



Clinical trial results:

A prospective, Phase 3, multi-center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (18F) PET ligand in men with suspected prostate cancer recurrence based on elevated PSA following prior therapy (Spotlight)

Summary

EudraCT number	2019-003382-18
Trial protocol	FI NL
Global end of trial date	12 October 2021

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023

Trial information

Trial identification

Sponsor protocol code	BED-PSMA-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 141,561

Notes:

Sponsors

Sponsor organisation name	Blue Earth Diagnostics, Ireland Ltd
Sponsor organisation address	6th Floor, Grand Canal Square, Dublin, Ireland, Dublin 2
Public contact	PSMA Clinical Manager, Blue Earth Diagnostics, Inc, +1 9199998670, contact@blueearthdx.com
Scientific contact	PSMA Clinical Manager, Blue Earth Diagnostics, Inc, +1 9199998670, contact@blueearthdx.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	12 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the patient-level correct detection rate (CDR) and region-level positive predictive value (PPV) of rhPSMA-7.3 (18F) positron emission tomography (PET) for biochemical recurrence (BCR) of prostate cancer using histopathology or imaging as a standard of truth (SoT).

Protection of trial subjects:

This study was conducted according to the principles of the Declaration of Helsinki and in accordance with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP). In addition, all relevant regulations and guidance were followed, including United States (US), European Union (EU) and national legislation. As this study was conducted during the coronavirus disease 2019 (COVID-19) global pandemic, relevant guidance from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) were followed, including, but not limited to, the FDA Guidance for Industry, Investigators, and Institutional Review Boards - Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (March 2020; updated 30 August 2021) and the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (Version 4, 04 February 2021). Prior to study initiation in each country, the study was authorized by the relevant Regulatory Agency/Competent Authority. All applicable privacy regulations (e.g. US Health Insurance Portability and Accountability Act [HIPAA] 1996; EU General Data Protection Regulation [GDPR] 2018; United Kingdom [UK] Data Protection Act 2018) were adhered to.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	04 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	United States: 375
Worldwide total number of subjects	391
EEA total number of subjects	16

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)	121
From 65 to 84 years	267
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 04 May 20 (first patient, screening visit) and 12 Oct 21 (database lock), with last patient, last visit on 28 Apr 21. It was conducted at 28 activated study sites (27 recruited) in 3 countries. Of the 420 patients screened, 391 patients met all the study eligibility criteria

Pre-assignment

Screening details:

Baseline safety evaluations performed at screening (Visit 1) comprised vital signs and recording of any adverse events (AEs) from the time of informed consent.

Period 1

Period 1 title	Full Analysis Set (FAS) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not relevant

Arms

Arm title	Single Arm
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Arm description:

All patients who were scheduled to receive the rhPSMA-7.3 (18F) injection having met the inclusion/exclusion criteria or who received the rhPSMA-7.3 (18F) injection.

Arm type	Experimental
Investigational medicinal product name	rhPSMA-7.3 (18F)
Investigational medicinal product code	rhPSMA-7.3 (18F)
Other name	flotufolastat F18
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

All patients were planned to receive a single dose of IMP, with an administered activity of 8 mCi (296 MBq) $\pm$ 20% of rhPSMA-7.3 (18F), delivered as an IV bolus injection followed by a 10 mL fast 0.9% sodium chloride flush. The mass dose administered was less than 100 μ g/patient. rhPSMA-7.3 (18F) was supplied as a sterile, aqueous solution for IV administration either in a multi-dose vial sealed with a synthetic rubber closure and aluminum overseal or in a single unit dose syringe depending on the manufacturing location

Number of subjects in period 1	Single Arm
Started	391
Completed	391

Baseline characteristics

Reporting groups

Reporting group title	Full Analysis Set (FAS)
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Reporting group description:

All patients who were scheduled to receive the rhPSMA-7.3 (18F) injection having met the inclusion/exclusion criteria or who received the rhPSMA-7.3 (18F) injection.

Reporting group values	Full Analysis Set (FAS)	Total	
Number of subjects	391	391	
Age categorical			
Age in years			
Units: Subjects			
< 65	121	121	
≥ 65	270	270	
Age continuous			
Age in years			
Units: years			
arithmetic mean	68.3		
standard deviation	± 7.92	-	
Gender categorical			
Gender as Male or Female			
Units: Subjects			
Female	0	0	
Male	391	391	
Race			
Race split into 3 substantive categories and also those for whom it was not reported			
Units: Subjects			
Black or African American	61	61	
White	295	295	
Other	14	14	
Not Reported	21	21	
Ethnicity			
Ethnicity split into 2 substantive groups and those for whom it was not reported			
Units: Subjects			
Hispanic or Latino	18	18	
Non-Hispanic or Latino	342	342	
Not Reported	31	31	
Total Gleason Score			
Gleason score (defined by the International Society of Urological Pathologists) was based on prostate biopsy.			
Units: Subjects			
≤6	39	39	
=7	232	232	
=8	41	41	
=9	63	63	
=10	1	1	
Missing	15	15	
Gleason Grade Group (GGG)			

GGG (defined by the International Society of Urological Pathologists) was based on prostate biopsy.			
Units: Subjects			
=1	39	39	
=2	104	104	
=3	116	116	
=4	41	41	
=5	64	64	
Missing	27	27	
TNM (Tumor-Node-Metastasis) Stage T			
Pathological TNM stage was used if available, otherwise the clinical TNM was used.			
Units: Subjects			
T1	4	4	
T1c	54	54	
T2	52	52	
T2a	15	15	
T2b	10	10	
T2c	63	63	
T3	10	10	
T3a	82	82	
T3b	68	68	
T3c	0	0	
T4	2	2	
TX	7	7	
Missing	24	24	
TNM Stage N			
Pathological TNM stage was used if available, otherwise the clinical TNM was used.			
Units: Subjects			
N0	249	249	
N1	53	53	
NX	61	61	
Missing	28	28	
TNM Stage M			
Pathological TNM stage was used if available, otherwise the clinical TNM was used.			
Units: Subjects			
M0	243	243	
M1	1	1	
M1a	0	0	
M1b	1	1	
M1c	0	0	
MX	106	106	
Missing	40	40	
Body Mass Index (BMI)			
BMI was calculated as weight in kg divided by height in m2.			
Units: Kg/m2			
arithmetic mean	28.68		
standard deviation	± 4.740	-	
Time since initial cancer diagnosis			
<<Time in months.>>			
Units: Months			
arithmetic mean	87.3		
standard deviation	± 65.70	-	

Time since diagnosis of biochemical recurrence			
Time since diagnosis of biochemical recurrence			
Units: Month			
geometric mean	17.1		
standard deviation	± 27.15	-	
Time since start of adjuvant treatment			
Time since start of adjuvant treatment.			
Units: month			
geometric mean	67.3		
standard deviation	± 50.26	-	
Time since end of adjuvant treatment			
Time since end of adjuvant treatment.			
Units: month			
geometric mean	60.2		
standard deviation	± 49.11	-	
Duration of adjuvant treatment			
Duration of adjuvant treatment.			
Units: month			
geometric mean	7.2		
standard deviation	± 16.05	-	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description: All patients who were scheduled to receive the rhPSMA-7.3 (18F) injection having met the inclusion/exclusion criteria or who received the rhPSMA-7.3 (18F) injection.	
Subject analysis set title	Efficacy Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: All patients who were scheduled to receive the rhPSMA-7.3 (18F) injection having met the inclusion/exclusion criteria or who received the rhPSMA-7.3 (18F) injection.	

Primary: Patient-Level CDR Reader 1

End point title	Patient-Level CDR Reader 1
End point description: Patient-level CDR was defined as the percentage of all patients scanned who had at least one TP lesion (localized correspondence between rhPSMA-7.3 (18F) PET imaging and the reference standard) regardless of any co-existing FP findings. To determine patient-level CDR, images were interpreted by 3 independent central PET readers. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven; True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F) PET findings.	
End point type	Primary
End point timeframe: In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.	

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: Percentage				
number (confidence interval 95%)	54.1 (48.8 to 59.3)	54.1 (48.8 to 59.3)		

Statistical analyses

Statistical analysis title	Patient Level CDR - Reader 1
Statistical analysis description: The co-primary endpoint of patient-level CDR of rhPSMA-7.3 (18F) PET. The hypothesis was H0: CDR ≤36.5% versus H1: CDR >36.5%.	
Comparison groups	Single Arm v Efficacy Analysis Population

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001 ^[2]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	54.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.8
upper limit	59.3
Variability estimate	Standard deviation

Notes:

[1] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the three independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the CDR.

[2] - H0: CDR ≤ 36.5%

Primary: Patient-Level CDR Reader 2

End point title	Patient-Level CDR Reader 2
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End point description:

Region-level PPV was defined as TP/[TP+FP], using all PET-positive regions) of rhPSMA-7.3 (18F) PET. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven; True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F). PET findings. PET positive lesions, as determined by the blinded, central read, will be subjected to the SoT algorithm to determine the patient level CDR and region level PPV.

End point type	Primary
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End point timeframe:

In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: Percentage				
number (confidence interval 95%)	51.4 (46.1 to 56.6)	51.4 (46.1 to 56.6)		

Statistical analyses

Statistical analysis title	Patient-Level CDR Reader 2
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Statistical analysis description:

The co-primary endpoint of patient-level CDR of rhPSMA-7.3 (18F) PET. The hypothesis was H0: CDR ≤36.5% versus H1: CDR >36.5%.

Comparison groups	Single Arm v Efficacy Analysis Population
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001 ^[4]
Method	Exact binomial test
Parameter estimate	Percentage
Point estimate	51.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.1
upper limit	56.6
Variability estimate	Standard deviation

Notes:

[3] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the three independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the CDR.

[4] - H0: CDR ≤ 36.5%

Primary: Patient-Level CDR Reader 3

End point title	Patient-Level CDR Reader 3
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End point description:

Patient-level CDR was defined as the percentage of all patients scanned who had at least one TP lesion (localized correspondence between rhPSMA-7.3 (18F) PET imaging and the reference standard) regardless of any co-existing FP findings. To determine patient-level CDR images were interpreted by 3 independent central PET readers. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven: True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F) PET findings.

End point type	Primary
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End point timeframe:

In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: percentage				
number (confidence interval 95%)	51.6 (46.4 to 56.9)	51.6 (46.4 to 56.9)		

Statistical analyses

Statistical analysis title	Patient-Level CDR Reader 3
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Statistical analysis description:

The co-primary endpoint of patient-level CDR of rhPSMA-7.3 (18F) PET. The hypothesis was H0: CDR

≤36.5% versus H1: CDR >36.5%.

Comparison groups	Single Arm v Efficacy Analysis Population
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001 ^[6]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	51.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.4
upper limit	56.9
Variability estimate	Standard deviation

Notes:

[5] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the 3 independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the CDR.

[6] - H0: CDR ≤ 36.5%

Primary: Region-level PPV Reader 1

End point title	Region-level PPV Reader 1
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End point description:

Region-level PPV was defined as TP/[TP+FP], using all PET-positive regions) of rhPSMA-7.3 (18F) PET. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven; True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F) PET findings. PET positive lesions, as determined by the blinded, central read, will be subjected to the SoT algorithm to determine the patient level CDR and region level PPV.

End point type	Primary
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End point timeframe:

In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: percentage				
number (confidence interval 95%)	46.2 (42.0 to 50.3)	46.2 (42.0 to 50.3)		

Statistical analyses

Statistical analysis title	Region-level PPV Reader 1
Statistical analysis description: The co-primary endpoint of region-level PPV of rhPSMA-7.3 (18F) PET. The hypothesis was H0: PPV $\leq$ 62.5% versus H1: PPV > 62.5%.	
Comparison groups	Single Arm v Efficacy Analysis Population
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 1 ^[8]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	46.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	42
upper limit	50.3
Variability estimate	Standard deviation

Notes:

[7] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the three independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the PPV.

[8] - H0: PPV $\leq$ 62.5%

Primary: Region-level PPV Reader 2

End point title	Region-level PPV Reader 2
End point description: Region-level PPV was defined as TP/[TP+FP], using all PET-positive regions) of rhPSMA-7.3 (18F) PET. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven; True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F) PET findings. PET positive lesions, as determined by the blinded, central read, will be subjected to the SoT algorithm to determine the patient level CDR and region level PPV.	
End point type	Primary
End point timeframe: In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.	

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: percentage				
number (confidence interval 95%)	60.3 (55.1 to 65.5)	60.3 (55.1 to 65.5)		

Statistical analyses

Statistical analysis title	Region-level PPV Reader 2
Statistical analysis description: The co-primary endpoint of region-level PPV of rhPSMA-7.3 (18F) PET. The hypothesis was H0: PPV $\leq$ 62.5% versus H1: PPV > 62.5%.	
Comparison groups	Single Arm v Efficacy Analysis Population
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.7954 ^[10]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	60.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.1
upper limit	65.5

Notes:

[9] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the three independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the PPV.

[10] - H0 PPV $\leq$ 62.5%

Primary: Region-level PPV Reader 3

End point title	Region-level PPV Reader 3
End point description: Region-level PPV was defined as TP/[TP+FP], using all PET-positive regions) of rhPSMA-7.3 (18F) PET. 3 different central readers (SoT consensus panel) then reviewed all available conventional images (historical, baseline and confirmatory imaging scans) and determined via consensus if representative rhPSMA-7.3 (18F) PET-positive lesions identified by the central PET readers were consistent with prostate cancer (SoT proven; True Positive [TP] lesions) or not consistent with prostate cancer (SoT not proven: False Positive [FP] lesions). These consensus reads of the confirmatory imaging for SoT assessment were directed by rhPSMA-7.3 (18F) PET findings. PET positive lesions, as determined by the blinded, central read, will be subjected to the SoT algorithm to determine the patient level CDR and region level PPV.	
End point type	Primary
End point timeframe: In the 60 days post-PET scan, patients were to undergo an image-guided confirmatory biopsy or confirmatory conventional imaging of any PET-positive lesion(s) for SoT assessment.	

End point values	Single Arm	Efficacy Analysis Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	366	366		
Units: percentage				
number (confidence interval 95%)	52.6 (47.6 to 57.5)	52.6 (47.6 to 57.5)		

Statistical analyses

Statistical analysis title	Region Level PPV Reader 3
Statistical analysis description: The co-primary endpoint of region-level PPV of rhPSMA-7.3 (18F) PET. The hypothesis was H0: PPV $\leq$ 62.5% versus H1: PPV > 62.5%.	
Comparison groups	Single Arm v Efficacy Analysis Population
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 1 ^[12]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	52.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.6
upper limit	57.5

Notes:

[11] - The endpoint was summarized as a percentage, together with a 2-sided exact 95% confidence interval (CI) for each of the three independent central PET readers. In addition, a 1-sided exact binomial test p-value was provided for each independent central PET reader for the PPV.

[12] - H0 PPV $\leq$ 62.5%

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were also monitored throughout the study from the time of informed consent until the last study visit.

Adverse event reporting additional description:

AEs (treatment emergent) were coded with MedDRA and data listed by patient: study site, patient identifier, age, race, AE (MedDRA SOC, PT and verbatim term), dates of onset and resolution, duration, CTCAE toxicity grade, seriousness, action taken, outcome and causality. Deaths, SAEs and AEs leading to discontinuation were listed by patient

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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Reporting groups

Reporting group title	Full Safety Population (FSP)
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Reporting group description:

<<All patients who received the rhPSMA-7.3 (18F) injection.>>

Serious adverse events	Full Safety Population (FSP)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 391 (0.51%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Full Safety Population (FSP)		
Total subjects affected by non-serious adverse events subjects affected / exposed	28 / 391 (7.16%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 391 (1.79%)		
occurrences (all)	7		
Flushing			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	2 / 391 (0.51%)		
occurrences (all)	2		
Injection site discomfort			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Sinus congestion			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	1 / 391 (0.26%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	2 / 391 (0.51%) 2 1 / 391 (0.26%) 1 1 / 391 (0.26%) 1		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 391 (0.26%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	4 / 391 (1.02%) 4 1 / 391 (0.26%) 1 1 / 391 (0.26%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 391 (0.26%) 1		
Renal and urinary disorders Ureterolithiasis subjects affected / exposed occurrences (all)	1 / 391 (0.26%) 1		
Musculoskeletal and connective tissue disorders			

Flank pain			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 391 (0.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2020	Updates based on feedback from the US FDA, including amendment of the co-primary efficacy endpoint. Clarify: definition for the co-primary endpoint of CDR. Update: co-primary endpoint of PPV; changed to a region-level not patient-level analysis (FDA recommended). Details added on how this was determined. Add: text to indicate the overall PPV will likely be decreased by patients with multiple PSMA PET-positive regions given histological confirmation of multiple lesions in the same patient is highly unlikely. Edits: secondary and exploratory endpoints for clarity. Add: details to stop enrollment of patients with a PSA <1 ng/mL if the proportion exceeds 60% at the planned interim analysis. Add: Optional Visit 2a. Clarify: dose of IMP could be 8 mCi (296 MBq) $\pm$ 20% of rhPSMA-7.3 (18F). Clarify: key assumptions. Edit: inclusion criteria regarding elevated PSA, clinically suspicious for biochemically recurrent disease to include nadir +2 ng/mL following focal gland therapies. Update: diluted volumes of IMP that can be used and to the shelf life of IMP. Clarify: wording around baseline conventional imaging, historical conventional imaging and addition of text for confirmatory imaging. Edit: process for biopsy/surgery, SoT algorithm and central reading plan. Clarify: assessment of impact on clinical management plan depends on clinical utility questionnaire completed pre- and post-PSMA PET scan. Clarify: timepoint for conventional imaging if historical conventional imaging took place greater than 90 days before Visit 1. Update: sample size and number of evaluable patients required before enrollment will stop. Update: analysis sets. Add: detail for the joint hypothesis for the co-primary endpoints. Add: planned interim analysis once 60% of the planned 190 positive cases have information. Minor typographical edits.

01 July 2020	Updates to ensure patient safety for COVID-19/implement BfArM feedback Screening extended 28-45 days Add: Visit 1 and Visit 2 combined Clarify: conventional imaging at non-participating institutions acceptable Clarify: patients with multiple PET-positive regions, confirmed at least 1 PET-positive lesion in each region needed for efficacy analyses Add: possible to delay biopsy and surgical procedures performed to obtain SoT histopathology and initial confirming imaging up to Day 60 for safety Clarify: inclusion criterion related to elevated PSA, clinically suspicious for biochemically recurrent disease Add: exclusion criterion: patients with hypersensitivity to the active substance or any of the IMP excipients Clarify: contrast-enhanced CT/MRI and radiopharmaceutical-based baseline conventional imaging performed at least 24 hours apart from investigational rhPSMA-7.3 (18F) PET scan Define: regions added: prostate bed, pelvic lymph nodes, and other Add: assessment of the most accessible and feasible lesion(s) for biopsy include safety consideration, and others already listed Clarify: patients with multiple lesions in a specific region, 1 TP lesion determines region truth regardless of concurrent FP findings in same region Increase from 2-3 independent central PET readers for the rhPSMA-7.3 (18F) PET scans and details of information provided added (Independent Review Charter) Add: Visit 3 could be performed by a licensed and credentialed clinician and conducted by telephone per site discretion Add: text on the replacement of dropout patients Update: SAE reporting email address; clarify: SAEs to be reported immediately Add: section detailing reasons patient enrollment may be temporarily halted/stopped Add: option for remote study monitoring instead of on-site monitoring (COVID-19) Clarify: Urgent Safety Measures include amendments made due to COVID-19 to ensure safety by minimizing potential exposure to SARS-CoV-2 Minor typographical edits
23 October 2020	Removal of the formal (hypothesis testing) interim analysis. Remove: the following exploratory objective and corresponding endpoint: assess an incremental rhPSMA-7.3 (18F) PET findings (e.g. more sites of involvement) compared to conventional imaging. Add: BMI to demographic information recorded at screening. Update: SAE reporting email address and medical monitor details. Minor typographical edits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: