



Clinical trial results:

A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath

Summary

EudraCT number	2014-000148-14
Trial protocol	HU DE DK GB NL ES PL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	PLX108-10
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02371369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mount Airy Road, Basking Ridge, NJ, United States, 07920
Public contact	Clinical Trial Information, Daiichi Sankyo, Inc., 1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Clinical Trial Information, Daiichi Sankyo, Inc., 1 908-992-6400, CTRinfo@dsi.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	Interim
Date of interim/final analysis	27 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the response rate of PLX3397 with that of placebo per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 in subjects with symptomatic, locally advanced pigmented villonodular synovitis (PVNS) or giant cell tumor of tendon sheath (GCT-TS).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	120
EEA total number of subjects	58

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)	113
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part 1 was a double-blind, randomized, placebo-controlled study in subjects with symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity. Part 2 is a long-term treatment phase in which subjects receive open-label pexidartinib.

Pre-assignment

Screening details:

Subjects were screened for inclusion and exclusion criteria. Screening procedures were performed after consent was obtained and within the 42 days before the first dose of study drug, unless otherwise noted.

Period 1

Period 1 title	Part 1 (randomized phase)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The pexidartinib and placebo capsules were identical in appearance to maintain the blind during Part 1.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pexidartinib (Part 1)

Arm description:

Subjects randomized to pexidartinib for 24 weeks administered twice a day.

Arm type	Experimental
Investigational medicinal product name	Pexidartinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1000 mg (5 capsules per day) for 2 weeks, then 800 mg (4 capsules per day) for 22 weeks; each capsule contained 200 mg of pexidartinib; oral administration twice a day.

Arm title	Placebo (Part 1)
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Arm description:

Subjects randomized to matching placebo for 24 weeks administered twice a day.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule matching pexidartinib capsule was administered orally (5 capsules per day) for 2 weeks, then matching placebo (4 capsules per day).

Number of subjects in period 1	Pexidartinib (Part 1)	Placebo (Part 1)
Started	61	59
Completed	52	48
Not completed	9	11
Subject noncompliance	-	1
Consent withdrawn by subject	1	6
Physician decision	-	3
Disease progression	-	1
Adverse event, non-fatal	8	-

Period 2

Period 2 title	Part 2 (open-label phase)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Pexidartinib (Parts 1 and 2)

Arm description:

Subjects received pexidartinib in Part 1 and Part 2 at their prescribed dose.

Arm type	Experimental
Investigational medicinal product name	Pexidartinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose in Part 2 was the pexidartinib dose received at the end of Part 1.

Arm title	Placebo (Part 1), Crossover Pexidartinib (Part 2)
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Arm description:

Subjects received placebo in Part 1 and pexidartinib in Part 2 at their prescribed dose.

Arm type	Experimental
Investigational medicinal product name	Pexidartinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose in Part 2 was the pexidartinib equivalent dose of placebo at the end of Part 1.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use
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Dosage and administration details:

Placebo capsule matching pexidartinib capsule was administered orally (5 capsules per day) for 2 weeks, then matching placebo (4 capsules per day).

Number of subjects in period 2	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)
Started	61	30
Completed	42	26
Not completed	19	4
Adverse event, serious fatal	-	1
Consent withdrawn by subject	12	1
Physician decision	1	-
Disease progression	1	-
Adverse event, non-fatal	4	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Pexidartinib (Part 1)
Reporting group description:	
Subjects randomized to pexidartinib for 24 weeks administered twice a day.	
Reporting group title	Placebo (Part 1)
Reporting group description:	
Subjects randomized to matching placebo for 24 weeks administered twice a day.	

Reporting group values	Pexidartinib (Part 1)	Placebo (Part 1)	Total
Number of subjects	61	59	120
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)	57	56	113
From 65-84 years	4	3	7
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.6	44.3	
standard deviation	± 13.2	± 13.6	-
Gender categorical			
Units: Subjects			
Female	35	36	71
Male	26	23	49

Subject analysis sets

Subject analysis set title	All Pexidartinib Treated
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all subjects who received pexidartinib in Part 1 and Part 2 (placebo crossed over to pexidartinib).	

Reporting group values	All Pexidartinib Treated		
Number of subjects	91		
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)	85		
From 65-84 years	6		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	45.6		
standard deviation	± 13.2		
Gender categorical			
Units: Subjects			
Female	51		
Male	40		

End points

End points reporting groups

Reporting group title	Pexidartinib (Part 1)
Reporting group description: Subjects randomized to pexidartinib for 24 weeks administered twice a day.	
Reporting group title	Placebo (Part 1)
Reporting group description: Subjects randomized to matching placebo for 24 weeks administered twice a day.	
Reporting group title	Pexidartinib (Parts 1 and 2)
Reporting group description: Subjects received pexidartinib in Part 1 and Part 2 at their prescribed dose.	
Reporting group title	Placebo (Part 1), Crossover Pexidartinib (Part 2)
Reporting group description: Subjects received placebo in Part 1 and pexidartinib in Part 2 at their prescribed dose.	
Subject analysis set title	All Pexidartinib Treated
Subject analysis set type	Intention-to-treat
Subject analysis set description: Includes all subjects who received pexidartinib in Part 1 and Part 2 (placebo crossed over to pexidartinib).	

Primary: Percentage of Subjects With Symptomatic, Locally Advanced Tenosynovial Giant Cell Tumor (TGCT) Achieving Complete or Partial Response to Pexidartinib Compared With That of Placebo per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at Week 25

End point title	Percentage of Subjects With Symptomatic, Locally Advanced Tenosynovial Giant Cell Tumor (TGCT) Achieving Complete or Partial Response to Pexidartinib Compared With That of Placebo per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at Week 25
End point description: Complete (CR) and partial responses (PR) were assessed based on centrally-read magnetic resonance imaging (MRI) scans and Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). A CR was defined as disappearance of all tumors and a PR was defined as at least a 30% decrease in the sum of diameters of target tumors using the baseline sum diameters as the reference. Best overall response was assessed in the ITT population.	
End point type	Primary
End point timeframe: Week 25	

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Percentage of subjects				
number (not applicable)				
CR	14.8	0		
PR	24.6	0		
Response (CR or PR)	39.3	0		

Statistical analyses

Statistical analysis title	Pexidartinib vs Placebo
Statistical analysis description:	
Treatment comparison between the pexidartinib and placebo groups at Week 25	
Comparison groups	Placebo (Part 1) v Pexidartinib (Part 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.0001
Method	Mixed effects model for repeated measure

Notes:

[1] - Treatment comparison analysis

Secondary: Mean Change From Baseline for Range of Motion (ROM) Score in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25

End point title	Mean Change From Baseline for Range of Motion (ROM) Score in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25
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End point description:

Range of motion (ROM) of the joint was assessed by a qualified, independent, and blinded or third-party assessors at the clinical site. Measurements were recorded in degrees. At baseline, the plane of movement with the smallest relative value (worst) was identified and this plane was used for evaluating the relative change of motion subsequently. Only the plane with the worst impaired ROM at baseline was selected for subsequent analyses. ROM was assessed in the ITT population.

End point type	Secondary
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End point timeframe:

Week 25

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Least square mean change from baseline				
least squares mean (standard error)				
Baseline (N=61, 58)	62.5 (± 3.2)	62.9 (± 2.9)		
Week 13 (N=52, 53)	13.0 (± 2.3)	4.8 (± 2.6)		
Week 25 (N=45, 43)	15.1 (± 2.1)	6.2 (± 2.4)		

Statistical analyses

Statistical analysis title	Pexidartinib vs Placebo
Statistical analysis description:	
Treatment comparison between the pexidartinib and placebo groups at Week 25	
Comparison groups	Pexidartinib (Part 1) v Placebo (Part 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.0043
Method	Mixed effects model for repeated measure

Notes:

[2] - Treatment comparison analysis

Secondary: Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response Based on Tumor Volume Score (TVS) After Receiving Pexidartinib Compared With Those on Placebo at Week 25

End point title	Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response Based on Tumor Volume Score (TVS) After Receiving Pexidartinib Compared With Those on Placebo at Week 25
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End point description:

Complete (CR) and partial responses (PR) were assessed using tumor volume score (TVS). A CR was defined as disappearance of all tumors and a PR was defined as at least a 30% decrease in the sum of diameters of target tumors using the baseline sum diameters as the reference. TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath was scored 10; a score of 0 indicated no evidence of tumor. Best overall response was assessed in the ITT population.

End point type	Secondary
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End point timeframe:

Week 25

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Percentage of subjects				
number (not applicable)				
CR	4.9	0		
PR	50.8	0		
Response (CR or PR)	55.7	0		

Statistical analyses

Statistical analysis title	Pexidartinib vs Placebo
Statistical analysis description:	
Treatment comparison between the pexidartinib and placebo groups at Week 25	
Comparison groups	Pexidartinib (Part 1) v Placebo (Part 1)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	< 0.0001
Method	Mixed effects model for repeated measure

Notes:

[3] - Treatment comparison analysis

Secondary: Mean Change From Baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Score in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25

End point title	Mean Change From Baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Score in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25
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End point description:

The Patient-reported Outcomes Measurement Information System (PROMIS) physical function scale was used to assess physical function of the upper and lower limbs. Physical function was assessed in the ITT population.

End point type	Secondary
End point timeframe:	Week 25

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Least square mean change from baseline				
least squares mean (standard error)				
Baseline (N=60, 57)	37.5 (± 0.6)	38.9 (± 0.8)		
Week 9 (N=38, 41)	2.8 (± 1.0)	-0.4 (± 0.8)		
Week 17 (N=39, 40)	3.2 (± 1.1)	0.2 (± 1.0)		
Week 25 (N=38, 31)	4.1 (± 1.1)	-0.9 (± 1.0)		

Statistical analyses

Statistical analysis title	Pexidartinib vs Placebo
Statistical analysis description:	
Treatment comparison between the pexidartinib and placebo groups at Week 25	
Comparison groups	Pexidartinib (Part 1) v Placebo (Part 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	= 0.0019
Method	Mixed effects model for repeated measure

Notes:

[4] - Treatment comparison analysis

Secondary: Mean Change From Baseline for Worst Stiffness Numeric Rating Scale Score (NRS) in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25

End point title	Mean Change From Baseline for Worst Stiffness Numeric Rating Scale Score (NRS) in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25
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End point description:

The Worst Stiffness Numeric Rating Scale (NRS) was a 1-item, self-administered questionnaire assessing the "worst" stiffness in the last 24 hours. The NRS for this item ranged from 0 (no stiffness) to 10 (stiffness as bad as you can imagine). Worst stiffness was assessed in the ITT population.

End point type	Secondary
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End point timeframe:

Week 25

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Least square mean change from baseline				
least squares mean (standard error)				
Baseline (N=59, 58)	5.6 (± 0.2)	5.9 (± 0.3)		
Week 9 (N=30, 38)	-1.5 (± 0.3)	-0.5 (± 0.3)		
Week 17 (N=37, 30)	-2.4 (± 0.3)	-0.4 (± 0.3)		
Week 25 (N=33, 35)	-2.5 (± 0.3)	-0.3 (± 0.3)		

Statistical analyses

Statistical analysis title	Pexidartinib vs Placebo
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Statistical analysis description:

Treatment comparison between the pexidartinib and placebo groups at Week 25

Comparison groups	Placebo (Part 1) v Pexidartinib (Part 1)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	< 0.0001
Method	Mixed effects model for repeated measure

Notes:

[5] - Treatment comparison analysis

Secondary: Proportion of Responders for Worst Pain NRS in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25

End point title	Proportion of Responders for Worst Pain NRS in Subjects Receiving Pexidartinib Compared With Those on Placebo at Week 25
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End point description:

The Brief Pain Inventory (BPI) Worst Pain NRS was a 1-item, self-administered questionnaire assessing the "worst" pain in the last 24 hours. The NRS for this item ranged from 0 (no pain) to 10 (pain as bad as you can imagine). Worst pain was assessed in the ITT population.

End point type	Secondary
End point timeframe:	
Week 25	

End point values	Pexidartinib (Part 1)	Placebo (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	59		
Units: Proportion of responders				
number (not applicable)				
Proportion of responders (N=35, 33)	15.3	31.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on RECIST 1.1 for Responders to Pexidartinib by Week 96

End point title	Duration of Response (DOR) Based on RECIST 1.1 for Responders to Pexidartinib by Week 96
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End point description:

Duration of response (DOR) is defined as the date of the first recorded response to the first date of documented disease progression. The overall number of responses and the number of subjects with and without disease progression was assessed in the ITT population. Median duration of response was not reached.

End point type	Secondary
End point timeframe:	
By Week 96	

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Number of responders				
number (not applicable)				
Number of responses	23	12	35	
Week 12 (Day 84); Without disease progression	23	12	35	
Week 12 (Day 84); With disease progression	0	0	0	
Week 24 (Day 168); Without disease progression	23	12	35	

Week 24 (Day 168); With disease progression	0	0	0	
Week 48 (Day 336); Without disease progression	15	9	24	
Week 48 (Day 336); With disease progression	1	0	1	
Week 72 (Day 504); Without disease progression	9	3	12	
Week 72 (Day 504); With disease progression	1	0	1	
Week 96 (Day 672); Without disease progression	2	1	3	
Week 96 (Day 672); With disease progression	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of TVS Response for Responders to Pexidartinib Among Subjects Randomized to Placebo Followed by Open-Label PLX3397 by Week 120

End point title	Duration of TVS Response for Responders to Pexidartinib Among Subjects Randomized to Placebo Followed by Open-Label PLX3397 by Week 120
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End point description:

TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath was scored 10; a score of 0 indicated no evidence of tumor. The overall number of responses and the number of subjects with and without disease progression was assessed in the ITT population. Median duration of response was not reached.

End point type	Secondary
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End point timeframe:

By Week 120

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Number of responders				
number (not applicable)				
Number of responses	34	18	52	
Week 12 (Day 84); Without disease progression	33	18	51	
Week 12 (Day 84); With disease progression	0	0	0	
Week 24 (Day 168); Without disease progression	32	18	50	
Week 24 (Day 168); With disease progression	0	0	0	

Week 48 (Day 336); Without disease progression	22	13	35	
Week 48 (Day 336); With disease progression	3	1	4	
Week 72 (Day 504); Without disease progression	13	3	16	
Week 72 (Day 504); With disease progression	3	1	4	
Week 96 (Day 672); Without disease progression	3	1	4	
Week 96 (Day 672); With disease progression	3	1	4	
Week 120 (Day 840); Without disease progression	1	0	1	
Week 120 (Day 840); With disease progression	3	1	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Frequent ($\geq 10\%$) Treatment-Emergent Adverse Events by Preferred Term

End point title	Percentage of Subjects Reporting Frequent ($\geq 10\%$) Treatment-Emergent Adverse Events by Preferred Term
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End point description:

Treatment-emergent adverse events (TEAEs) were defined as adverse events that started or worsened after the first dose of treatment and within 28 days after the last dose. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 was used to grade adverse events. Any Grade and Grade ≥ 3 (severe) TEAEs are reported. TEAEs were coded using MedDRA version 17.1. All safety events were assessed in the Safety Analysis Set.

End point type	Secondary
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End point timeframe:

After the first dose of treatment up to 28 days after the last dose.

End point values	Pexidartinib (Part 1)	Placebo (Part 1)	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	59	61	30
Units: Percentage of subjects				
number (not applicable)				
Any Hair color changes	67.2	3.4	73.8	83.3
Grade ≥ 3 Hair color changes	0	0	0	0
Any Pruritis	9.8	3.4	16.4	20.0
Grade ≥ 3 Pruritis	0	0	1.6	0
Any Rash maculopapular	9.8	1.7	14.8	10.0
Grade ≥ 3 Rash maculopapular	0	0	1.6	0
Any Pruritis generalized	8.2	0	8.2	10.0
Grade ≥ 3 Pruritis generalized	0	0	0	0

Any Erythema	1.6	0	3.3	20.0
Grade >=3 Erythema	0	0	0	0
Any Dry skin	3.3	3.4	6.6	10.0
Grade >=3 Dry skin	0	0	0	3.3
Any Photosensitivity reaction	0	0	1.6	10.0
Grade >=3 Photosensitivity reaction	0	0	0	0
Any Nausea	37.7	40.7	44.3	20.0
Grade >=3 Nausea	0	0	0	0
Any Diarrhea	19.7	25.4	26.2	30.0
Grade >=3 Diarrhea	0	0	0	0
Any Vomiting	19.7	5.1	23.0	6.7
Grade >=3 Vomiting	1.6	0	1.6	0
Any Abdominal Pain	16.4	10.2	21.3	6.7
Grade >=3 Abdominal Pain	0	0	0	0
Any Dry mouth	9.8	3.4	13.1	13.3
Grade >=3 Dry mouth	0	0	0	0
Any Constipation	11.5	5.1	14.8	10.0
Grade >=3 Constipation	0	0	0	0
Any Stomatitis	6.6	1.7	8.2	10.0
Grade >=3 Stomatitis	0	0	0	0
Any Fatigue	54.1	35.6	55.7	26.7
Grade >=3 Fatigue	0	0	0	0
Any Edema peripheral	13.1	3.4	16.4	20.0
Grade >=3 Edema peripheral	0	0	0	0
Any Face edema	13.1	1.7	14.8	20.0
Grade >=3 Face edema	0	0	1.6	3.3
Any Asthenia	9.8	5.1	11.5	20.0
Grade >=3 Asthenia	0	0	0	0
Any Pyrexia	6.6	1.7	8.2	13.3
Grade >=3 Pyrexia	0	0	0	0
Any AST increased	39.3	0	44.3	16.7
Grade >=3 AST increased	9.8	0	9.8	6.7
Any ALT increased	27.9	1.7	31.1	23.3
Grade >=3 ALT increased	9.8	0	9.8	10.0
Any ALP increased	14.8	0	14.8	3.3
Grade >=3 ALP increased	6.6	0	6.6	3.3
Any LDH increased	11.5	0	11.5	10.0
Grade >=3 LDH increased	1.6	0	1.6	0
Any Weight increased	3.3	0	4.9	10.0
Grade >=3 Weight increased	0	0	0	0
Any Dysgeusia	24.6	1.7	27.9	23.3
Grade >=3 Dysgeusia	0	0	0	0
Any Headache	19.7	18.6	23.0	20.0
Grade >=3 Headache	0	0	1.6	0
Any Dizziness	9.8	15.3	13.1	13.3
Grade >=3 Dizziness	1.6	0	1.6	0
Any Paresthesia	1.6	1.7	8.2	10.0
Grade >=3 Paresthesia	0	0	0	0
Any Memory impairment	0	1.7	1.6	10.0
Grade >=3 Memory impairment	0	0	0	0
Any Arthralgia	23.0	25.4	27.9	30.0
Grade >=3 Arthralgia	3.3	1.7	3.3	0

Any Pain in extremity	6.6	6.8	9.8	13.3
Grade ≥3 Pain in extremity	0	1.7	0	0
Any Periorbital edema	18.0	1.7	24.6	13.3
Grade ≥3 Periorbital edema	1.6	0	1.6	0
Any Eyelid edema	3.3	0	4.9	10.0
Grade ≥3 Eyelid edema	0	0	0	0
Any Decreased appetite	16.4	10.2	18.0	10.0
Grade ≥3 Decreased appetite	0	0	0	0
Any Hypertension	14.8	10.2	19.7	30.0
Grade ≥3 Hypertension	4.9	0	4.9	6.7
Any Upper respiratory tract infection	1.6	0	11.5	3.3
Grade ≥3 Upper respiratory tract infection	0	0	0	0
Any Cough	4.9	5.1	6.6	10.0
Grade ≥3 Cough	0	0	0	0
Any Dyspnea	1.6	0	4.9	10.0
Grade ≥3 Dyspnea	0	0	0	0
Any Insomnia	4.9	3.4	4.9	10.0
Grade ≥3 Insomnia	0	0	0	0
Any Rash	14.8	5.1	27.9	23.3
Grade ≥3 Rash	1.6	0	1.6	0

End point values	All Pexidartinib Treated			
Subject group type	Subject analysis set			
Number of subjects analysed	91			
Units: Percentage of subjects				
number (not applicable)				
Any Hair color changes	76.9			
Grade ≥3 Hair color changes	0			
Any Pruritis	17.6			
Grade ≥3 Pruritis	1.1			
Any Rash maculopapular	13.2			
Grade ≥3 Rash maculopapular	1.1			
Any Pruritis generalized	8.8			
Grade ≥3 Pruritis generalized	0			
Any Erythema	8.8			
Grade ≥3 Erythema	0			
Any Dry skin	7.7			
Grade ≥3 Dry skin	1.1			
Any Photosensitivity reaction	4.4			
Grade ≥3 Photosensitivity reaction	0			
Any Nausea	36.3			
Grade ≥3 Nausea	0			
Any Diarrhea	27.5			
Grade ≥3 Diarrhea	0			
Any Vomiting	17.6			
Grade ≥3 Vomiting	1.1			
Any Abdominal Pain	16.5			
Grade ≥3 Abdominal Pain	0			

Any Dry mouth	13.2			
Grade >=3 Dry mouth	0			
Any Constipation	13.2			
Grade >=3 Constipation	0			
Any Stomatitis	8.8			
Grade >=3 Stomatitis	0			
Any Fatigue	46.2			
Grade >=3 Fatigue	0			
Any Edema peripheral	17.6			
Grade >=3 Edema peripheral	0			
Any Face edema	16.5			
Grade >=3 Face edema	2.2			
Any Asthenia	14.3			
Grade >=3 Asthenia	0			
Any Pyrexia	9.9			
Grade >=3 Pyrexia	0			
Any AST increased	35.2			
Grade >=3 AST increased	8.8			
Any ALT increased	28.6			
Grade >=3 ALT increased	9.9			
Any ALP increased	11.0			
Grade >=3 ALP increased	5.5			
Any LDH increased	11.0			
Grade >=3 LDH increased	1.1			
Any Weight increased	6.6			
Grade >=3 Weight increased	0			
Any Dysgeusia	26.4			
Grade >=3 Dysgeusia	0			
Any Headache	22.0			
Grade >=3 Headache	1.1			
Any Dizziness	13.2			
Grade >=3 Dizziness	1.1			
Any Paresthesia	8.8			
Grade >=3 Paresthesia	0			
Any Memory impairment	4.4			
Grade >=3 Memory impairment	0			
Any Arthralgia	28.6			
Grade >=3 Arthralgia	2.2			
Any Pain in extremity	11.0			
Grade >=3 Pain in extremity	0			
Any Periorbital edema	20.0			
Grade >=3 Periorbital edema	1.1			
Any Eyelid edema	6.6			
Grade >=3 Eyelid edema	0			
Any Decreased appetite	15.4			
Grade >=3 Decreased appetite	0			
Any Hypertension	13.1			
Grade >=3 Hypertension	5.5			
Any Upper respiratory tract infection	8.8			
Grade >=3 Upper respiratory tract infection	0			
Any Cough	7.7			

Grade ≥ 3 Cough	0			
Any Dyspnea	7.7			
Grade ≥ 3 Dyspnea	0			
Any Insomnia	6.6			
Grade ≥ 3 Insomnia	0			
Any Rash	26.4			
Grade ≥ 3 Rash	1.1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response to Pexidartinib Compared With That of Placebo per RECIST 1.1 by Week 49

End point title	Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response to Pexidartinib Compared With That of Placebo per RECIST 1.1 by Week 49
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End point description:

CR and PR were assessed based on centrally-read MRI scans and RECIST 1.1. A CR was defined as disappearance of all tumors and a PR was defined as at least a 30% decrease in the sum of diameters of target tumors using the baseline sum diameters as the reference. Best overall response was assessed in the ITT population.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Percentage of subjects				
number (not applicable)				
CR	24.6	23.3	24.2	
PR	29.5	30.0	29.7	
Response (CR or PR)	54.1	53.3	53.8	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline for ROM Score in Subjects Receiving Pexidartinib Compared with those on Placebo by Week 49

End point title	Mean Change From Baseline for ROM Score in Subjects Receiving Pexidartinib Compared with those on Placebo by
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End point description:

Range of motion (ROM) of the joint was assessed by a qualified, independent, and blinded or third-party assessors at the clinical site. Measurements were recorded in degrees. At baseline, the plane of movement with the smallest relative value (worst) was identified and this plane was used for evaluating the relative change of motion subsequently. Only the plane with the worst impaired ROM at baseline was selected for subsequent analyses. ROM was assessed in the ITT population. ROM was assessed in the ITT population.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Mean change from baseline arithmetic mean (standard deviation)				
Baseline (N=61, 30, 91)	62.5 (± 24.8)	66.5 (± 22.9)	63.8 (± 24.2)	
Week 25 (N=45, 24, 69)	15.6 (± 14.9)	13.1 (± 12.9)	14.8 (± 14.2)	
Week 49 (N=33, 22, 55)	14.4 (± 19.5)	12.0 (± 13.4)	13.4 (± 17.3)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline in the PROMIS Physical Function Score in Subjects Receiving Pexidartinib Compared With Those on Placebo by Week 49

End point title	Mean Change From Baseline in the PROMIS Physical Function Score in Subjects Receiving Pexidartinib Compared With Those on Placebo by Week 49
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End point description:

The PROMIS physical function scale was used to assess physical function of the upper and lower limbs. Physical function was assessed in the ITT population.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Mean change from baseline arithmetic mean (standard deviation)				
Baseline (N=60, 30, 90)	37.5 (± 4.9)	38.7 (± 6.9)	37.9 (± 5.6)	
Week 25 (N=38, 16, 54)	3.6 (± 4.9)	4.9 (± 6.3)	4.0 (± 5.4)	
Week 49 (N=25, 14, 39)	4.7 (± 4.4)	7.6 (± 6.3)	5.8 (± 5.2)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline for Worst Stiffness Numeric Rating Scale Score in Subjects Receiving Pexidartinib Compared With Those on Placebo by Week 49

End point title	Mean Change From Baseline for Worst Stiffness Numeric Rating Scale Score in Subjects Receiving Pexidartinib Compared With Those on Placebo by Week 49
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End point description:

The Worst Stiffness Numeric Rating Scale (NRS) was a 1-item, self-administered questionnaire assessing the "worst" stiffness in the last 24 hours. The NRS for this item ranged from 0 (no stiffness) to 10 (stiffness as bad as you can imagine). Worst stiffness was assessed in the ITT population.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Mean change from baseline arithmetic mean (standard deviation)				
Baseline (N=59, 26, 85)	5.6 (± 1.7)	5.7 (± 2.3)	5.6 (± 1.9)	
Week 25 (N=33, 18, 51)	-2.7 (± 2.2)	-3.0 (± 3.1)	-2.8 (± 2.5)	
Week 49 (N=22, 10, 32)	-3.5 (± 1.9)	-2.2 (± 2.8)	-3.1 (± 2.3)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline for Worst Pain NRS in Subjects

Receiving Pexidartinib Compared With Those on Placebo by Week 49

End point title	Mean Change From Baseline for Worst Pain NRS in Subjects Receiving Pexidartinib Compared With Those on Placebo by Week 49
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End point description:

The Brief Pain Inventory (BPI) Worst Pain NRS was a 1-item, self-administered questionnaire assessing the "worst" pain in the last 24 hours. The NRS for this item ranged from 0 (no pain) to 10 (pain as bad as you can imagine). Worst pain was assessed in the ITT population.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Mean change from baseline arithmetic mean (standard deviation)				
Baseline (N=59, 26, 85)	5.6 (± 1.6)	5.2 (± 2.5)	5.5 (± 1.9)	
Week 25 (N=33, 18, 51)	-2.7 (± 2.2)	-2.6 (± 3.1)	-2.7 (± 2.5)	
Week 49 (N=22, 10, 32)	-3.3 (± 1.7)	-2.8 (± 3.4)	-3.2 (± 2.3)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response Based on TVS After Receiving Pexidartinib Compared With Those on Placebo by Week 49

End point title	Percentage of Subjects With Symptomatic, Locally Advanced TGCT Achieving Complete or Partial Response Based on TVS After Receiving Pexidartinib Compared With Those on Placebo by Week 49
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End point description:

Best overall response (CR or PR) was assessed using tumor volume score (TVS) in the ITT population. TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath was scored 10; a score of 0 indicated no evidence of tumor.

End point type	Other pre-specified
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End point timeframe:

By Week 49

End point values	Pexidartinib (Parts 1 and 2)	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	30	91	
Units: Percentage of subjects				
number (not applicable)				
Best overall response (CR or PR)	63.9	66.7	64.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event were monitored throughout the study from the time the subject signed the informed consent form to 28 days after the final treatment dose.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Pexidartinib (Part 1)
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Reporting group description:

Subjects randomized to pexidartinib for 24 weeks administered twice a day.

Reporting group title	Placebo (Part 1)
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Reporting group description:

Subjects randomized to matching placebo for 24 weeks administered twice a day.

Reporting group title	Pexidartinib (Parts 1 and 2)
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Reporting group description:

Subjects received pexidartinib in Part 1 and Part 2 at their prescribed dose.

Reporting group title	Placebo (Part 1), Crossover Pexidartinib (Part 2)
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Reporting group description:

Subjects received placebo in Part 1 and pexidartinib in Part 2 at their prescribed dose.

Reporting group title	All Pexidartinib Treated
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Reporting group description:

Subjects received pexidartinib in Part 1 and Part 2 (placebo crossed over to pexidartinib).

Serious adverse events	Pexidartinib (Part 1)	Placebo (Part 1)	Pexidartinib (Parts 1 and 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 61 (13.11%)	1 / 59 (1.69%)	9 / 61 (14.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenosquamous carcinoma of the cervix			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endometrial cancer			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	2 / 61 (3.28%)	0 / 59 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			

subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Local swelling			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hepatitis A			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	12 / 91 (13.19%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenosquamous carcinoma of the cervix			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 30 (0.00%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 30 (0.00%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			

Migraine			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
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			
Local swelling			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hepatitis A			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 30 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pexidartinib (Part 1)	Placebo (Part 1)	Pexidartinib (Parts 1 and 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 61 (98.36%)	55 / 59 (93.22%)	61 / 61 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	3 / 59 (5.08%)	4 / 61 (6.56%)
occurrences (all)	7	5	7
Vascular disorders			

Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 15	6 / 59 (10.17%) 6	12 / 61 (19.67%) 21
Hypotension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	0 / 59 (0.00%) 0	0 / 61 (0.00%) 0
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	33 / 61 (54.10%) 49	21 / 59 (35.59%) 26	34 / 61 (55.74%) 53
Face edema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 8	1 / 59 (1.69%) 1	9 / 61 (14.75%) 11
Edema peripheral alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 9	2 / 59 (3.39%) 2	10 / 61 (16.39%) 12
Asthenia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 7	3 / 59 (5.08%) 5	7 / 61 (11.48%) 12
Pyrexia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 4	1 / 59 (1.69%) 1	5 / 61 (8.20%) 5
Influenza like illness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	0 / 59 (0.00%) 0	4 / 61 (6.56%) 5
Chest pain alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	6
Dyspnea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	3
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	4
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	3
Investigations			
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 61 (39.34%)	0 / 59 (0.00%)	27 / 61 (44.26%)
occurrences (all)	48	0	58
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 61 (27.87%)	1 / 59 (1.69%)	19 / 61 (31.15%)
occurrences (all)	44	1	53
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	9 / 61 (14.75%)	0 / 59 (0.00%)	9 / 61 (14.75%)
occurrences (all)	26	0	30
Blood lactate dehydrogenase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 61 (11.48%)	0 / 59 (0.00%)	7 / 61 (11.48%)
occurrences (all)	12	0	13
White blood cell count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	6 / 61 (9.84%)
occurrences (all)	0	0	8
Weight increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	3
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	8
Blood creatine phosphokinase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	3
Cardiac disorders			
Bradycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 61 (24.59%)	1 / 59 (1.69%)	17 / 61 (27.87%)
occurrences (all)	24	1	26
Headache			

subjects affected / exposed	11 / 61 (18.03%)	11 / 59 (18.64%)	14 / 61 (22.95%)
occurrences (all)	16	15	22
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 61 (9.84%)	9 / 59 (15.25%)	8 / 61 (13.11%)
occurrences (all)	7	12	12
Paresthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	5 / 61 (8.20%)
occurrences (all)	0	0	6
Memory impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Neuropathy peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	5
Blood and lymphatic system disorders			
Anemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	6 / 61 (9.84%)
occurrences (all)	0	0	10
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	11
Leukopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	5
Thrombocytopenia			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	0 / 59 (0.00%) 0	2 / 61 (3.28%) 2
Ear and labyrinth disorders Tinnitus alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vertigo alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0	 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0	 2 / 61 (3.28%) 2 2 / 61 (3.28%) 2
Eye disorders Periorbital edema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Eye edema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Eyelid edema alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vision blurred alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	 11 / 61 (18.03%) 13 6 / 61 (9.84%) 6 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0	 1 / 59 (1.69%) 1 2 / 59 (3.39%) 2 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0	 15 / 61 (24.59%) 19 6 / 61 (9.84%) 6 3 / 61 (4.92%) 5 5 / 61 (8.20%) 5
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Vomiting	 23 / 61 (37.70%) 40 12 / 61 (19.67%) 17	 24 / 59 (40.68%) 26 15 / 59 (25.42%) 18	 27 / 61 (44.26%) 60 16 / 61 (26.23%) 26

subjects affected / exposed	12 / 61 (19.67%)	3 / 59 (5.08%)	14 / 61 (22.95%)
occurrences (all)	16	3	21
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 61 (16.39%)	6 / 59 (10.17%)	13 / 61 (21.31%)
occurrences (all)	12	8	15
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 61 (11.48%)	3 / 59 (5.08%)	9 / 61 (14.75%)
occurrences (all)	8	3	10
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 61 (9.84%)	2 / 59 (3.39%)	8 / 61 (13.11%)
occurrences (all)	6	2	8
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 61 (6.56%)	1 / 59 (1.69%)	5 / 61 (8.20%)
occurrences (all)	4	2	5
Skin and subcutaneous tissue disorders			
Hair color changes			
alternative assessment type: Non-systematic			
subjects affected / exposed	41 / 61 (67.21%)	2 / 59 (3.39%)	45 / 61 (73.77%)
occurrences (all)	46	2	53
Pruritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 61 (16.39%)	2 / 59 (3.39%)	10 / 61 (16.39%)
occurrences (all)	11	2	10
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 61 (13.11%)	2 / 59 (3.39%)	17 / 61 (27.87%)
occurrences (all)	9	3	28
Rash maculo-papular			
alternative assessment type: Non-systematic			

subjects affected / exposed	6 / 61 (9.84%)	1 / 59 (1.69%)	9 / 61 (14.75%)
occurrences (all)	8	1	15
Erythema			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	2 / 61 (3.28%)
occurrences (all)	0	0	2
Pruritis generalized			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	5 / 61 (8.20%)
occurrences (all)	0	0	6
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	5
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	3 / 61 (4.92%)
occurrences (all)	0	0	3
Skin hypopigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	4 / 61 (6.56%)
occurrences (all)	0	0	6
Photosensitivity reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Rash pruritic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Dermatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 61 (0.00%)	0 / 59 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

<p>Arthralgia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 61 (22.95%)</p> <p>17</p>	<p>15 / 59 (25.42%)</p> <p>18</p>	<p>17 / 61 (27.87%)</p> <p>21</p>
<p>Pain in extremity</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 61 (6.56%)</p> <p>6</p>	<p>4 / 59 (6.78%)</p> <p>4</p>	<p>6 / 61 (9.84%)</p> <p>8</p>
<p>Back pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	<p>4 / 61 (6.56%)</p> <p>5</p>
<p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 61 (6.56%)</p> <p>5</p>	<p>3 / 59 (5.08%)</p> <p>3</p>	<p>5 / 61 (8.20%)</p> <p>7</p>
<p>Upper respiratory tract infection</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	<p>7 / 61 (11.48%)</p> <p>10</p>
<p>Sinusitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	<p>4 / 61 (6.56%)</p> <p>7</p>
<p>Cellulitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	<p>0 / 61 (0.00%)</p> <p>0</p>
<p>Cystitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	<p>0 / 61 (0.00%)</p> <p>0</p>
Metabolism and nutrition disorders			

Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	10 / 61 (16.39%) 13	6 / 59 (10.17%) 6	11 / 61 (18.03%) 15
Hypercholesterolemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 8	0 / 59 (0.00%) 0	7 / 61 (11.48%) 13
Fluid retention alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	0 / 59 (0.00%) 0	3 / 61 (4.92%) 4
Hyperglycemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	0 / 59 (0.00%) 0	1 / 61 (1.64%) 1

Non-serious adverse events	Placebo (Part 1), Crossover Pexidartinib (Part 2)	All Pexidartinib Treated	
Total subjects affected by non-serious adverse events subjects affected / exposed	30 / 30 (100.00%)	91 / 91 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumor pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	5 / 91 (5.49%) 8	
Vascular disorders Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Hypotension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 13 2 / 30 (6.67%) 2	21 / 91 (23.08%) 34 2 / 91 (2.20%) 2	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	8 / 30 (26.67%)	42 / 91 (46.15%)	
occurrences (all)	12	65	
Face edema			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 30 (20.00%)	15 / 91 (16.48%)	
occurrences (all)	10	21	
Edema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 30 (20.00%)	16 / 91 (17.58%)	
occurrences (all)	7	19	
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 30 (20.00%)	13 / 91 (14.29%)	
occurrences (all)	11	23	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 30 (13.33%)	9 / 91 (9.89%)	
occurrences (all)	4	9	
Influenza like illness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 30 (0.00%)	4 / 91 (4.40%)	
occurrences (all)	0	5	
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	3 / 91 (3.30%)	
occurrences (all)	2	3	
Malaise			
subjects affected / exposed	2 / 30 (6.67%)	3 / 91 (3.30%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>3</p> <p>3 / 30 (10.00%)</p> <p>3</p> <p>1 / 30 (3.33%)</p> <p>1</p>	<p>7 / 91 (7.69%)</p> <p>9</p> <p>6 / 91 (6.59%)</p> <p>6</p> <p>5 / 91 (5.49%)</p> <p>5</p>	
<p>Psychiatric disorders</p> <p>Insomnia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>4</p>	<p>6 / 91 (6.59%)</p> <p>7</p>	
<p>Investigations</p> <p>Aspartate aminotransferase increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alanine aminotransferase increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood alkaline phosphatase increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood lactate dehydrogenase increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>alternative assessment type: Non-systematic</p>	<p>5 / 30 (16.67%)</p> <p>10</p> <p>7 / 30 (23.33%)</p> <p>13</p> <p>1 / 30 (3.33%)</p> <p>1</p> <p>3 / 30 (10.00%)</p> <p>4</p>	<p>32 / 91 (35.16%)</p> <p>68</p> <p>26 / 91 (28.57%)</p> <p>66</p> <p>10 / 91 (10.99%)</p> <p>31</p> <p>10 / 91 (10.99%)</p> <p>17</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood bilirubin increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood creatine phosphokinase increased</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 30 (3.33%)</p> <p>2</p> <p>3 / 30 (10.00%)</p> <p>3</p> <p>1 / 30 (3.33%)</p> <p>1</p> <p>2 / 30 (6.67%)</p> <p>4</p>	<p>7 / 91 (7.69%)</p> <p>10</p> <p>6 / 91 (6.59%)</p> <p>6</p> <p>5 / 91 (5.49%)</p> <p>9</p> <p>5 / 91 (5.49%)</p> <p>7</p>	
<p>Cardiac disorders</p> <p>Bradycardia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 30 (6.67%)</p> <p>2</p>	<p>2 / 91 (2.20%)</p> <p>2</p>	
<p>Nervous system disorders</p> <p>Dysgeusia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dizziness</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Paresthesia</p> <p>alternative assessment type: Non-systematic</p>	<p>7 / 30 (23.33%)</p> <p>10</p> <p>6 / 30 (20.00%)</p> <p>8</p> <p>4 / 30 (13.33%)</p> <p>4</p>	<p>24 / 91 (26.37%)</p> <p>36</p> <p>20 / 91 (21.98%)</p> <p>30</p> <p>12 / 91 (13.19%)</p> <p>16</p>	

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>4</p>	<p>8 / 91 (8.79%)</p> <p>10</p>	
<p>Memory impairment</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>5</p>	<p>4 / 91 (4.40%)</p> <p>6</p>	
<p>Neuropathy peripheral</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 30 (0.00%)</p> <p>0</p>	<p>4 / 91 (4.40%)</p> <p>5</p>	
<p>Blood and lymphatic system disorders</p> <p>Anemia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 30 (3.33%)</p> <p>1</p> <p>2 / 30 (6.67%)</p> <p>2</p> <p>2 / 30 (6.67%)</p> <p>5</p> <p>2 / 30 (6.67%)</p> <p>2</p>	<p>7 / 91 (7.69%)</p> <p>11</p> <p>6 / 91 (6.59%)</p> <p>13</p> <p>5 / 91 (5.49%)</p> <p>10</p> <p>4 / 91 (4.40%)</p> <p>4</p>	
<p>Ear and labyrinth disorders</p> <p>Tinnitus</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vertigo</p> <p>alternative assessment type: Non-systematic</p>	<p>2 / 30 (6.67%)</p> <p>2</p>	<p>4 / 91 (4.40%)</p> <p>4</p>	

subjects affected / exposed	2 / 30 (6.67%)	4 / 91 (4.40%)	
occurrences (all)	2	4	
Eye disorders			
Periorbital edema			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 30 (13.33%)	19 / 91 (20.88%)	
occurrences (all)	5	24	
Eye edema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 30 (0.00%)	6 / 91 (6.59%)	
occurrences (all)	0	6	
Eyelid edema			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 30 (10.00%)	6 / 91 (6.59%)	
occurrences (all)	4	9	
Vision blurred			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 30 (3.33%)	6 / 91 (6.59%)	
occurrences (all)	2	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 30 (20.00%)	33 / 91 (36.26%)	
occurrences (all)	7	67	
Diarrhea			
subjects affected / exposed	9 / 30 (30.00%)	25 / 91 (27.47%)	
occurrences (all)	20	46	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	16 / 91 (17.58%)	
occurrences (all)	2	23	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	15 / 91 (16.48%)	
occurrences (all)	2	17	
Constipation			
alternative assessment type: Non-systematic			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry mouth</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 30 (10.00%)</p> <p>5</p> <p>4 / 30 (13.33%)</p> <p>4</p> <p>3 / 30 (10.00%)</p> <p>3</p>	<p>12 / 91 (13.19%)</p> <p>15</p> <p>12 / 91 (13.19%)</p> <p>12</p> <p>8 / 91 (8.79%)</p> <p>8</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Hair color changes</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritis</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash maculo-papular</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritis generalized</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry skin</p>	<p>25 / 30 (83.33%)</p> <p>32</p> <p>6 / 30 (20.00%)</p> <p>8</p> <p>7 / 30 (23.33%)</p> <p>11</p> <p>3 / 30 (10.00%)</p> <p>4</p> <p>6 / 30 (20.00%)</p> <p>7</p> <p>3 / 30 (10.00%)</p> <p>3</p>	<p>70 / 91 (76.92%)</p> <p>85</p> <p>16 / 91 (17.58%)</p> <p>18</p> <p>24 / 91 (26.37%)</p> <p>39</p> <p>12 / 91 (13.19%)</p> <p>19</p> <p>8 / 91 (8.79%)</p> <p>9</p> <p>8 / 91 (8.79%)</p> <p>9</p>	

alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 30 (10.00%)	7 / 91 (7.69%)	
occurrences (all)	4	9	
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	5 / 91 (5.49%)	
occurrences (all)	2	5	
Skin hypopigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 30 (3.33%)	5 / 91 (5.49%)	
occurrences (all)	1	7	
Photosensitivity reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 30 (10.00%)	4 / 91 (4.40%)	
occurrences (all)	3	4	
Rash pruritic			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	3 / 91 (3.30%)	
occurrences (all)	3	4	
Dermatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	2 / 91 (2.20%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 30 (30.00%)	26 / 91 (28.57%)	
occurrences (all)	17	38	
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 30 (13.33%)	10 / 91 (10.99%)	
occurrences (all)	6	14	
Back pain			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	6 / 91 (6.59%) 7	
Infections and infestations Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Upper respiratory tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Sinusitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Cellulitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Cystitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 0 / 30 (0.00%) 0 2 / 30 (6.67%) 2 2 / 30 (6.67%) 3	6 / 91 (6.59%) 8 8 / 91 (8.79%) 11 4 / 91 (4.40%) 7 2 / 91 (2.20%) 2 2 / 91 (2.20%) 3	
Metabolism and nutrition disorders Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Hypercholesterolemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Fluid retention alternative assessment type: Non-systematic	3 / 30 (10.00%) 4 2 / 30 (6.67%) 3	14 / 91 (15.38%) 19 9 / 91 (9.89%) 16	

subjects affected / exposed	2 / 30 (6.67%)	5 / 91 (5.49%)	
occurrences (all)	4	8	
Hyperglycemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 30 (6.67%)	3 / 91 (3.30%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2014	Clarified treatment procedures (e.g. maximum number of cycles) of pexidartinib, revised inclusion and exclusion criteria, modified sample size, updated treatment composition, and clarified dose modification guidelines.
11 February 2015	Revised inclusion criteria, clarified blinding/unblinding procedures, updated list of participating countries, clarified location of Schedule of Events, updated medical monitor, and updated assessment methods.
25 March 2016	Updated formulation of pexidartinib, clarified inclusion and exclusion criteria, revised study assessments, clarified study procedures, and updated efficacy endpoints and dose modification guidelines.
19 July 2016	Revised study procedures and statistical analyses, updated efficacy endpoints, and clarified unblinding procedures.
10 October 2016	Updated Risk Information and Change in Study Conduct section and new safety data and measures were included.
10 February 2017	Clarified study inclusion and exclusion criteria, updated methods for pharmacogenomics analysis, clarified criteria of completion for assessments, clarified study procedures for subjects who complete Part 2, and updated MedDRA version reference.
11 September 2017	Sequential hierarchy of the secondary efficacy endpoints was changed and the medical monitor was updated.
15 December 2017	Updated safety data for pexidartinib and revised the criteria for pexidartinib dose modification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 September 2016	Enrollment was stopped; no new subjects were permitted to start the study drug. Subjects on placebo in Part 1 were no longer allowed to enter Part 2 to receive open-label pexidartinib. After Part 1 was completed, subjects who wished to continue onto the open-label part of the study (Part 2) were unblinded and those on placebo were discontinued. Investigators and subjects were informed of the new safety information and decided whether to continue in the study. The frequency of liver function testing was increased and gamma-glutamyl transpeptidase was added to the laboratory panel. These changes were implemented in the protocol version 6.0 dated 10 Oct 2016.	-

Notes:

Limitations and caveats

None reported