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 newly diagnosed prostate cancer

Summary

EudraCT number	2019-003381-40
Trial protocol	DE FI NL
Global end of trial date	21 June 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-301

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	18 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2021
Global end of trial reached?	Yes
Global end of trial date	21 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central blinded image evaluation [BIE]) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during radical prostatectomy (RP) and pelvic lymph node dissection (PLND). At least one positive pelvic LN on PET (N1) and one positive lymph node (LN) as determined by histopathology (pN1) on the same side of the pelvis (left or right) will be deemed a True Positive (TP) at the patient level.

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) was 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 Aug 21) and the EMA Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (Version 4, 04 Feb 21). 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 2018; United Kingdom [UK] Data Protection Act 2018) were adhered to.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	02 March 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	Finland: 18
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	United States: 238
Country: Number of subjects enrolled	Netherlands: 14
Worldwide total number of subjects	356
EEA total number of subjects	118

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)	163
From 65 to 84 years	193
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was from 02 Mar 20 (first patient, screening visit) and 18 Feb 22 (database lock), with the last patient, last visit on 21 Jun 21. It was conducted at 34 activated study sites (31 recruited) in 4 countries. Of the 372 patients screened, 356 patients met all the study eligibility criteria. 16 patients were screen failures so not included

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Single Arm

Arm description:

All patients 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) ± 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 µg/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	356
Completed	356

Baseline characteristics

Reporting groups	
Reporting group title	Single Arm
Reporting group description:	
The FAS comprised 356 patients who were scheduled to receive the rhPSMA-7.3 (18F) injection and met the inclusion/exclusion criteria	

Reporting group values	Single Arm	Total	
Number of subjects	356	356	
Age categorical			
Age in years split into 2 groups			
Units: Subjects			
< 65 years	163	163	
≥ 65 years	193	193	
Age continuous			
Age in years			
Units: years			
arithmetic mean	64.9		
standard deviation	± 6.98	-	
Gender categorical			
Gender as Male or Female			
Units: Subjects			
Female	0	0	
Male	356	356	
Race			
Race split into 3 substantive categories and also those for whom it was not reported			
Units: Subjects			
Black or African American	30	30	
White	289	289	
Other	4	4	
Not Reported	33	33	
Ethnicity			
Ethnicity split into 2 substantive groups and those for whom it was not reported			
Units: Subjects			
Hispanic or Latino	17	17	
Non-Hispanic or Latino	311	311	
Not Reported	28	28	
Total Gleason Score			
Gleason score (defined by the International Society of Urological Pathologists) was based on prostate biopsy.			
Units: Subjects			
=7	160	160	
=8	87	87	
=9	97	97	
=10	6	6	
≤ 6	6	6	
Gleason Grade Group (GGG)			
GGG (defined by the International Society of Urological Pathologists) was based on prostate biopsy.			

Units: Subjects			
=1	6	6	
=2	50	50	
=3	110	110	
=4	87	87	
=5	103	103	
TNM (Tumor-Node-Metastasis) Stage T			
TNM Stage T			
Units: Subjects			
T1	16	16	
T1a	2	2	
T1c	127	127	
T2	58	58	
T2a	18	18	
T2b	25	25	
T2c	33	33	
T3	20	20	
T3a	21	21	
T3b	12	12	
T3c	1	1	
T4	2	2	
TX	9	9	
Missing	12	12	
TNM Stage M			
TNM Stage M			
Units: Subjects			
M0	290	290	
M1	4	4	
M1a	1	1	
M1b	1	1	
MX	48	48	
Missing	12	12	
Prostate-specific antigen (PSA) Characterization (ng/mL)			
PSA Characterization (ng/mL)			
Units: Subjects			
0 to 0.5	0	0	
>0.5 to 1.0	0	0	
>1.0 to 2.0	2	2	
>2.0 to 5.0	62	62	
>5.0 to 10.0	134	134	
>10.0	158	158	
Baseline Risk Category			
Baseline Risk Category. High-risk or Very-high risk defined as meeting any one of these criteria: T-stage T3 (including T3a and T3b) or T4, GGG 4 or 5, Primary Gleason pattern 5, or PSA >20 ng/mL..			
Units: Subjects			
High-risk or Very-high risk	241	241	
Immediate-risk	115	115	
TNM Stage N			
TNM Stage N			
Units: Subjects			
N0	284	284	

N1	11	11	
NX	49	49	
Missing	12	12	

Body Mass Index			
Body mass index on Day 1			
Units: Kg/m2			
arithmetic mean	28.20		
standard deviation	± 4.341	-	
Time since initial cancer diagnosis			
Time since initial cancer diagnosis relative to the date of informed consent.			
Units: Months			
arithmetic mean	2.9		
standard deviation	± 10.27	-	
Time since last PSA measurement			
Time since last PSA measurement			
Units: Months			
arithmetic mean	2.5		
standard deviation	± 2.83	-	
Last PSA Measurement (ng/mL)			
Last PSA measurement (ng/mL)			
Units: ng/mL			
arithmetic mean	15.090		
standard deviation	± 18.2450	-	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description:	
All patients who received the rhPSMA-7.3 (18F) injection	
Subject analysis set title	EAP
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis	

Primary: Specificity Reader 1

End point title	Specificity Reader 1
End point description:	
The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.	
End point type	Primary
End point timeframe:	
Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.	

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	226	226		
Units: percentage				
number (confidence interval 95%)	92.9 (88.8 to 95.9)	92.9 (88.8 to 95.9)		

Statistical analyses

Statistical analysis title	Specificity
Statistical analysis description:	
The co-primary endpoint of patient-level specificity (TN/[TN+FP]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the EAP. The hypothesis was: H0: Specificity ≤Sp0 versus H1: Specificity >Sp0 (Sp0=performance goal of 82.5%, based on high specificity of other PSMA ligands used for lymph node staging. Specificity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.	
Comparison groups	Single Arm v EAP
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	92.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	88.8
upper limit	95.9

Notes:

[1] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[2] - H0: Specificity ≤ 82.5%

Primary: Specificity Reader 2

End point title	Specificity Reader 2

End point description:

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

End point type	Primary

End point timeframe:

Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	226	226		
Units: percentage				
number (confidence interval 95%)	93.8 (89.8 to 96.6)	93.8 (89.8 to 96.6)		

Statistical analyses

Statistical analysis title	Specificity

Statistical analysis description:

The co-primary endpoint of patient-level sensitivity (TP/[TP+FN]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the EAP. The hypothesis was: H0: Sensitivity ≤Se0 versus H1: Sensitivity >Se0 (Se0=performance goal of 22.5%, based on low sensitivity of other PSMA ligands used for lymph node staging. Sensitivity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.

Comparison groups	Single Arm v EAP
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	93.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	89.8
upper limit	96.6

Notes:

[3] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[4] - H0: Sensitivity ≤ 82.5%

Primary: Specificity Reader 3

End point title	Specificity Reader 3

End point description:

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

End point type	Primary

End point timeframe:

Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	226	226		
Units: percentage				
number (confidence interval 95%)	96.9 (93.7 to 98.7)	96.9 (93.7 to 98.7)		

Statistical analyses

Statistical analysis title	Specificity

Statistical analysis description:

The co-primary endpoint of patient-level specificity (TN/[TN+FP]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the PPN. The hypothesis was: H0: Specificity ≤Sp0 versus H1: Specificity >Sp0 (Sp0=performance goal of 82.5%, based on high specificity of other PSMA ligands used for lymph node staging. Specificity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.

Comparison groups	Single Arm v EAP
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	96.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	93.7
upper limit	98.7

Notes:

[5] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have
successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[6] - H0: Specificity ≤ 82.5%

Primary: Sensitivity Reader 1

End point title	Sensitivity Reader 1

End point description:

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

End point type	Primary

End point timeframe:

Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	70	70		
Units: percentage				
number (confidence interval 95%)	30.0 (19.6 to 42.1)	30.0 (19.6 to 42.1)		

Statistical analyses

Statistical analysis title	Sensitivity

Statistical analysis description:

The co-primary endpoint of patient-level sensitivity (TP/[TP+FN]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the PPN. The hypothesis was: H0: Sensitivity ≤Se0 versus H1: Sensitivity >Se0 (Se0=performance goal of 22.5%, based on low sensitivity of other PSMA ligands used for lymph node staging. Sensitivity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.

Comparison groups	Single Arm v EAP
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.09 [8]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	30

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.6
upper limit	42.1

Notes:

[7] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have
successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[8] - H0: Sensitivity ≤ 22.5%

Primary: Sensitvity Reader 2

End point title	Sensitvity Reader 2

End point description:

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

End point type	Primary

End point timeframe:

Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	70	70		
Units: Percentage				
number (confidence interval 95%)	27.1 (17.2 to 39.1)	27.1 (17.2 to 39.1)		

Statistical analyses

Statistical analysis title	Sensitivity

Statistical analysis description:

The co-primary endpoint of patient-level sensitivity (TP/[TP+FN]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the PPN. The hypothesis was: H0: Sensitivity ≤Se0 versus H1: Sensitivity >Se0 (Se0=performance goal of 22.5%, based on low sensitivity of other PSMA ligands used for lymph node staging. Sensitivity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.

Comparison groups	Single Arm v EAP
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.213 [10]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	27.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	17.2
upper limit	39.1

Notes:

[9] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have
successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[10] - H0: Sensitivity ≤ 22.5%

Primary: Sensitivity Reader 3

End point title	Sensitivity Reader 3

End point description:

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (18F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

End point type	Primary

End point timeframe:

Patients were to receive treatment within 60 days post-IMP administration, with treatment decision based on rhPSMA-7.3 (18F) PET and conventional imaging.

End point values	Single Arm	EAP		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	70	70		
Units: Percentage				
number (confidence interval 95%)	22.9 (13.7 to 34.4)	22.9 (13.7 to 34.4)		

Statistical analyses

Statistical analysis title	Sensitivity

Statistical analysis description:

The co-primary endpoint of patient-level sensitivity (TP/[TP+FN]) of rhPSMA-7.3 (18F) PET (determined by central BIE) to detect PLN metastases compared to surgical pathology, was performed using the PPN. The hypothesis was: H0: Sensitivity ≤Se0 versus H1: Sensitivity >Se0 (Se0=performance goal of 22.5%, based on low sensitivity of other PSMA ligands used for lymph node staging. Sensitivity % with corresponding 95% CIs were estimated for 3 blinded readers and the majority evaluation.

Comparison groups	Single Arm v EAP
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.518 [12]
Method	Exact binomial
Parameter estimate	Percentage
Point estimate	22.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	13.7
upper limit	34.4

Notes:

[11] - The analysis was performed using a 1-sided 0.025 exact binomial test. In addition to the rates, exact 2-sided 95% CIs were provided. If the predefined goal was met by the same 2 of 3 blinded independent readers (both tests reached statistical significance [P<0.05] for the same 2 readers), the study was considered to have
successfully demonstrated the effectiveness of the rhPSMA-7.3 (18F) in detecting N1 disease.
[12] - H0: Sensitivity ≤ 22.5%

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded throughout the study from informed consent at screening until the last study visit. AEs reported in EudraCT are treatment-emergent.

Adverse event reporting additional description:

AEs were coded using MedDRA and data listed by patient, including 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 also listed by patient

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Full Safety Population (FSP)

Reporting group description:

All patients who received the rhPSMA-7.3 (18F) injection. The FSP was used for all safety summaries.

Serious adverse events	Full Safety Population (FSP)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 356 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Full Safety Population (FSP)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 356 (7.87%)		
Injury, poisoning and procedural complications			
Tracheal deviation			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		

Hypertension subjects affected / exposed occurrences (all) Thrombophlebitis subjects affected / exposed occurrences (all)	2 / 356 (0.56%) 2 1 / 356 (0.28%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 356 (0.28%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	1 / 356 (0.28%) 1 5 / 356 (1.40%) 5		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all)	1 / 356 (0.28%) 1 3 / 356 (0.84%) 3 1 / 356 (0.28%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Proctalgia subjects affected / exposed occurrences (all) Nausea	1 / 356 (0.28%) 1 1 / 356 (0.28%) 1		

subjects affected / exposed	3 / 356 (0.84%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Nervousness			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria traumatic			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Lower urinary tract symptoms			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 356 (0.28%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 356 (0.28%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	 1 / 356 (0.28%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2020	Several updates based on feedback from the US FDA. Update: studies evaluating 68Ga-PSMA-11 PET or 18F-DCFPyL-PSMA PET in the Study Rationale, including addition of point estimate ranges for the studies quoted. Clarify: study rationale that the study was to be performed in patients eligible for curative intent, locoregional therapy. Clarify: baseline conventional imaging was required if not performed in the 60 days prior to screening. Clarify: assessment of objectives and endpoints was based on central BIE. Add: exploratory objective added to "evaluate the number of PET-positive pelvic LNs by central BIE as compared to the number of pathologic positive LNs (by local histopathology analysis) in each region", with corresponding endpoint. Clarifiy: dose of IMP could be 8 mCi (296 MBq) ± 20% rhPSMA-7.3 (18F). Add: to allow discussion of rhPSMA-7.3 (18F) PET results and further procedures/treatment plan to be conducted by telephone at the clinician's discretion. Clarify: physical examination would be focused in nature. Clarify: safety follow-up visit was to be conducted within 1 to 3 days post-IMP administration. Add: interim look at the percentage of pN1 and pN0 patients after enrollment of 150 patients. Amend: inclusion criterion 4 to remove primary treatment with EBRT. Clarify: additions to standard of care surgical treatments for patients with M0 and M1 disease on local PET interpretation. Clarify: added to confirmatory imaging when used as SoT. Define: unrelated AE updated. Update: sample size and number of evaluable patients required before enrollment will stop, plus the number of positive and negative cases required for enrollment to stop. Update: analysis sets. Clarify: rhPSMA-7.3 (18F) would be considered effective in detecting N1 disease if the co-primary endpoints were met by the same 2 of 3 readers. Other minor typographical edits and clarifications.
04 June 2020	Germany specific Several updates to implement feedback from BfArM: Add: text on the replacement of patients who dropout. Exclusion criterion added for patients with known hypersensitivity to the active substance or any excipients of the IMP.

01 July 2020	Patient safety and BfArM feedbackfeedback (COVID-19): Add: latest NCCN Guidelines. Combine: exploratory objectives/endpoints 2 & 3. Extend: screening: 28-45 days (COVID-19). Add: Visits 1 and 2 combined option, screening evaluation could occur on day of rhPSMA-7.3 (18F) administration (COVID-19) and clarify that the procedure was to combine IMP manufacture visits. Extend: safety follow-up visit to within 1-5 days (COVID-19). Extend: period from Visit 2 to the scheduled surgery and/or follow up procedures up to 60 (COVID-19). Clarify: study population to be treatment naïve and receive standard of care and clarifications added to inclusion criteria risk definitions. Add: exclusion criterion for patients with hypersensitivity to active substance or any IMP excipient. Add: baseline conventional imaging to be performed at least 24 hours prior to the investigational rhPSMA-7.3 (18F) PET scan. Add: focused physical examination could be performed by a clinician and could be by telephone. Specify: when collected, pre-sacral LNs to be placed in a separate packet from other specimens prior to pathology assessment. Increase: from 2-3 central readers for the rhPSMA-7.3 (18F) PET scans and the information they were provided add: Independent Review Charter. Clarify: conventional imaging performed at non-participating institutions allowed if scans were reviewed by study site. Add: text on replacement of dropouts. Amend: time from end of injection of rhPSMA-7 (18F) to imaging start from 50-90 mins to 50-70 mins. Update: SAE reporting email address and clarify SAEs to be reported immediately. Add: criteria to temporarily halt/stop enrollment. Add: exclude patients with known hypersensitivity to the active substance or any IMP excipient. Add: option for remote study monitoring (COVID-19). Clarify: urgent safety measures may include amendments made due to the COVID-19 pandemic to ensure patient safety by minimizing SARS-CoV-2 exposure. Minor typographical edit.
29 September 2020	Updates to implement feedback from BfArM: Remove: reference to remote consent and pre-screening via telephone contact, which were not permitted in Germany. Administrative change to update the Medical Monitor details.

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: