Clinical trial results:
PAZOPANIB Efficacy and Tolerance in Desmoids Tumors : Phase 2 Clinical Trial (DESMOPAZ)

Summary

EudraCT number	2011-006037-42
Trial protocol	FR
Global end of trial date	15 July 2019

Results information

Result version number	v1 (current)
This version publication date	24 March 2022
First version publication date	24 March 2022

Trial information

Trial identification

Sponsor protocol code	IB2011-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01876082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Bergonié
Sponsor organisation address	229 cours de l'Argonne, Bordeaux, France, 33076
Public contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr
Scientific contact	Regulatory Affairs Management Desk, Institut Bergonié, drci@bordeaux.unicancer.fr

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

Global end of trial reached?	Yes
Global end of trial date	15 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy evaluation in terms of non progression rate at 6 months of treatment with Pazopanib and methotrexate-vinblastine.

Protection of trial subjects:

A supervisory committee is constitued to review the patient ellibility, ensure the patient protetion and evaluate the benefit/risk ratio.
An IDMC is constitued to review the intermediary analysis and evaluate the safety and the efficacy

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	65
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Age ≥ 18 years;
ECOG ≤ 1;
Histologically confirmed desmoid tumor;
Disease progression before the patient's inclusion : completion of two similar imaging obtained within 6 months apart (a tolerance of 6 weeks is accepted)
Measurable target lesion (RECIST criteria) ;

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PAZOPANIB

Arm description:

After inclusion and screening, patients received pazopanib 800 mg per day orally for up to 1 year.

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

Dosage and administration details:

• 800 mg per day
• oral administration
• at least 1 hour before or 2 hours after a meal,
• until disease progression or for 12 months maximum

Arm title	Vinblastine and Methotrexate

Arm description:

Intravenous methotrexate (30 mg/m²) plus vinblastine (5 mg/m²), once a week for 6 months and then every 2 weeks for 6 months.

Arm type	Control
Investigational medicinal product name	Vinblastine and Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

vinblastine 5 mg / m² and methotrexate 30 mg / m²(D1, D8, D15, D21, 6 months and then D1, D15) 28 days per cycle until disease progression or for 12 months.

Number of subjects in period 1	PAZOPANIB	Vinblastine and Methotrexate
Started	48	24
Completed	46	20
Not completed	2	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	1
treatment interruption >= 21 days (cycle 1)	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PAZOPANIB
Reporting group description:	
After inclusion and screening, patients received pazopanib 800 mg per day orally for up to 1 year.	
Reporting group title	Vinblastine and Methotrexate
Reporting group description:	
Intravenous methotrexate (30 mg/m²) plus vinblastine (5 mg/m²), once a week for 6 months and then every 2 weeks for 6 months.	

Reporting group values	PAZOPANIB	Vinblastine and Methotrexate	Total
Number of subjects	48	24	72
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	35.5	42.5	
full range (min-max)	30.6 to 56.0	30.5 to 54.0	-
Gender categorical Units: Subjects			
Female	31	15	46
Male	17	9	26

End points

End points reporting groups

Reporting group title	PAZOPANIB
Reporting group description:	
After inclusion and screening, patients received pazopanib 800 mg per day orally for up to 1 year.	
Reporting group title	Vinblastine and Methotrexate
Reporting group description:	
Intravenous methotrexate (30 mg/m²) plus vinblastine (5 mg/m²), once a week for 6 months and then every 2 weeks for 6 months.	

Primary: Percentage of Patients Remaining Alive and Progression-free at 6 Months as per RECIST 1.1 After the Day of Randomisation (6-month Non-progression Rate).

End point title	Percentage of Patients Remaining Alive and Progression-free at 6 Months as per RECIST 1.1 After the Day of Randomisation (6-month Non-progression Rate).[1]
End point description:	
Percentage of patients remaining alive and progression-free at 6 months as per RECIST 1.1 after the day of randomisation. Progression is defined using New Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of diameters of target lesions (taking as reference the smallest sum on study), or a unequivocal progression of existing non-target lesions, or the appearance of one or more new lesions.	
End point type	Primary
End point timeframe:	
6 months	

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 analysis was performed since this trial is non comparative

End point values	PAZOPANIB	Vinblastine and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	20		
Units: Percentage of patients				
number (confidence interval 95%)	84.8 (71.1 to 93.7)	45.0 (23.1 to 68.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 2 years

End point title	Overall survival rate at 2 years
End point description:	
Overall survival (OS) defined as the time from randomization to death (due to any cause). Patients alive were censored at the date of last follow-up or last patient contact. Overall survival was estimated as a function of time using Kaplan-Meier method.1- and 2-Year OS rates were reported.	
End point type	Secondary

End point timeframe:

Randomization to disease progression, or death due to any cause, whichever occurs first; until 2 years after the last patient randomized.

End point values	PAZOPANIB	Vinblastine and Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	20		
Units: Percentage of participants				
number (confidence interval 95%)	97.8 (85.6 to 99.7)	100 (100 to 100)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events are reported from the signature of the informed consent form to 30 days after the patient study end participation

Adverse event reporting additional description:

Adverse events (AEs) were graded and coded according to the CTCAE V4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	PAZOPANIB

Reporting group description:

After inclusion and screening, patients received pazopanib 800 mg per day orally for up to 1 year.

Reporting group title	Vinblastine and Methotrexate

Reporting group description:

Intravenous methotrexate (30 mg/m²) plus vinblastine (5 mg/m²), once a week for 6 months and then every 2 weeks for 6 months.

Serious adverse events	PAZOPANIB	Vinblastine and Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 48 (41.67%)	10 / 22 (45.45%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: 1 SAE LOCAL TUMOR BLEEDING 1 SAE LOSS OF TUMOR SUBSTANCE		
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hematoma			

subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 48 (4.17%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	1 / 48 (2.08%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - Other, specify	Additional description: MEATOPLASTY		
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions - Other, specify	Additional description: HOSPITALIZATION FOR CRYOTHERAPY		
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders - Other, specify	Additional description: HEMOPTYSIS		

subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 48 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 48 (4.17%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paresthesia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders - Other, specify	Additional description: PARKINSON'S DISEASE AGGRAVATION		
subjects affected / exposed	0 / 48 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	11 / 48 (22.92%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders - Other, specify	Additional description: POLYCYTHEMIA		
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 48 (2.08%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - Other, specify	Additional description: FOOD POISONING		
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Hepatobiliary disorders - Other, specify	Additional description: 1 SAE ACUTE HEPATIC CYTOLYSIS 1 SAE HEPATIC CYTOLYSIS		
subjects affected / exposed	0 / 48 (0.00%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PAZOPANIB	Vinblastine and Methotrexate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 48 (100.00%)	22 / 22 (100.00%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	5 / 48 (10.42%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
Hypertension			
subjects affected / exposed	22 / 48 (45.83%)	0 / 22 (0.00%)	
occurrences (all)	27	0	
General disorders and administration site conditions			
Edema limbs			

subjects affected / exposed	3 / 48 (6.25%)	1 / 22 (4.55%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	40 / 48 (83.33%)	20 / 22 (90.91%)	
occurrences (all)	45	19	
Fever			
subjects affected / exposed	3 / 48 (6.25%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
Flu like symptoms			
subjects affected / exposed	3 / 48 (6.25%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 48 (4.17%)	2 / 22 (9.09%)	
occurrences (all)	2	2	
Pain			
subjects affected / exposed	4 / 48 (8.33%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
Reproductive system and breast disorders			
Uterine hemorrhage			
subjects affected / exposed	3 / 48 (6.25%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	4 / 48 (8.33%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	4 / 48 (8.33%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	3 / 48 (6.25%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 48 (8.33%)	1 / 22 (4.55%)	
occurrences (all)	4	1	

Insomnia			
subjects affected / exposed	5 / 48 (10.42%)	1 / 22 (4.55%)	
occurrences (all)	6	1	
Psychiatric disorders - Other, specify			
subjects affected / exposed	4 / 48 (8.33%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 48 (31.25%)	7 / 22 (31.82%)	
occurrences (all)	16	8	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 48 (25.00%)	4 / 22 (18.18%)	
occurrences (all)	12	4	
Blood bilirubin increased			
subjects affected / exposed	3 / 48 (6.25%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
GGT increased			
subjects affected / exposed	3 / 48 (6.25%)	3 / 22 (13.64%)	
occurrences (all)	8	3	
Investigations - Other, specify			
subjects affected / exposed	6 / 48 (12.50%)	0 / 22 (0.00%)	
occurrences (all)	8	0	
Neutrophil count decreased			
subjects affected / exposed	4 / 48 (8.33%)	10 / 22 (45.45%)	
occurrences (all)	5	14	
Platelet count decreased			
subjects affected / exposed	5 / 48 (10.42%)	0 / 22 (0.00%)	
occurrences (all)	6	0	
Weight loss			
subjects affected / exposed	5 / 48 (10.42%)	2 / 22 (9.09%)	
occurrences (all)	6	2	
Nervous system disorders			
Dysesthesia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			

subjects affected / exposed	13 / 48 (27.08%)	1 / 22 (4.55%)	
occurrences (all)	13	1	
Headache			
subjects affected / exposed	21 / 48 (43.75%)	4 / 22 (18.18%)	
occurrences (all)	32	5	
Nervous system disorders - Other, specify			
subjects affected / exposed	0 / 48 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Paresthesia			
subjects affected / exposed	2 / 48 (4.17%)	6 / 22 (27.27%)	
occurrences (all)	2	6	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 48 (4.17%)	5 / 22 (22.73%)	
occurrences (all)	2	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 48 (33.33%)	6 / 22 (27.27%)	
occurrences (all)	29	6	
Bloating			
subjects affected / exposed	4 / 48 (8.33%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
Constipation			
subjects affected / exposed	6 / 48 (12.50%)	12 / 22 (54.55%)	
occurrences (all)	6	15	
Diarrhea			
subjects affected / exposed	37 / 48 (77.08%)	9 / 22 (40.91%)	
occurrences (all)	60	10	
Dry mouth			
subjects affected / exposed	4 / 48 (8.33%)	1 / 22 (4.55%)	
occurrences (all)	4	1	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 48 (2.08%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Gastrointestinal disorders - Other, specify			

subjects affected / exposed	9 / 48 (18.75%)	2 / 22 (9.09%)	
occurrences (all)	12	2	
Gastrointestinal pain			
subjects affected / exposed	8 / 48 (16.67%)	1 / 22 (4.55%)	
occurrences (all)	9	1	
Mucositis oral			
subjects affected / exposed	13 / 48 (27.08%)	7 / 22 (31.82%)	
occurrences (all)	17	11	
Nausea			
subjects affected / exposed	26 / 48 (54.17%)	16 / 22 (72.73%)	
occurrences (all)	34	19	
Stomach pain			
subjects affected / exposed	0 / 48 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	4	
Toothache			
subjects affected / exposed	3 / 48 (6.25%)	1 / 22 (4.55%)	
occurrences (all)	3	3	
Vomiting			
subjects affected / exposed	15 / 48 (31.25%)	6 / 22 (27.27%)	
occurrences (all)	24	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 48 (12.50%)	4 / 22 (18.18%)	
occurrences (all)	6	4	
Dry skin			
subjects affected / exposed	7 / 48 (14.58%)	0 / 22 (0.00%)	
occurrences (all)	8	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	16 / 48 (33.33%)	0 / 22 (0.00%)	
occurrences (all)	22	0	
Pruritus			
subjects affected / exposed	4 / 48 (8.33%)	1 / 22 (4.55%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders - Other, specify			

subjects affected / exposed	36 / 48 (75.00%)	3 / 22 (13.64%)	
occurrences (all)	50	3	
Skin hypopigmentation			
subjects affected / exposed	10 / 48 (20.83%)	0 / 22 (0.00%)	
occurrences (all)	10	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	12 / 48 (25.00%)	0 / 22 (0.00%)	
occurrences (all)	13	0	
Eye disorders - Other, specify			
subjects affected / exposed	7 / 48 (14.58%)	1 / 22 (4.55%)	
occurrences (all)	8	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 48 (27.08%)	2 / 22 (9.09%)	
occurrences (all)	17	2	
Back pain			
subjects affected / exposed	10 / 48 (20.83%)	1 / 22 (4.55%)	
occurrences (all)	11	1	
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	6 / 48 (12.50%)	4 / 22 (18.18%)	
occurrences (all)	6	7	
Myalgia			
subjects affected / exposed	8 / 48 (16.67%)	5 / 22 (22.73%)	
occurrences (all)	9	6	
Tumor pain			
subjects affected / exposed	6 / 48 (12.50%)	0 / 22 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	8 / 48 (16.67%)	1 / 22 (4.55%)	
occurrences (all)	9	1	
Tooth infection			
subjects affected / exposed	4 / 48 (8.33%)	1 / 22 (4.55%)	
occurrences (all)	4	1	

Urinary tract infection subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 5	0 / 22 (0.00%) 0	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	17 / 48 (35.42%) 21	5 / 22 (22.73%) 5	
Hypomagnesemia subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	0 / 22 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2012	Protocol V3 dated 05-jun-2012
04 February 2013	Protocol V4 dated 23-oct-2012
28 August 2013	Protocol V5 dated 24-jul-2013
06 December 2013	Protocol V6 dated 07-aug-2013
02 May 2014	Protocol V7 dated 10-mar-2014
11 September 2015	Protocol V8 dated 10-jun-2015
19 May 2016	Protocol V9 dated 05-apr-2016
28 November 2016	Protocol V10 dated 19-aug-2016
10 August 2017	Protocol V11 dated 29-may-2017
08 January 2018	Protocol V12 dated 28-nov-2017

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported