



Clinical trial results:

A multi-center, double-blind, randomized, placebo-controlled, parallel group, exploratory Phase 2 study to assess efficacy and safety of selexipag in adult subjects with Raynaud's Phenomenon secondary to Systemic Sclerosis

Summary

EudraCT number	2014-000865-34
Trial protocol	GB DE
Global end of trial date	07 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	AC-065C202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02260557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland,
Public contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com
Scientific contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.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	18 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2015
Global end of trial reached?	Yes
Global end of trial date	07 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the activity of selexipag on Raynaud attack frequency in subjects with Raynaud's Phenomenon (RP) secondary to Systemic Sclerosis (SSc).

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Good Clinical Practice (GCP) Guidelines, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy:

The following commonly used therapies in the management of RP and SSc were allowed if they had been initiated at least one month prior to the Screening visit and their dose was to remain unchanged during study treatment up to end of treatment: Calcium channel blockers (CCBs), Nitrates or nitric oxide donors, Endothelin receptor antagonists (ERAs), Alpha-blockers, Antithrombotic agents, Non-steroidal anti-inflammatory drugs (occasional use), angiotensin-converting-enzyme inhibitors, Beta-blockers, Clonidine, Systemic corticosteroids, Fluoxetine

Evidence for comparator: -

Actual start date of recruitment	14 October 2014
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	France: 16
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	United Kingdom: 27
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	63
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 92 subjects at 16 sites in 3 countries (France, Germany, UK) were screened and 91 of them entered a single-blind placebo run-in period. Of the 90 subjects who completed the run-in period, 74 were randomized in the double-blind treatment period.

Pre-assignment

Screening details:

A single-blind placebo run-in period was performed prior to randomization, during which the number of RP attacks was collected. The last 7 days of the run-in period were used as baseline week for the assessments derived from eDiary data.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The sponsor and all clinical trial team (CTT) members and CRO staff remained blinded to the treatment until study closure

Arms

Are arms mutually exclusive?	Yes
Arm title	Selexipag

Arm description:

During the 3-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated every 3 days in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d.. This was followed by a 5-week maintenance phase, during which patients continued the treatment at their individual MTD. Dose reduction was allowed at any time in case of tolerability issues.

Arm type	Experimental
Investigational medicinal product name	Selexipag
Investigational medicinal product code	ACT-293987
Other name	NS304
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet contained 200 µg of selexipag

Arm title	Placebo
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Arm description:

Matching placebo was administered following the same administration schedule as described for selexipag

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching selexipag tablets

Number of subjects in period 1	Selexipag	Placebo
Started	36	38
Completed	29	35
Not completed	7	3
Consent withdrawn by subject	2	-
Physician decision	-	1
Adverse event, non-serious	4	-
Subject decision (no efficacy)	-	1
Adverse event, serious non-fatal	-	1
Subject decision (tolerability related)	1	-

Baseline characteristics

Reporting groups

Reporting group title	Selexipag
Reporting group description:	
During the 3-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated every 3 days in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d.. This was followed by a 5-week maintenance phase, during which patients continued the treatment at their individual MTD. Dose reduction was allowed at any time in case of tolerability issues.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered following the same administration schedule as described for selexipag	

Reporting group values	Selexipag	Placebo	Total
Number of subjects	36	38	74
Age categorical			
Units: Subjects			
18-64 years old	30	33	63
65-84 years old	6	5	11
Age continuous			
Units: years			
arithmetic mean	52.7	52.6	-
standard deviation	± 12.2	± 11.9	-
Gender categorical			
Units:			
Female	29	31	60
Male	7	7	14
Systemic sclerosis (SSc) classification			
Number of subjects in each SSc subtypes at baseline			
Units: Subjects			
Limited cutaneous SSc	22	22	44
Diffuse cutaneous SSc	12	14	26
Other	2	2	4
Number of subjects with digital ulcers (DU) at baseline			
Units: Subjects			
DU present	4	7	11
DU absent	32	31	63
Number of Raynaud's Phenomenon (RP) attacks in the last 7 days prior to randomization			
Units: RP attacks			
arithmetic mean	22.1	21.6	-
standard deviation	± 16.1	± 14.7	-
Time since first Raynaud's symptom			
Units: Years			
arithmetic mean	14.9	13.4	-
standard deviation	± 10.7	± 10.7	-

End points

End points reporting groups

Reporting group title	Selexipag
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Reporting group description:

During the 3-week titration phase, treatment was initiated at 200 µg twice daily (b.i.d.) and up-titrated every 3 days in 200 µg b.i.d. increments up to the maximum tolerated dose (MTD) for each individual patient but not above 1600 µg b.i.d.. This was followed by a 5-week maintenance phase, during which patients continued the treatment at their individual MTD. Dose reduction was allowed at any time in case of tolerability issues.

Reporting group title	Placebo
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Reporting group description:

Matching placebo was administered following the same administration schedule as described for selexipag

Subject analysis set title	Full analysis set
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Subject analysis set type	Full analysis
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Subject analysis set description:

The FAS included all randomized patients who had received at least one dose of study drug during the double-blind period and were evaluated according to the study drug to which they were randomized. The FAS was used for demographics and baseline characteristics.

Subject analysis set title	Per protocol set
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PPS comprised data from all subjects included in the FAS who:

- had at least 7 RP attacks on at least 5 different days in the week prior to the randomization visit;
- did not receive any of the forbidden concomitant medications from run-in treatment start date up to date of last study drug intake;
- did not prematurely discontinue study treatment before Day 30;
- had a rate of RP assessment $\geq 70\%$ during the maintenance period.

The PPS was used for the efficacy endpoint and quality of life

Subject analysis set title	DB Safety set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The DB-SS Included all subjects who had received at least one dose of study treatment during the double-blind period and were evaluated based on the actual treatment received.

This set was used for the report of adverse events during the double-blind treatment period.

Primary: Average number of Raynaud's phenomenon (RP) attacks per week during the maintenance treatment period

End point title	Average number of Raynaud's phenomenon (RP) attacks per week during the maintenance treatment period
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End point description:

The number of RP attacks was determined from daily entries in an eDiary during the baseline week (last 7 days prior to randomization) and the maintenance period.

An RP attack is defined as an episode of at least a 2-phase color change in fingers, in response to cold exposure or emotion, consisting of pallor and/or cyanosis and reactive hyperemia associated with finger discomfort (i.e., pain or tingling, or numbness). The main analysis was performed on the per-protocol set using a Bayesian approach.

End point type	Primary
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End point timeframe:

Every day during the maintenance period, i.e., for 5 weeks starting from Day 26

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	32		
Units: Average number of RP attacks arithmetic mean (standard deviation)				
RP attacks during baseline week	22.38 (\pm 15.93)	21.53 (\pm 13.46)		
RP attacks per week during maintenance period	18.02 (\pm 14.13)	14.16 (\pm 10.27)		

Statistical analyses

Statistical analysis title	Negative-binomial [NB] regression Bayesian model
Statistical analysis description:	
Bayesian criterion of efficacy and criterion of significance based on posterior probability distributions were used.	
The analysis was adjusted for the mean-centered number of RP attacks during the baseline week and the treatment group [selexipag or placebo] were included as covariate.	
Comparison groups	Placebo v Selexipag
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0 ^[2]
Method	Posterior probability for efficacy
Parameter estimate	Mean difference (posterior distribution)
Point estimate	3.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	6.6
Variability estimate	Standard deviation
Dispersion value	1.9

Notes:

[1] - A difference (selexipag minus placebo) < -4, with probability ≥ 0.50 , in the average number of RP attacks per week during the maintenance period was targeted as a proof of efficacy. A difference (selexipag minus placebo) < 0 with probability ≥ 0.95 was targeted as criteria of significance

[2] - Posterior probability to observe a treatment difference (selexipag minus placebo) < -4 (efficacy criteria). P-value for significance (diff. selexipag minus placebo < 0) was 0.03

Other pre-specified: Change from baseline in quality of life as assessed by the Scleroderma Health Assessment Questionnaire (SHAQ) at end of treatment (EOT)

End point title	Change from baseline in quality of life as assessed by the Scleroderma Health Assessment Questionnaire (SHAQ) at end of treatment (EOT)
End point description:	
The SHAQ is a validated self-administered questionnaire used to evaluate change over time of physical disability in subjects with SSc. An overall SHAQ score was calculated and can range from 0 (no disability) to 3 (severe disability). The analyses were performed using the per protocol set.	
End point type	Other pre-specified
End point timeframe:	
At baseline and Week 8	

End point values	Selexipag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Overall SHAQ score at baseline	0.63 (± 0.6)	0.58 (± 0.42)		
Overall SHAQ score at EOT	0.62 (± 0.61)	0.6 (± 0.55)		
Change from baseline to EOT in overall SHAQ score	-0.01 (± 0.17)	0.02 (± 0.22)		

Statistical analyses

Statistical analysis title	Treatment difference in the overall SHAQ score
Statistical analysis description:	
Scores were analyzed using non-parametric ANCOVA, considering the score at baseline as covariate	
Comparison groups	Selexipag v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 ^[3]
Method	ANCOVA

Notes:

[3] - p-value based on Mann-Whitney test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (start of the double-blind period to end of study (30 days after last study drug intake)

Adverse event reporting additional description:

Double-blind (DB) treatment-emergent adverse events (AEs), defined as AEs with onset on or after the DB treatment start date and up to the end of treatment / study treatment discontinuation plus 30 days, were considered here.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Placebo, double-blind period
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Reporting group description:

Subjects were exposed to placebo for a median duration of 55.5 days (range: 21.0 to 63.0 days).

Reporting group title	Selexipag, double-blind period
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Reporting group description:

Subjects were exposed to selexipag for a median duration of 55.5 days (range: 3.0 to 62.5 days). The median individual maintenance dose (i.e., dose to which each subject was exposed for the longest duration during the maintenance period) was 600 µg.

Serious adverse events	Placebo, double-blind period	Selexipag, double-blind period	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	2 / 36 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
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			
Skin ulcer			

subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo, double-blind period	Selexipag, double-blind period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 38 (78.95%)	35 / 36 (97.22%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 38 (2.63%)	4 / 36 (11.11%)	
occurrences (all)	1	4	
Raynaud's phenomenon			
subjects affected / exposed	2 / 38 (5.26%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 38 (36.84%)	23 / 36 (63.89%)	
occurrences (all)	20	78	
Dizziness			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 3	8 / 36 (22.22%) 14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 38 (7.89%)	6 / 36 (16.67%)	
occurrences (all)	3	7	
Chest pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 38 (10.53%)	13 / 36 (36.11%)	
occurrences (all)	5	18	
Diarrhoea			
subjects affected / exposed	5 / 38 (13.16%)	10 / 36 (27.78%)	
occurrences (all)	7	15	
Dry mouth			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	4	
Abdominal pain upper			
subjects affected / exposed	4 / 38 (10.53%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Frequent bowel movements			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Constipation			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 36 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 36 (8.33%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 36 (5.56%) 2	
Skin and subcutaneous tissue disorders Skin ulcer subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 5	0 / 36 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 36 (2.78%) 1	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	8 / 36 (22.22%) 14	
Pain in jaw subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	8 / 36 (22.22%) 12	
Myalgia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 3	5 / 36 (13.89%) 6	
Arthralgia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	5 / 36 (13.89%) 9	
Back pain subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	4 / 36 (11.11%) 4	
Muscle spasms subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 36 (5.56%) 4	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	4 / 36 (11.11%) 9	
Influenza subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 36 (8.33%) 3	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 36 (5.56%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported