Clinical trial results:
An open-label, multi-center everolimus roll-over protocol for patients who have completed a previous Novartis-sponsored everolimus study and are judged by the investigator to benefit from continued everolimus treatment

Summary

EudraCT number	2012-004707-12
Trial protocol	CZ NL IT ES
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	CRAD001C2X01B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01789281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	28 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aimed to better characterize the long-term safety of everolimus in subjects currently being treated in a Novartis-sponsored studies and who were receiving clinical benefit on the current study treatment as judged by the Investigator

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2013
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: 2
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 3
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	34
EEA total number of subjects	11

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)	26
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There was no screening period. Patients enrolled into trial directly from the parent protocol.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

Participants who were receiving everolimus in a Novartis-sponsored study

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was provided by the investigator in 2.5 mg, 5 mg or 10 mg tablets for daily oral administration. The starting dose of everolimus was the same as the last dose that was given in the parent study. Dose modification thereafter was done at the discretion of the Investigator based upon what is in the subject’s best interest.

Arm title	Everolimus+Sandostatin LAR

Arm description:

Participants who were receiving everolimus in combination with Sandostatin LAR depot in a Novartis-sponsored study

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was provided by the investigator in 2.5 mg, 5 mg or 10 mg tablets for daily oral administration. The starting dose of everolimus was the same as the last dose that was given in the parent study. Dose modification thereafter was done at the discretion of the Investigator based upon what is in the subject’s best interest.

Investigational medicinal product name	Sandostatin LAR Depot
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

The dose and frequency of Sandostatin LAR Intramuscular injections was the same as the last dose that was given in the parent study.

Number of subjects in period 1	Everolimus	Everolimus+Sandostatin LAR
Started	22	12
Completed	0	2
Not completed	22	10
Consent withdrawn by subject	1	-
Disease progression	15	4
Adverse event, non-fatal	5	5
Administrative problems	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
Participants who were receiving everolimus in a Novartis-sponsored study	
Reporting group title	Everolimus+Sandostatin LAR
Reporting group description:	
Participants who were receiving everolimus in combination with Sandostatin LAR depot in a Novartis-sponsored study	

Reporting group values	Everolimus	Everolimus+Sandostatin LAR	Total
Number of subjects	22	12	34
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	9	26
From 65-84 years	5	3	8
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	58.6	57.9	
standard deviation	± 9.52	± 11.30	-
Sex: Female, Male Units: Participants			
Female	9	6	15
Male	13	6	19

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description:	
Participants who were receiving everolimus in a Novartis-sponsored study	
Reporting group title	Everolimus+Sandostatin LAR
Reporting group description:	
Participants who were receiving everolimus in combination with Sandostatin LAR depot in a Novartis-sponsored study	

Primary: Percentage of participants with Adverse Events (AEs) and Serious Adverse events (SAEs)

End point title	Percentage of participants with Adverse Events (AEs) and Serious Adverse events (SAEs)[1]
End point description:	
Any sign or symptom that occurs during the study treatment plus the 30 days post treatment. All SAEs were captured in safety database from enrollment. Safety data collection was changed in the protocol amendment released in March 2016: AEs and SAEs were captured in the clinical database from protocol amendment release (18 March 2016). Hence, SAEs from both safety database and clinical database are summarized separately.	
End point type	Primary
End point timeframe:	
SAEs collected in safety database from baseline to end of the treatment (EOT) plus 30 days, up to approximately 7 years. AEs/SAEs collected in clinical database from protocol amendment date 18 March 2016 to EOT plus 30 days, up to approximately 4.5 years	

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: No statistical analyses were planned for this endpoint

End point values	Everolimus	Everolimus+Sandostatin LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	12		
Units: Participants				
SAEs (Safety database)	6	9		
Treatment-related SAEs (Safety database)	1	4		
AEs (Clinical Database)	7	7		
Tretament-related AEs (Clinical Database)	4	4		
SAEs (Clinical Database)	2	4		
Treatment-related SAEs (Clinical Database)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with clinical benefit

End point title	Percentage of patients with clinical benefit

End point description:

Percentage of patients with clinical benefit as judged by the investigator. Confirmation of clinical benefit was collected in clinical database after protocol amendment (release date 18 Mach 2016). Clinical benefit assessment before protocol amendment was done retrospectively.

End point type	Secondary

End point timeframe:

After 3 months from baseline, every 3 months, until end of treatment, assessed up to 7 years

End point values	Everolimus	Everolimus+Sandostatin LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: Participants				
At 3 months	9	7		
At 6 months	8	7		
At 9 months	8	7		
At 12 months	8	7		
At 15 months	8	7		
At 18 months	8	7		
At 21 months	8	7		
At 24 months	6	7		
At 27 months	5	7		
At 30 months	3	7		
At 33 months	2	7		
At 36 months	1	7		
At 39 months	1	7		
At 42 months	1	6		
At 45 months	1	6		
At 48 months	1	6		
At 51 months	1	6		
At 54 months	0	6		
At 57 months	0	5		
At 60 months	0	5		
At 63 months	0	4		
At 66 months	0	4		
At 69 months	0	3		
At 72 months	0	3		
At 75 months	0	3		
At 78 months	0	2		
At 81 months	0	1		
At 84 months	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were collected in safety database from enrollment to end of treatment (EOT) plus 30 days, up to approx. 7 years. Non-serious AEs were collected in clinical database from protocol amendment (18 March 2016) to EOT plus 30 days, up to approx. 4.5 years

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0.

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus

Reporting group title	Everolimus + Sandostatin LAR

Reporting group description:

Everolimus + Sandostatin LAR

Reporting group title	All subjects

Reporting group description:

All subjects

Serious adverse events	Everolimus	Everolimus + Sandostatin LAR	All subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	9 / 12 (75.00%)	15 / 34 (44.12%)
number of deaths (all causes)	1	2	3
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Renal cell carcinoma			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			

subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve incompetence			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Thrombocytopenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nephropathy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 12 (25.00%)	5 / 34 (14.71%)
occurrences causally related to treatment / all	1 / 2	2 / 3	3 / 5
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			

subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid intake reduced			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Everolimus	Everolimus + Sandostatin LAR	All subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)	5 / 12 (41.67%)	8 / 34 (23.53%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Oedema peripheral			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	4	4
Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pneumonitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Investigations			
Blood chromogranin A increased			

subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Blood triglycerides increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Skin abrasion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Cardiac disorders			
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	4	4
Iron deficiency anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	3 / 12 (25.00%)	3 / 34 (8.82%)
occurrences (all)	0	7	7
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Duodenal stenosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Intestinal obstruction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	2	2
Large intestinal obstruction			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Stomatitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences (all)	1	2	3
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	3	3

Skin and subcutaneous tissue disorders			
Onychoclasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Dry skin			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Psoriasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	3	3
Costochondritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Spinal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	5	5
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	2 / 34 (5.88%)
occurrences (all)	1	4	5

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Hyperglycaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 12 (16.67%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Vitamin B12 deficiency			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	1 / 34 (2.94%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2016	The main purpose of the amendment was to change the primary endpoint to safety to better characterize the long-term safety of the compound. In addition, the protocol was amended to include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit.

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.

The protocol was designed to collect SAEs and protocol defined AESIs in the Safety database. The protocol was amended in 2016 (3 years after study was initiated) to include all AEs (non-SAEs, SAEs, and AESIs) to be collected in the clinical database.

Notes: