Clinical trial results:
A multicenter, open-label, single-arm study of the safety and antitumoral efficacy of nivolumab in combination with selective internal radiation therapy (SIRT) using SIR-Spheres for the treatment of patients with hepatocellular carcinoma that are candidates for locoregional therapies.

Summary

EudraCT number	2017-000232-34
Trial protocol	ES
Global end of trial date	30 April 2020

Results information

Result version number	v1 (current)
This version publication date	06 February 2022
First version publication date	06 February 2022

Trial information

Trial identification

Sponsor protocol code	NASIR-HCC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03380130
WHO universal trial number (UTN)	-
Other trial identifiers	BMS protocol code: CA209-992

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra/Universidad de Navarra
Sponsor organisation address	Avenida Pío XII, 36, Pamplona, Spain, 31008
Public contact	UCEC, Clinica Universidad de Navarra, 34 948255400, ucicec@unav.es
Scientific contact	UCEC, Clinica Universidad de Navarra, 34 948255400, ucicec@unav.es

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	27 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2020
Global end of trial reached?	Yes
Global end of trial date	30 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of nivolumab in combination with SIRT using SIR-Spheres.
The secondary objective is to evaluate the antitumoral activity of nivolumab in combination with SIRT using SIR-Spheres.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2017
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: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	20
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Child Pugh A subjects with intermediate or advanced hepatocellular carcinoma who are candidates to locoregional therapies but not good candidates to TACE were recruited.

Pre-assignment

Screening details:

40 patients were planned. 53 patients were screened, there were 11 screening failures and 42 patients received SIRT and are included in the safety analysis, while 41 received at least one dose of nivolumab and are included in the efficacy analysis. 14 patients completed the study as planned.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Experimental group

Arm description:

Nivolumab in combination with SIR-Spheres Y90 resin microspheres. Patients were treated wih SIR-Spheres followed 3 weeks later by nivolumab every 2 weeks for up to 24 doses or until discontinuation based on protocol instructions.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered IV starting 3 weeks after SIRT at a dose of 240 mg IV over 30 minutes every 2 weeks for up to 24 doses unless tumor progression, unacceptable toxicity or death.

Investigational medicinal product name	SIR-Spheres
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Implantation

Dosage and administration details:

SIR-Spheres Y90 resin microspheres was the non-investigational product. Y90 activity was calculated according to targeted liver volume and status of cirrhosis. SIRT evaluation and treatment were performed as a single-day procedure at Clínica Universidad de Navarra.

Number of subjects in period 1	Experimental group
Started	42
Completed	14
Not completed	28
Physician decision	4
Disease progression	17

Adverse event, non-fatal	7

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	42	42	
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)	20	20	
From 65-84 years	22	22	
85 years and over	0	0	
Age continuous Units: years			
median	65		
inter-quartile range (Q1-Q3)	49 to 79	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	36	36	

End points

End points reporting groups

Reporting group title	Experimental group

Reporting group description:

Nivolumab in combination with SIR-Spheres Y90 resin microspheres. Patients were treated wih SIR-Spheres followed 3 weeks later by nivolumab every 2 weeks for up to 24 doses or until discontinuation based on protocol instructions.

Primary: Safety

End point title	Safety[1]

End point description:

The primary endpoints were the rate and type of adverse events (AEs), serious AEs (SAEs), events of liver decompensation, and transient and permanent drug discontinuations due to toxicity.

End point type	Primary

End point timeframe:

End of follow up

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: Safety was the primary endpoint. Results are shown in the corresponding section.

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Safety	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

End point type	Secondary

End point timeframe:

End of follow up

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
number (confidence interval 95%)	41.5 (26.3 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

End point type	Secondary

End point timeframe:

End of follow up

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage				
number (confidence interval 95%)	92.7 (80.1 to 98.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary

End point timeframe:

End of follow up

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (inter-quartile range (Q1-Q3))	8.8 (7.0 to 10.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

End of follow up

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (inter-quartile range (Q1-Q3))	9.0 (7.0 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

End of follow up

End point values	Experimental group			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (inter-quartile range (Q1-Q3))	20.9 (17.7 to 24.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed continuously during the study and for 100 days post last treatment and evaluated according to the NCI CTCAE Version 4.03 dated 14-Jun-2010.

Adverse event reporting additional description:

Additional information: 2 SAEs in the same subject (Pyrexia and Liver abscess) were related to SIRT.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	ND

Reporting groups

Reporting group title	Experimental group

Reporting group description: -

Serious adverse events	Experimental group		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 42 (50.00%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	6		
Vascular disorders			
Ischaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Seizure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Performance status decreased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pyrexia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoperitoneum			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hepatic function abnormal			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			

subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium bacteraemia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Postoperative wound infection				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Haematoma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin ulcer			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Surgical and medical procedures			
Radiotherapy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		

Cough			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Asthmatic attack			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	18		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	17		
Blood bilirubin increased			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	12		
Blood creatine increased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		
Amylase increased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Spinal fracture			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	4		
Dizziness			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	13 / 42 (30.95%)		
occurrences (all)	16		
Leukopenia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	6		
Anaemia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Eosinophilia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Monocytosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 42 (23.81%)		
occurrences (all)	10		
Diarrhoea			

subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Chronic gastritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Epigastric discomfort			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatobiliary disorders			

Hyperbilirubinaemia subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 11		
Hypertransaminasaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Autoimmune hepatitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 2		
Hepatic function abnormal subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Liver abscess subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Portal vein thrombosis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 8		
Rash subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4		
Dermatitis subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Skin lesion subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Skin ulcer subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Renal and urinary disorders			

Renal impairment subjects affected / exposed occurrences (all) Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Nephritis subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) Thyroiditis subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all)	 5 / 42 (11.90%) 5 2 / 42 (4.76%) 2 1 / 42 (2.38%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain	 13 / 42 (30.95%) 13 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Soft tissue mass			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Escherichia infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Peritonitis bacterial subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Pneumonia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2			
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2			
Gout subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Underweight subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1			
Vitamin D deficiency				

subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2017	Addition of Hospital de Cruces as a new study site (no. 09). Approved by the IEC/REC on 13/October/2017 and notified to AEMPS on 17/October/2017
10 January 2018	Substantial modifications and updates to IB version 16, ICF/PIS version 3.0 and protocol version 3.0 (Addition of the EQ5-CD questionnaire, minimal change of the SIR-Spheres Activity calculation method and addition of an ICF/PIS for post-progression treatment). Approved by the IEC/REC on 12/February/2018 and by AEMPS on 15/February/2018
03 September 2018	Substantial modification to IB version 17 (update of the reference safety information), ICF/PIS version 4.0 (updated with the new European data protection regulation). Approved by the IEC/REC on 01/October/2018 and by AEMPS on 19/October/2018

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.

It was determined that the reported protocol deviations had no impact on the interpretability of the study results. The major deviations were notified to the corresponding authorities and a root cause analysis was carried out in each case.

Notes: