8)	63.2 (58.0 to 68.4)		
Reader 2: Sensitivity (n=249, 249)	73.5 (68.0 to 79.0)	60.6 (54.6 to 66.7)		
Reader 2: Specificity (n=329, 329)	69.6 (64.6 to 74.6)	64.7 (59.6 to 69.9)		
Reader 3: Sensitivity (n=249, 249)	88.8 (84.8 to 92.7)	75.5 (70.2 to 80.8)		
Reader 3: Specificity (n=329, 329)	52.6 (47.2 to 58.0)	51.4 (46.0 to 56.8)		
Majority Rule: Sensitivity (n=249, 249)	80.3 (75.4 to 85.3)	68.7 (62.9 to 74.4)		
Majority Rule: Specificity (n=329, 329)	63.8 (58.6 to 69.0)	61.7 (56.4 to 67.0)		

Statistical analyses

Statistical analysis title	Reader 1: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001 ^[3]
Method	Mcnemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	14.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	22.4

Notes:

[2] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1-sided McNemar's tests.

[3] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Reader 1: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI

Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	= 0.0004 ^[5]
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	9.7

Notes:

[4] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

[5] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Reader 2: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.0002 ^[7]
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	12.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	21

Notes:

[6] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

[7] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Reader 2: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
P-value	< 0.0001 ^[9]
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	11.8

Notes:

[8] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

[9] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Reader 3: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.0001 ^[11]
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	19.9

Notes:

[10] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

[11] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Reader 3: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[12]
P-value	= 0.0011 ^[13]
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	8.4

Notes:

[12] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

[13] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Majority Rule: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI

Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.0003 ^[15]
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	19.2

Notes:

[14] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

[15] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Statistical analysis title	Majority Rule: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	1156
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[16]
P-value	= 0.0004 ^[17]
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	9.3

Notes:

[16] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

[17] - The hypothesis tests were 1-sided McNemar's tests with a significance level of 0.025 for sensitivity.

Secondary: Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Female Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth

End point title	Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Female Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth
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End point description:

Sensitivity: TP/(TP+FN). TP: subjects with abnormal PET MPI and disease positive by truth standard and FN: subjects with normal PET MPI and disease positive by truth standard. Specificity: TN/(TN+ FP). TN: subjects with normal PET MPI and disease negative by truth standard and FP: subjects with abnormal PET MPI and disease negative by truth standard. Truth standard was presence of CAD as evidenced by presence of stenosis of $\geq 50\%$ in ≥ 1 coronary artery or major branch of a coronary artery as determined by QCA analysis. Subjects considered to have CAD if QCA revealed $\geq 50\%$ stenosis of ≥ 1 major coronary artery or major branch. Sensitivity, specificity calculated for 3 readers and majority rule using each subject judgement (positive or negative) by at least 2 of 3 readers. SMITT population. Here, "number of subjects analyzed"= subjects who were analysed for a specific reader (combined sensitivity or specificity) and "n" = subjects who were evaluable for specified categories.

End point type	Secondary
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End point timeframe:

Up to 60 days

End point values	Flurpiridaz (18F): All Subjects	SPECT MPI		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	188	188		
Units: percent				
number (confidence interval 95%)				
Reader 1: Sensitivity (n=41, 41)	82.9 (71.4 to 94.4)	58.5 (43.5 to 73.6)		
Reader 1: Specificity (n=147, 147)	72.8 (65.6 to 80.0)	63.3 (55.5 to 71.1)		
Reader 2: Sensitivity (n=41, 41)	78.0 (65.4 to 90.7)	56.1 (40.9 to 71.3)		
Reader 2: Specificity (n=147, 147)	75.5 (68.6 to 82.5)	68.7 (61.2 to 76.2)		
Reader 3: Sensitivity (n=41, 41)	92.7 (84.7 to 100.0)	75.6 (62.5 to 88.8)		
Reader 3: Specificity (n=147, 147)	59.2 (51.2 to 67.1)	58.5 (50.5 to 66.5)		
Majority Rule: Sensitivity (n=41, 41)	82.9 (71.4 to 94.4)	65.9 (51.3 to 80.4)		
Majority Rule: Specificity (n=147, 147)	72.8 (65.6 to 80.0)	66.0 (58.3 to 73.6)		

Statistical analyses

Statistical analysis title	Reader 1: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.0127
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	24.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	43.4

Notes:

[18] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 1: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[19]
P-value	= 0.0001
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	20.2

Notes:

[19] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 2: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.0195
Method	Mcnemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	22
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	41.7

Notes:

[20] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 2: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[21]
P-value	= 0.0004
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	16.8

Notes:

[21] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 3: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.0174
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	17.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	32.4

Notes:

[22] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 3: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[23]
P-value	= 0.024
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	11.3

Notes:

[23] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Majority Rule: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	= 0.0448
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	17.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	35.6

Notes:

[24] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Majority Rule: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[25]
P-value	= 0.0004
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	17

Notes:

[25] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Secondary: Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Subjects With Body-mass Index (BMI) ≥ 30 Kilograms Per Square Meter (kg/m^2) When the Diagnosis of CAD by ICA Was the Standard of Truth

End point title	Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Subjects With Body-mass Index (BMI) ≥ 30 Kilograms Per Square Meter (kg/m^2) When the Diagnosis of CAD by ICA Was the Standard of Truth
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End point description:

Sensitivity: $\text{TP}/(\text{TP}+\text{FN})$. TP: subjects with abnormal PET MPI and disease positive by truth standard and FN: subjects with normal PET MPI and disease positive by truth standard. Specificity: $\text{TN}/(\text{TN}+\text{FP})$. TN: subjects with normal PET MPI and disease negative by truth standard and FP: subjects with abnormal PET MPI and disease negative by truth standard. Truth standard was presence of CAD as evidenced by presence of stenosis of $\geq 50\%$ in ≥ 1 coronary artery or major branch of coronary artery determined by QCA analysis. Subjects considered to have CAD if QCA revealed $\geq 50\%$ stenosis of ≥ 1 major coronary artery or major branch. Sensitivity, specificity calculated for 3 readers and majority rule using each subject judgement (positive or negative) by at least 2 of 3 readers. SMITT population. Here, "number of subjects analyzed" = subjects who were analysed for a specific reader (combined sensitivity or specificity) and "n" = subjects who were evaluable for specified categories.

End point type	Secondary
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End point timeframe:

Up to 60 days

End point values	Flurpiridaz (18F): All Subjects	SPECT MPI		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	298	298		
Units: percent				
number (confidence interval 95%)				
Reader 1: Sensitivity (n=117, 117)	72.6 (64.6 to 80.7)	60.7 (51.8 to 69.5)		
Reader 1: Specificity (n=181, 181)	68.0 (61.2 to 74.8)	61.3 (54.2 to 68.4)		
Reader 2: Sensitivity (n=117, 117)	70.1 (61.8 to 78.4)	63.2 (54.5 to 72.0)		
Reader 2: Specificity (n=181, 181)	74.0 (67.6 to 80.4)	62.4 (55.4 to 69.5)		
Reader 3: Sensitivity (n=117, 117)	88.0 (82.2 to 93.9)	74.4 (66.4 to 82.3)		
Reader 3: Specificity (n=181, 181)	53.6 (46.3 to 60.9)	50.8 (43.5 to 58.1)		
Majority Rule: Sensitivity (n=117, 117)	76.9 (69.3 to 84.6)	69.2 (60.9 to 77.6)		
Majority Rule: Specificity (n=181, 181)	66.9 (60.0 to 73.7)	61.9 (54.8 to 69.0)		

Statistical analyses

Statistical analysis title	Reader 1: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.0116
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	23.9

Notes:

[26] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 1: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI

Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[27]
P-value	= 0.0003
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	16.2

Notes:

[27] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 2: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.1085
Method	Mcnemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	18.9

Notes:

[28] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 2: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[29]
P-value	< 0.0001
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	11.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	21.1

Notes:

[29] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 3: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.0017
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	23.5

Notes:

[30] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 3: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[31]
P-value	= 0.0034
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	12.1

Notes:

[31] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Majority Rule: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.0641
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	7.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	19

Notes:

[32] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Majority Rule: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[33]
P-value	= 0.001
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	14.6

Notes:

[33] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Secondary: Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Diabetic Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth

End point title	Sensitivity and Specificity of Flurpiridaz (18F) Injection PET MPI Compared SPECT MPI for Diabetic Subjects When the Diagnosis of CAD by ICA Was the Standard of Truth
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End point description:

Sensitivity: TP/(TP+FN). TP: subjects with abnormal PET MPI and disease positive by truth standard and FN: subjects with normal PET MPI and disease positive by truth standard. Specificity: TN/(TN+ FP). TN: subjects with normal PET MPI and disease negative by truth standard and FP: subjects with abnormal PET MPI and disease negative by truth standard. Truth standard was presence of CAD as evidenced by presence of stenosis of $\geq 50\%$ in ≥ 1 coronary artery or major branch of coronary artery determined by QCA analysis. Subjects considered to have CAD if QCA revealed $\geq 50\%$ stenosis of ≥ 1 major coronary artery or major branch. Sensitivity and specificity calculated for 3 readers and majority rule using each subject judgement (positive or negative) by at least 2 of 3 readers. SMITT population. Here, "number of subjects analyzed"= subjects who were analysed for a specific reader (combined sensitivity or specificity) and "n" = subjects who were evaluable for specified categories.

End point type	Secondary
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End point timeframe:

Up to 60 days

End point values	Flurpiridaz (18F): All Subjects	SPECT MPI		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	194	194		
Units: percent				
number (confidence interval 95%)				
Reader 1: Sensitivity (n=91, 91)	72.5 (63.4 to 81.7)	61.5 (51.5 to 71.5)		
Reader 1: Specificity (n=103, 103)	60.2 (50.7 to 69.6)	56.3 (46.7 to 65.9)		
Reader 2: Sensitivity (n=91, 91)	69.2 (59.7 to 78.7)	62.6 (52.7 to 72.6)		
Reader 2: Specificity (n=103, 103)	69.9 (61.0 to 78.8)	58.3 (48.7 to 67.8)		
Reader 3: Sensitivity (n=91, 91)	90.1 (84.0 to 96.2)	81.3 (73.3 to 89.3)		
Reader 3: Specificity (n=103, 103)	47.6 (37.9 to 57.2)	39.8 (30.4 to 49.3)		
Majority Rule: Sensitivity (n=91, 91)	75.8 (67.0 to 84.6)	71.4 (62.1 to 80.7)		
Majority Rule: Specificity (n=103, 103)	61.2 (51.8 to 70.6)	51.5 (41.8 to 61.1)		

Statistical analyses

Statistical analysis title	Reader 1: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.0294
Method	Mcnemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	24.6

Notes:

[34] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 1: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI

Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[35]
P-value	= 0.0117
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	16.1

Notes:

[35] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 2: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.1444
Method	Mcnemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	20.3

Notes:

[36] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 2: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[37]
P-value	= 0.0001
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	23.7

Notes:

[37] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Reader 3: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority ^[38]
P-value	= 0.044
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	18.9

Notes:

[38] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Reader 3: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[39]
P-value	= 0.0022
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	20.3

Notes:

[39] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Statistical analysis title	Majority Rule: Sensitivity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority ^[40]
P-value	= 0.2164
Method	McNemar
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	4.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	17.2

Notes:

[40] - The test of sensitivity comparison between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a 1-sided McNemar's test at a significance level of 0.025 using 1- sided McNemar's tests.

Statistical analysis title	Majority Rule: Specificity
Comparison groups	Flurpiridaz (18F): All Subjects v SPECT MPI
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[41]
P-value	= 0.0006
Method	Nam's RMLE
Parameter estimate	Difference between PET MPI and SPECT MPI
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	22

Notes:

[41] - The test of specificity noninferiority between Flurpiridaz (18F) Injection PET MPI and SPECT MPI was performed with a paired test for noninferiority at a 1-sided significance level of 0.025 using Nam's RMLE method (margin=0.1).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent to end of follow up (up to 77 days)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Flurpiridaz (18F): Safety Population
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Reporting group description:

Subjects received 2 IV boluses of Flurpiridaz (18F) Injection in large peripheral vein: 1 at rest then 1 during stress on same day within 60 days prior to ICA. Flurpiridaz(18F) Injection administered were not to exceed total of 14 mCi (520 MBq). Flurpiridaz was administered on Day 1. SPECT agents 99mTc based myocardial tracers e.g. [99mTc]tetrofosmin or [99mTc]sestamibi were administered per American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location. Same stress type (pharmacologic or exercise) was used for SPECT and Flurpiridaz(18F) Injection PETMPI. Also, if pharmacological stress was used, same agent, dose of pharmacological stress agent was used for both types of imaging for same subject. Pharmacological stress agents administered according to respective Package Insert or American Society of Nuclear Cardiology or European Association of Cardiovascular Imaging standards corresponding to study site location.

Serious adverse events	Flurpiridaz (18F): Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 604 (3.31%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural fever			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 604 (0.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	2 / 604 (0.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery perforation			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Left ventricular dysfunction			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			

subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular stent thrombosis			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria chronic			

subjects affected / exposed	1 / 604 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Flurpiridaz (18F): Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 604 (24.01%)		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	32 / 604 (5.30%)		
occurrences (all)	32		
Nervous system disorders			
Headache			
subjects affected / exposed	80 / 604 (13.25%)		
occurrences (all)	80		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	68 / 604 (11.26%)		
occurrences (all)	68		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2018	Amendment 1: Left ventricular ejection fraction (LVEF) <50% was removed from exclusion criterion (8). The purpose of exclusion criterion 8 was to eliminate known/confirmed heart failure. The inclusion of an EF lower limit to specify which subjects should be included did 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 was not relevant to the aim of excluding those with a heart failure diagnosis as a whole. Even if the purpose was to exclude only subjects 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 (18F) 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 determined that these concerns were minimal, given: (1) there were no unique concerns regarding drug/illicit drug interactions, particularly given that Flurpiridaz is administered to subjects in one sitting (as opposed to repeatedly) at a tracer dose;
03 August 2018	Amendment 1 (Continued): (2) concerns of confounding the correlation between the anatomical gold standard of the QCA and the PET MPI blinded reads were minimal. It was 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 believed that these discrepancies were likely to be minimal and encountered infrequently, and (3) subjects were already being screened for psychiatric conditions which could impair participation in all study visits (exclusion #12). Substance abuse is an axis II disorder and investigators were counselled to exclude subjects with ongoing drug abuse that may have led to poor compliance in the manual of procedures. Given the short-term follow up of this study, it was unlikely that occult substance abuse (missed as part of the medical history) would frequently impair subject follow up. Since the Sponsor believed that active substance abuse was 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 was not justified. • Guidance regarding use of beta blocker therapy was added. To ensure that the PET and SPECT MPI were conducted according to guidelines and in accordance with standard clinical care, study sites were 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 acknowledged 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).

03 August 2018	Amendment 1 (Continued): • Clarification that an additional blood sample at screening could be analysed by the local lab to determine if the subject met exclusion criteria. Dependence on central lab results for screening purposes would 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 added a significant hurdle to subject 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 was expected to be less than 7 days. Permitting screening through the use of local labs permitted subject 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 could still be used for screening if local labs were not drawn. The determination of whether to draw local labs for this purpose rested with the investigator and depended on the rapidity with which the study visits occurred (e.g., if the window between screening and ICA was brief, local labs were advised, if this window was more lengthy than local labs were not drawn). Significant discordance between local and central lab results was unlikely since the central and local labs would be drawn in the same sitting at screening. If they did occur the local lab would take precedence for the screening purposes. The safety data set was to use exclusively the central labs to analyse changes in biochemistry, since all patients would systematically have labs analysed centrally at screening and pre- and post-scan timepoints. • Safety reporting for AEs and SAEs was updated and clarified.
18 November 2019	Amendment 02: • Clarification of time points for recording vital signs. • Clarification in text that urine would be collected at pre-treatment time points only. • Medical Director details were updated following a change in personnel.
22 July 2021	Amendment 03: • 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).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 March 2020	The study was paused in 2Q 2020 to avoid exposing patients to an increased risk of COVID-19 infection when attending hospital visits. Clinical study activities were resumed progressively starting at the beginning of 3Q 2020, in full respect of country regulations and hospital conditions (e.g., restrictions to the conduct of clinical studies, COVID screening for access to hospitals).	31 July 2020

Notes:

Limitations and caveats

None reported