



Clinical trial results:

An Open-Label, Randomized, Phase 2 Study of the Safety and Tolerability of Pirfenidone When Administered to Patients With Systemic SclerosisRelated Interstitial Lung Disease

Summary

EudraCT number	2013-001353-28
Trial protocol	IT
Global end of trial date	16 September 2014

Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

Trial information

Trial identification

Sponsor protocol code	PSSc-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01933334
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase 2, multinational, open-label, randomized, parallel-group study to evaluate safety and tolerability of pirfenidone in participants with systemic sclerosis-related interstitial lung disease (SSc-ILD).

Protection of trial subjects:

This study was conducted according to the principles of Good Clinical Practices (GCP) as described in the International Conference on Harmonisation (ICH) document, Guidance for Industry-E6, Good Clinical Practice: Consolidated Guidance, and in keeping with local legal and regulatory requirements and the Declaration of Helsinki as currently endorsed by regional regulatory health authorities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	63
EEA total number of subjects	6

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)	54

From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened based on the the diagnosis of SSc which was based on the American College of Rheumatology, with SSc disease duration less than (<) 7 years. The diagnosis of SSc-ILD was to be confirmed by a high-resolution computed tomography scan (obtained 2 years before written informed consent).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pirfenidone: 4-Week Titration Group
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Arm description:

Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

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

Dosage and administration details:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

Arm title	Pirfenidone: 2-Week Titration Group
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Arm description:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

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

Dosage and administration details:

Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

Number of subjects in period 1	Pirfenidone: 4-Week Titration Group	Pirfenidone: 2-Week Titration Group
Started	31	32
Completed	29	27
Not completed	2	5
Consent withdrawn by subject	1	-
Adverse event	1	5

Baseline characteristics

Reporting groups

Reporting group title	Pirfenidone: 4-Week Titration Group
Reporting group description: Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).	
Reporting group title	Pirfenidone: 2-Week Titration Group
Reporting group description: Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).	

Reporting group values	Pirfenidone: 4-Week Titration Group	Pirfenidone: 2-Week Titration Group	Total
Number of subjects	31	32	63
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	51.9 ± 12.52	49.3 ± 12.08	-
Gender categorical Units: Subjects			
Female	26	26	52
Male	5	6	11

End points

End points reporting groups

Reporting group title	Pirfenidone: 4-Week Titration Group
Reporting group description: Participants received one 267 milligrams (mg) oral pirfenidone capsule three times daily (TID) (801 mg per day [mg/day]) for 2 weeks followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).	
Reporting group title	Pirfenidone: 2-Week Titration Group
Reporting group description: Participants received one 267 mg oral pirfenidone capsule TID (801 mg/day) for 1 week followed by two 267 mg oral pirfenidone capsules TID (1602 mg/day) for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).	

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (AEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (AEs) ^[1]
End point description: Percentage of participants who had treatment-emergent AEs, defined as newly occurring or worsening after first dose. Participants with multiple occurrences of an AE within a category were counted once within the category. Safety population included all randomized participants who provided written informed consent and received at least one dose of study treatment.	
End point type	Primary
End point timeframe: From baseline up to 28 days after the last dose of study drug (last dose = Week 16)	
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 planned for the safety endpoint.	

End point values	Pirfenidone: 4-Week Titration Group	Pirfenidone: 2-Week Titration Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: percentage of participants				
number (not applicable)	96.8	96.9		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment-Emergent Serious Adverse Events (SAEs) ^[2]
End point description: An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of	

dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety Population.

End point type	Primary
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End point timeframe:

From baseline up to 28 days after the last dose of study drug (last dose = Week 16)

Notes:

[2] - 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 planned for the safety endpoint.

End point values	Pirfenidone: 4-Week Titration Group	Pirfenidone: 2-Week Titration Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: percentage of participants				
number (not applicable)	0	9.4		

Statistical analyses

No statistical analyses for this end point

Secondary: University of California at Los Angeles (UCLA) Scleroderma Clinical Trial Consortium (SCTC) Gastrointestinal Trial (GIT) Questionnaire Scale Scores

End point title	University of California at Los Angeles (UCLA) Scleroderma Clinical Trial Consortium (SCTC) Gastrointestinal Trial (GIT) Questionnaire Scale Scores
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End point description:

UCLA SCTC GIT Scale 2.0 is a 34-item self-administered questionnaire to obtain participant's assessment of frequency of GI symptoms in preceding 7 days and how symptoms affected his/her life. All but 2 items were scored on a 0-3 scale (0=better health, 3=worse health); remaining 2 items were scored as 0 (better health), 1 (worse health). The 34 items are divided into 7 scales (reflux, distention/bloating, fecal soilage, diarrhea, social functioning, emotional well-being, and constipation). Individual scale score was calculated as the average of items in scale. Individual scale score ranged from 0-3 for reflux, distention/bloating, fecal soilage, social functioning, and emotional well-being; 0-2 for diarrhea; and 0-2.5 for constipation. A total score was also calculated as average of 6 of 7 scales (omitting constipation) and ranged from 0-2.83. For individual and total scores 0 indicated better health and higher score indicates worse health. Safety Population. CFB=change from baseline.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 4, 8, 12, and 16

End point values	Pirfenidone: 4-Week Titration Group	Pirfenidone: 2-Week Titration Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31 ^[3]	32 ^[4]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Reflux: Baseline (n=31, 32)	0.3347 (± 0.29117)	0.3398 (± 0.34083)		

Reflux: Week 4 (n=31, 32)	0.3548 (± 0.36529)	0.4727 (± 0.4327)		
Reflux: CFB Week 4 (n=31, 32)	0.0202 (± 0.26437)	0.1328 (± 0.36469)		
Reflux: Week 8 (n=31, 32)	0.4389 (± 0.46573)	0.466 (± 0.39881)		
Reflux: CFB Week 8 (n=31, 32)	0.1043 (± 0.41664)	0.1261 (± 0.36875)		
Reflux: Week 12 (n=30, 27)	0.3417 (± 0.33142)	0.4306 (± 0.41069)		
Reflux: CFB Week 12 (n=30, 27)	0.0042 (± 0.26155)	0.088 (± 0.35494)		
Reflux: Week 16 (n=28, 25)	0.3348 (± 0.39682)	0.395 (± 0.3727)		
Reflux: CFB Week 16 (n=28, 25)	-0.0045 (± 0.3182)	0.075 (± 0.25259)		
Distention/Bloating: Baseline (n=31, 32)	0.5968 (± 0.58693)	0.3984 (± 0.571)		
Distention/Bloating: Week 4 (n=31, 32)	0.4919 (± 0.65346)	0.6406 (± 0.65049)		
Distention/Bloating: CFB Week 4 (n=31, 32)	-0.1048 (± 0.50734)	0.2422 (± 0.41874)		
Distention/Bloating: Week 8 (n=31, 32)	0.4247 (± 0.57188)	0.5703 (± 0.60985)		
Distention/Bloating: CFB Week 8 (n=31, 32)	-0.172 (± 0.43245)	0.1719 (± 0.4728)		
Distention/Bloating: Week 12 (n=30, 27)	0.425 (± 0.56152)	0.537 (± 0.7061)		
Distention/Bloating: CFB Week 12 (n=30, 27)	-0.1833 (± 0.47766)	0.213 (± 0.59929)		
Distention/Bloating: Week 16 (n=28, 25)	0.4286 (± 0.48523)	0.48 (± 0.61627)		
Distention/Bloating: CFB Week 16 (n=28, 25)	-0.1518 (± 0.45307)	0.12 (± 0.45139)		
Diarrhea: Baseline (n=31, 32)	0.2742 (± 0.48026)	0.3281 (± 0.48542)		
Diarrhea: Week 4 (n=31, 32)	0.2258 (± 0.48026)	0.3125 (± 0.48775)		
Diarrhea: CFB Week 4 (n=31, 32)	-0.0484 (± 0.43503)	-0.0156 (± 0.5748)		
Diarrhea: Week 8 (n=31, 32)	0.3226 (± 0.556)	0.2813 (± 0.37968)		
Diarrhea: CFB Week 8 (n=31, 32)	0.0484 (± 0.58245)	-0.0469 (± 0.46419)		
Diarrhea: Week 12 (n=30, 27)	0.2 (± 0.48423)	0.2778 (± 0.46685)		
Diarrhea: CFB Week 12 (n=30, 27)	-0.0667 (± 0.58329)	-0.0556 (± 0.56045)		
Diarrhea: Week 16 (n=28, 25)	0.25 (± 0.51819)	0.34 (± 0.51478)		
Diarrhea: CFB Week 16 (n=28, 25)	-0.0179 (± 0.61587)	0.04 (± 0.57591)		
Social Functioning: Baseline (n=31, 32)	0.1893 (± 0.43585)	0.125 (± 0.28078)		
Social Functioning: Week 4 (n=31, 32)	0.1775 (± 0.27199)	0.1563 (± 0.26072)		
Social Functioning: CFB Week 4 (n=31, 32)	-0.0118 (± 0.28143)	0.0313 (± 0.25893)		
Social Functioning: Week 8 (n=31, 32)	0.1936 (± 0.33647)	0.1886 (± 0.31322)		
Social Functioning: CFB Week 8 (n=31, 32)	0.0044 (± 0.37997)	0.0635 (± 0.29233)		

Social Functioning: Week 12 (n=30, 27)	0.1944 (± 0.30028)	0.1173 (± 0.23488)		
Social Functioning: CFB Week 12 (n=30, 27)	-0.0011 (± 0.3573)	0.0432 (± 0.25154)		
Social Functioning: Week 16 (n=28, 25)	0.01667 (± 0.27596)	0.06 (± 0.13502)		
Social Functioning: CFB Week 16 (n=28, 25)	-0.0131 (± 0.40515)	0.0133 (± 0.16607)		
Emotional Wellbeing: Baseline (n=31, 32)	0.1326 (± 0.4191)	0.0937 (± 0.26033)		
Emotional Wellbeing: Week 4 (n=30, 32)	0.0778 (± 0.32516)	0.0937 (± 0.21697)		
Emotional Wellbeing: CFB Week 4 (n=30, 32)	-0.0593 (± 0.14808)	0 (± 0.17831)		
Emotional Wellbeing: Week 8 (n=31, 32)	0.0825 (± 0.2968)	0.1181 (± 0.33273)		
Emotional Wellbeing: CFB Week 8 (n=31, 32)	-0.0502 (± 0.19846)	0.0243 (± 0.11887)		
Emotional Wellbeing: Week 12 (n=30, 27)	0.0852 (± 0.30979)	0.0493 (± 0.13182)		
Emotional Wellbeing: CFB Week 12 (n=30, 27)	-0.0482 (± 0.14786)	0.0123 (± 0.12055)		
Emotional Wellbeing: Week 16 (n=28, 25)	0.0833 (± 0.39959)	0.0266 (± 0.0803)		
Emotional Wellbeing: CFB Week 16 (n=28, 25)	-0.0357 (± 0.12851)	0 (± 0.10627)		
Fecal Soilage: Baseline (n=31, 32)	0.129 (± 0.42755)	0.0313 (± 0.17678)		
Fecal Soilage: Week 4 (n=31, 32)	0.129 (± 0.42755)	0.0313 (± 0.17678)		
Fecal Soilage: CFB Week 4 (n=31, 32)	0 (± 0)	0 (± 0)		
Fecal Soilage: Week 8 (n=31, 32)	0.1613 (± 0.45437)	0.0313 (± 0.17678)		
Fecal Soilage: CFB Week 8 (n=31, 32)	0.0323 (± 0.17961)	0 (± 0)		
Fecal Soilage: Week 12 (n=30, 27)	0.1333 (± 0.43417)	0.037 (± 0.19245)		
Fecal Soilage: CFB Week 12 (n=30, 27)	0 (± 0)	0.037 (± 0.19245)		
Fecal Soilage: Week 16 (n=28, 25)	0.1071 (± 0.41627)	0.04 (± 0.2)		
Fecal Soilage: CFB Week 16 (n=28, 25)	0 (± 0)	0.04 (± 0.2)		
Constipation: Baseline (n=31, 32)	0.1694 (± 0.2613)	0.2422 (± 0.40899)		
Constipation: Week 4 (n=30, 32)	0.15 (± 0.29066)	0.2656 (± 0.34159)		
Constipation: CFB Week 4 (n=30, 32)	-0.025 (± 0.30336)	0.0234 (± 0.42293)		
Constipation: Week 8 (n=31, 32)	0.1613 (± 0.46345)	0.2578 (± 0.39901)		
Constipation: CFB Week 8 (n=31, 32)	-0.0081 (± 0.38989)	0.0156 (± 0.2535)		
Constipation: Week 12 (n=30, 27)	0.2111 (± 0.36075)	0.2407 (± 0.38904)		
Constipation: CFB Week 12 (n=30, 27)	0.0528 (± 0.49008)	0.037 (± 0.37148)		
Constipation: Week 16 (n=28, 25)	0.1518 (± 0.27504)	0.18 (± 0.29333)		
Constipation: CFB Week 16 (n=28, 25)	-0.0179 (± 0.42453)	0.02 (± 0.37444)		
Total Score: Baseline (n=32, 31)	0.2761 (± 0.32679)	0.2194 (± 0.24262)		

Total Score: Week 4 (n=32, 31)	0.2432 (± 0.31264)	0.2845 (± 0.28528)		
Total Score: CFB Week 4 (n=32, 31)	-0.033 (± 0.13591)	0.0651 (± 0.20058)		
Total Score: Week 8 (n=32, 31)	0.2706 (± 0.29132)	0.2759 (± 0.26133)		
Total Score: CFB Week 8 (n=32, 31)	-0.0055 (± 0.20053)	0.0564 (± 0.15749)		
Total Score: Week 12 (n=27, 30)	0.2299 (± 0.27136)	0.2416 (± 0.25329)		
Total Score: CFB Week 12 (n=27, 30)	-0.0492 (± 0.17709)	0.0564 (± 0.1679)		
Total Score: Week 16 (n=25, 28)	0.2284 (± 0.26906)	0.2237 (± 0.19767)		
Total Score: CFB Week 16 (n=25, 28)	-0.0372 (± 0.20737)	0.0481 (± 0.14444)		

Notes:

[3] - n = number of participants analyzed at specified time

[4] - n = number of participants analyzed at specified time

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 28 days after the last dose of study drug (last dose = Week 16)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Pirfenidone: 2-Week Titration Group
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Reporting group description:

Participants received one 267 mg oral pirfenidone capsule (801 mg/day) TID for 1 week followed by two 267 mg oral pirfenidone capsules (1602 mg/day) TID for 1 week (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 14 weeks (maintenance period).

Reporting group title	Pirfenidone: 4-Week Titration Group
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Reporting group description:

Participants received one 267 mg oral pirfenidone capsule (801 mg/day) TID for 2 weeks followed by two 267 mg oral pirfenidone capsules (1602 mg/day) TID for 2 weeks (titration period) and then three 267 mg oral pirfenidone capsules TID (2403 mg/day) for 12 weeks (maintenance period).

Serious adverse events	Pirfenidone: 2-Week Titration Group	Pirfenidone: 4-Week Titration Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	0 / 31 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (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			
Interstitial lung disease			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 32 (3.13%) 0 / 1 0 / 0	0 / 31 (0.00%) 0 / 0 0 / 0	
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Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pirfenidone: 2-Week Titration Group	Pirfenidone: 4-Week Titration Group	
Total subjects affected by non-serious adverse events subjects affected / exposed	31 / 32 (96.88%)	30 / 31 (96.77%)	
Vascular disorders Hot flush subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1 3 / 32 (9.38%) 3	2 / 31 (6.45%) 2 0 / 31 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia	2 / 32 (6.25%) 3 2 / 32 (6.25%) 2 2 / 32 (6.25%) 2 13 / 32 (40.63%) 18 3 / 32 (9.38%) 4	5 / 31 (16.13%) 6 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 10 / 31 (32.26%) 12 1 / 31 (3.23%) 2	

subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	0 / 31 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	10 / 32 (31.25%) 11	4 / 31 (12.90%) 4	
Dysphonia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 31 (6.45%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	4 / 31 (12.90%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	5 / 31 (16.13%) 7	
Investigations Weight decreased subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	1 / 31 (3.23%) 1	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	3 / 31 (9.68%) 3	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 4	2 / 31 (6.45%) 2	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 6	5 / 31 (16.13%) 5	
Headache subjects affected / exposed occurrences (all)	14 / 32 (43.75%) 18	14 / 31 (45.16%) 19	
Hypoaesthesia			

subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 31 (3.23%) 1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 32 (12.50%)	2 / 31 (6.45%)	
occurrences (all)	4	2	
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Constipation			
subjects affected / exposed	5 / 32 (15.63%)	2 / 31 (6.45%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	9 / 32 (28.13%)	10 / 31 (32.26%)	
occurrences (all)	14	11	
Dry mouth			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	4 / 32 (12.50%)	4 / 31 (12.90%)	
occurrences (all)	6	5	
Flatulence			
subjects affected / exposed	2 / 32 (6.25%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 32 (18.75%)	7 / 31 (22.58%)	
occurrences (all)	7	10	
Nausea			
subjects affected / exposed	16 / 32 (50.00%)	15 / 31 (48.39%)	
occurrences (all)	18	19	
Stomach discomfort			
subjects affected / exposed	3 / 32 (9.38%)	4 / 31 (12.90%)	
occurrences (all)	3	5	

Vomiting subjects affected / exposed occurrences (all)	9 / 32 (28.13%) 9	9 / 31 (29.03%) 11	
Skin and subcutaneous tissue disorders			
Erythema subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 31 (6.45%) 3	
Photosensitivity reaction subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	2 / 31 (6.45%) 2	
Pruritus subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 5	4 / 31 (12.90%) 5	
Rash subjects affected / exposed occurrences (all)	8 / 32 (25.00%) 10	5 / 31 (16.13%) 5	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 5	4 / 31 (12.90%) 6	
Back pain subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 6	3 / 31 (9.68%) 4	
Joint swelling subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 31 (0.00%) 0	
Muscle spasms subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 31 (6.45%) 2	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 31 (6.45%) 2	
Myalgia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 31 (6.45%) 2	
Pain in extremity			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 31 (6.45%) 2	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 32 (3.13%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	3 / 32 (9.38%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Pneumonia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	2 / 32 (6.25%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 32 (15.63%)	2 / 31 (6.45%)	
occurrences (all)	5	3	
Decreased appetite			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2014	This amendment was done to include a change of mycophenolate mofetil to mycophenolate which is inclusive of mycophenolate mofetil or mycophenolate acid. Additional global changes included an administrative change to clarify the Mahler Dyspnea Index includes the Baseline Dyspnea Index (BDI) in addition to the Translational Dyspnea Index (TDI) as part of it standard assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported