Clinical trial results:
A phase II clinical trial of radium-223 activity in patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status

Summary

EudraCT number	2016-001888-36
Trial protocol	ES
Global end of trial date	28 February 2021

Results information

Result version number	v1 (current)
This version publication date	12 March 2022
First version publication date	12 March 2022

Trial information

Trial identification

Sponsor protocol code	MedOPP098

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03002220
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medica Scientia Innovation Research (MEDSIR)
Sponsor organisation address	Av Diagonal 211 Torre Glories - 27th floor, Barcelona , Spain, 08018
Public contact	Alicia Garcia, Medica Scientia Innovation Research (MEDSIR), 0034 932214135, alicia.garcia@medsir.org
Scientific contact	Alicia Garcia, Medica Scientia Innovation Research (MEDSIR), 0034 932214135, alicia.garcia@medsir.org

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	29 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of radium-223 in asymptomatic patients with mCRPC who have progressed while on abiraterone acetate or enzalutamide treatment.

Protection of trial subjects:

Standard of Care

Background therapy:

Radium-223 (molecular formula 223RaCl2) is an alpha-emitting radioisotope that targets areas of bone with hight turnover as metastasis, and it is excreted by the small intestine. When compared with beta-emitters, radium-223 delivers a high quantity of energy per track length with short tissue penetration.

Evidence for comparator: -

Actual start date of recruitment	16 November 2016
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	Spain: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	6
From 65 to 84 years	29
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

Between Oct 2016 and July 2018, a total of 52 patients with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression were enrolled at 9 sites. All the patients, being either under abiraterone acetate or enzalutamide, were assigned to a single arm, and administered with Radium-223.

Pre-assignment

Screening details:

-Aged ≥ 18, signed IC
-Histologically confirmed prostate adenocarcinoma
-Bone metastases
-Serum testosterone ≤ 1.7 nmol/L
-Received a minimum of 2W abiraterone acetate or enzalutamide, discontinued 4 weeks before trial
-Receiving LHRH
-Stable dose bone-targeting therapy
-Asymptomatic PC
-ECOG 0-1
-Life expectancy ≥ 12M
-No other trials

Period 1

Period 1 title	Radium-223 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Unique Arm - Blinding procedure not required

Arms

Arm title	Radium-223

Arm description:

The patient will be treated with radium-223 at a dose of 55 kBq (after 2015 NIST implementation) per kilogram body weight, given at four- week intervals for six intravenous (IV) injections.

Arm type	Experimental
Investigational medicinal product name	Radium-223
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

55 kBq per kilogram body weight, given at four- week intervals for six intravenous (IV) injections.

Number of subjects in period 1	Radium-223
Started	52
Completed	52

Baseline characteristics

Reporting groups	
Reporting group title	Radium-223

Reporting group description: -

Reporting group values	Radium-223	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	6	
From 65-84 years	29	29	
85 years and over	17	17	
Age continuous Units: years			
median	76.1		
full range (min-max)	69.4 to 82.3	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	52	52	

Subject analysis sets	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients with determination of CTC that accomplish selection criteria and receive at least one drug dose.

Subject analysis set title	AR-V7[-]
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with no AR-V7 mutation.

Subject analysis set title	AR-V7[+]
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AR-V7 mutation.

Subject analysis set title	AR-V7 NA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AR-V7 status not available

Reporting group values	mITT	AR-V7[-]	AR-V7[+]
Number of subjects	52	35	5
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)	6		
From 65-84 years	29		
85 years and over	17		
Age continuous			
Units: years			
median	76.1		
full range (min-max)	69.4 to 82.3		
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	52	35	5

Reporting group values	AR-V7 NA		
Number of subjects	12		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female	0		
Male	12		

End points

End points reporting groups

Reporting group title	Radium-223
Reporting group description:	
The patient will be treated with radium-223 at a dose of 55 kBq (after 2015 NIST implementation) per kilogram body weight, given at four- week intervals for six intravenous (IV) injections.	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients with determination of CTC that accomplish selection criteria and receive at least one drug dose.	
Subject analysis set title	AR-V7[-]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with no AR-V7 mutation.	
Subject analysis set title	AR-V7[+]
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AR-V7 mutation.	
Subject analysis set title	AR-V7 NA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AR-V7 status not available	

Primary: Radiological rPFS

End point title	Radiological rPFS
End point description:	
The primary endpoint of this study is to assess the efficacy of radium-223 in terms of radiological rPFS. The null hypothesis is that median rPFS is lower or equal than 3 months.	
End point type	Primary
End point timeframe:	
Once the treatment phase is completed, patients will enter a follow-up period with radiological tumor assessment every three months (±7 working days) until disease progression and safety evaluation during 2 years from the last dose of study treatment.	

End point values	Radium-223	mITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: Months	52	52		

Statistical analyses

Statistical analysis title	rPFS Analysis (Primary Endpoint)
Statistical analysis description:	
Study met primary endpoint with a median rPFS of 5.53 months (95% confidence interval (CI), 5.3 to 5.5).	

We rejected the null hypothesis that median rPFS was lower or equal than 3 months. Based on maximum likelihood exponential test the p-value was <0.001. Based on one-arm one-sided log-rank test the p-value was 0.025. The number of patients with disease progression or death in the study was 37 (71.2%).

Comparison groups	Radium-223 v mITT
Number of subjects included in analysis	104
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	< 0.05
Method	maximum-likelihood exponential test
Parameter estimate	Median difference (final values)
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	5.53

Notes:

[1] - The primary analysis was based on one-arm one-sample log-rank test with an alpha 0.05 level of significance.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected up to three months after patient's disease progression. Safety evaluation after progression will include follow-up of symptomatic skeletal related events until reach 2 years from the last dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups

Reporting group title	Intention to Treat

Reporting group description: -

Serious adverse events	Intention to Treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 52 (23.08%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	3		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal cord compression			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left femur and humerus fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Intention to Treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 52 (86.54%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 52 (26.92%)		
occurrences (all)	21		
Fatigue			

subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) General physical health deterioration subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 6 3 / 52 (5.77%) 4 4 / 52 (7.69%) 5 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Reproductive system and breast disorders Cough subjects affected / exposed occurrences (all)	 2 / 52 (3.85%) 2		
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 52 (1.92%) 1 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Psychiatric disorders			

Disorientation subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Depressed mood subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Cardiac disorders Aortic valve incompetence subjects affected / exposed occurrences (all) Cardiac failure congestive subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Nervous system disorders Burning sensation subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 2 2 / 52 (3.85%) 2 1 / 52 (1.92%) 1 1 / 52 (1.92%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 29		

Leukopenia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Neutropenia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 3		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 5		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Diplopia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	7 / 52 (13.46%) 11		
Vomiting subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4		
Epigastric discomfort subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 2		
Nausea subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 9		
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Renal and urinary disorders			
Urosepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Nephrolithiasis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 52 (21.15%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	6 / 52 (11.54%)		
occurrences (all)	6		
Costal pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Limb discomfort			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	2		
Osteoporotic fracture			

subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Osteoporosis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	6		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	3		
Groin pain			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Haemophilus infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Streptococcal infection			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Hyperglycaemia			

subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2016	Change of the location of the laboratory responsible for processing blood samples coming from patients
26 November 2018	Two hospitals decided to leave the study (Hospital Gregorio Marañón in Madrid, with Dr. Jose Ángel Arranz as PI and Clinical Hospital San Carlos, with Dr. Javier Puenteas PI) replaced by Hospital Universitario Son Espases, with Dr. Aránzazu Gonzalez del Alba as IP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported