Clinical trial results:
A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP PHASE 2A STUDY TO ASSESS THE EFFICACY OF RO5459072 IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

Summary

EudraCT number	2015-004476-30
Trial protocol	GB PT DE PL FR
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	14 June 2018
First version publication date	14 June 2018

Trial information

Trial identification

Sponsor protocol code	BP30037

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02701985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, 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	10 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, double-blind, placebo-controlled, two-treatment arm, parallel-group study designed to evaluate the effects of RO5459072 treatment on disease activity and symptoms of Sjogren's syndrome in adult participants with moderate to severe primary Sjogren's syndrome. The total duration of the study for each participant will be approximately 18 weeks (including screening).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2016
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	Germany: 13
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	75
EEA total number of subjects	53

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)	64
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 75 patients were randomized in a 1:1 ratio to RO5459072 or placebo (38 patients in the RO5459072 treatment group and 37 patients in the placebo group).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching-placebo capsules was administered orally, 2 times a day, for up to 12 weeks.

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:

Matching-placebo capsules was administered orally, 2 times a day with food.

Arm title	RO5459072

Arm description:

RO5459072 at a dose of 100 milligrams (as capsules) was administered orally, 2 times a day, for up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	RO5459072
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

RO5459072 at a dose of 100 milligrams (as capsules) was administered orally, 2 times a day with food.

Number of subjects in period 1	Placebo	RO5459072
Started	37	38
Completed	34	32
Not completed	3	6
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching-placebo capsules was administered orally, 2 times a day, for up to 12 weeks.	
Reporting group title	RO5459072
Reporting group description:	
RO5459072 at a dose of 100 milligrams (as capsules) was administered orally, 2 times a day, for up to 12 weeks.	

Reporting group values	Placebo	RO5459072	Total
Number of subjects	37	38	75
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)	32	32	64
From 65-84 years	5	6	11
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	52.3	52.1	
standard deviation	± 11.8	± 13.2	-
Sex: Female, Male			
Units: Subjects			
Female	36	32	68
Male	1	6	7
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	5
White	33	35	68
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	35	38	73
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching-placebo capsules was administered orally, 2 times a day, for up to 12 weeks.	
Reporting group title	RO5459072
Reporting group description:	
RO5459072 at a dose of 100 milligrams (as capsules) was administered orally, 2 times a day, for up to 12 weeks.	

Primary: Percentage of Participants With a Clinically Relevant Decrease in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) Score

End point title	Percentage of Participants With a Clinically Relevant Decrease in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) Score
End point description:	
The efficacy of RO5459072 in patients with primary Sjogren's Syndrome Disease is evaluated in terms of the percentage of participants with a clinically relevant decrease in ESSDAI Score, where a clinically relevant decrease in ESSDAI score is defined as a decrease of ≥ 3 points.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Percentage of Participants				
number (confidence interval 95%)	37.8 (20.86 to 54.86)	42.1 (25.09 to 59.12)		

Statistical analyses

Statistical analysis title	Comparison of Placebo and RO5459072
Statistical analysis description:	
The proportion of patients who have ≥ 3 point reduction from baseline in ESSDAI score after 12 weeks of treatment was compared between the two treatment arms using a Pearson Chi-square test (two sided p-values, alpha 0.05). The difference in proportions and corresponding 95% confidence interval (CI) are provided. Patients with missing data at Week 12 will be treated as non-responders in the analysis.	
Comparison groups	RO5459072 v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7955
Method	Chi-square with Schouten Correction
Parameter estimate	Difference in Response Rates
Point estimate	4.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.55
upper limit	29.08

Secondary: Percentage of Participants With a Clinically Relevant Decrease in EULAR Sjogren's Syndrome Patient-Reported Index (ESSPRI) Score

End point title	Percentage of Participants With a Clinically Relevant Decrease in EULAR Sjogren's Syndrome Patient-Reported Index (ESSPRI) Score

End point description:

The efficacy of RO5459072 in patients with primary Sjogren's Syndrome Disease is evaluated in terms of the percentage of participants with a clinically relevant decrease in ESSPRI Score, where a clinically relevant decrease in ESSPRI score is defined as a decrease of ≥ 1 point.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Percentage of Participants				
number (confidence interval 95%)	56.8 (39.44 to 74.07)	57.9 (40.88 to 74.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSDAI Score at Week 12

End point title	Change From Baseline in ESSDAI Score at Week 12

End point description:

Change from baseline in ESSDAI Score is defined as the change in score between baseline (Week -1) and Week 12. The ESSDAI is a physician-assessed disease activity index for primary Sjögren's syndrome developed by the EULAR consortium. It consists of 44 items in 12 organ-specific 'domains' contributing to disease activity (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system [PNS], central nervous system [CNS], hematological, biological). Each domain is assessed for activity level (i.e., no, low, moderate, high) and assigned a numerical score based on pre-determined weighting of each individual domain. An overall score is then

calculated as the sum of all individual weighted domain scores.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline in ESSDAI Score|	11.27 (± 5.71)	11.79 (± 4.69)		
Change From Baseline in ESSDAI Score at Week 12|	-3.06 (± 3.96)	-3.25 (± 4.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI Score at Week 12

End point title	Change From Baseline in ESSPRI Score at Week 12

End point description:

Change from baseline in ESSPRI Score is defined as the change in score between baseline (Week -1) and Week 12. The ESSPRI is a patient-reported, subjective symptom index for primary Sjögren's syndrome developed by the EULAR consortium. It consists of three questions covering the cardinal symptoms of Sjögren's syndrome: dryness, fatigue and pain (articular and/or muscular). Each domain scored on scale of 0-10, and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline in ESSPRI Score|	7.34 (± 1.19)	6.98 (± 0.98)		
Change From Baseline in ESSPRI Score at Week 12|	-1.35 (± 1.67)	-1.51 (± 1.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 36 Health Survey (SF-36) Mental Score at Week 12

End point title	Change From Baseline in Short Form 36 Health Survey (SF-36) Mental Score at Week 12

End point description:

Change from baseline in Short Form-36 Health Survey (SF-36) Mental score is defined as the change in score between baseline (Week -1) and Week 12. The SF-36 was used to assess health-related quality of life at baseline and at on-treatment visits. The SF-36 consisted of 36 questions covering 8 domains (general health, physical functioning, role-functioning physical, bodily pain, social functioning, role-functioning emotional, mental health, and vitality), with each domain scoring on a scale 0-100. Reported here is the mental health domain score.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline|	42.09 (± 11.18)	40.52 (± 9.27)		
Change from Baseline at Week 12|	4.52 (± 7.15)	3.02 (± 9.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SF-36 Physical Score at Week 12

End point title	Change From Baseline in SF-36 Physical Score at Week 12

End point description:

Change from baseline in SF-36 Physical Score is defined as the change in score between baseline (Week -1) and Week 12. The SF-36 was used to assess health-related quality of life at baseline and at on-treatment visits. The SF-36 consisted of 36 questions covering 8 domains (general health, physical functioning, role-functioning physical, bodily pain, social functioning, role-functioning emotional, mental health, and vitality), with each domain scoring on a scale 0-100.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline in SF-36 Physical Score|	40.86 (± 6.82)	40.71 (± 6.94)		
Change From Baseline at Week 12|	2.46 (± 6.09)	3.01 (± 5.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI Dryness Component Score at Week 12

End point title	Change From Baseline in ESSPRI Dryness Component Score at Week 12

End point description:

Change from baseline in ESSPRI dryness component score is defined as the change in score between baseline (Week -1) and Week 12.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline|	7.54 (± 1.57)	7.45 (± 1.25)		
Change From Baseline at Week 12|	-1.15 (± 1.56)	-1.77 (± 2.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI Fatigue Component Score at Week 12

End point title	Change From Baseline in ESSPRI Fatigue Component Score at Week 12

End point description:

Change from baseline in ESSPRI fatigue component score is defined as the change in score between baseline (Week -1) and Week 12. The ESSPRI score consists of three questions covering the cardinal symptoms of Sjögren’s syndrome: dryness, fatigue and pain (articular and/or muscular). Each domain scored on scale of 0-10.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline|	7.22 (± 1.81)	7.24 (± 1.84)		
Change From Baseline at Week 12|	-1.29 (± 2.24)	-1.94 (± 2.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI Pain Component Score at Week 12

End point title	Change From Baseline in ESSPRI Pain Component Score at Week 12

End point description:

Change from baseline in ESSPRI pain component score is defined as the change in score between baseline (Week -1) and Week 12. The ESSPRI score consists of three questions covering the cardinal symptoms of Sjögren's syndrome: dryness, fatigue and pain (articular and/or muscular). Each domain scored on scale of 0-10.

End point type	Secondary

End point timeframe:

Baseline (Week -1), Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline|	7.27 (± 1.71)	6.26 (± 2.05)		
Change From Baseline at Week 12|	-1.62 (± 2.70)	-0.97 (± 2.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tear Flow Rate at Weeks 2, 6, and 12

End point title	Change From Baseline in Tear Flow Rate at Weeks 2, 6, and 12

End point description:

Un-stimulated tear production rate was measured from both eyes (without the use of analgesics/ anesthetic drops) at baseline and at on-treatment visits using the Schirmer method. A thin strip of filter

paper (Schirmer strip, e.g., 35 x 5 mm) was placed at the junction of the lateral and middle thirds of the lower eyelid of each eye. The maximum length of wetting along the strip at the end of the test period was measured.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: volume/time				
arithmetic mean (standard deviation)				
Baseline in Tear Flow Rate|	7.53 (± 9.66)	7.84 (± 10.15)		
Change from Baseline at Week 2|	-0.54 (± 5.02)	-0.81 (± 5.06)		
Change from Baseline at Week 6|	-1.39 (± 6.32)	-0.95 (± 7.95)		
Change from Baseline at Week 12|	-2.38 (± 6.47)	-1.65 (± 7.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mechanically Stimulated Salivary Flow Rate at Weeks 2, 6, and 12

End point title	Change From Baseline in Mechanically Stimulated Salivary Flow Rate at Weeks 2, 6, and 12

End point description:

Change from baseline in mechanically stimulated salivary flow rate is defined as the change in flow (mL/min) between baseline (Week -1) and Week 2, Week 6 and Week 12. Using a mechanical stimulation method of a piece of neutral wax, paraffin, silicone, unflavored chewing gum, or similar chewable, unflavored, nonabsorbent material, patients were instructed to chew for a period of 5 minutes. The stimulated salivary flow rate was calculated assuming a specific gravity of 1 (i.e., 1 mL saliva = 1 g) and expressed in mL per minute.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: mL/min				
arithmetic mean (standard deviation)				
Baseline|	0.45 (± 0.29)	0.55 (± 0.58)		
Change from Baseline at Week 2|	0.10 (± 0.33)	-0.01 (± 0.33)		
Change from Baseline at Week 6|	0.10 (± 0.31)	0.11 (± 0.47)		
Change from Baseline at Week 12|	0.12 (± 0.30)	0.24 (± 0.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Anti-Sjögren's-Syndrome-Related Antigen A at Weeks 6, and 12

End point title	Change From Baseline in Anti-Sjögren's-Syndrome-Related Antigen A at Weeks 6, and 12

End point description:

Anti-Sjögren's-syndrome-related antigen A is a type of antibody found in the auto-antibody titers.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: U/mL				
arithmetic mean (standard deviation)				
Baseline|	214.52 (± 58.06)	217.78 (± 53.96)		
Change from Baseline at Week 6|	-4.82 (± 16.05)	-1.47 (± 13.90)		
Change from Baseline at Week 12|	-2.57 (± 18.97)	-5.20 (± 11.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Anti-Sjögren's-Syndrome-Related Antigen B at Weeks 6, and 12

End point title	Change From Baseline in Anti-Sjögren's-Syndrome-Related Antigen B at Weeks 6, and 12

End point description:

Anti-Sjögren's-syndrome-related antigen B is a type of antibody found in the auto-antibody titers.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: U/mL				
arithmetic mean (standard deviation)				
Baseline|	101.66 (± 130.48)	76.94 (± 120.76)		
Change from Baseline at Week 6|	1.94 (± 15.20)	-2.55 (± 13.09)		
Change from Baseline at Week 12|	1.35 (± 13.52)	-4.47 (± 12.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rheumatoid Factor at Weeks 6, and 12

End point title	Change From Baseline in Rheumatoid Factor at Weeks 6, and 12

End point description:

Rheumatoid factor is a type of auto-antibody found in the auto-antibody titers.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: kU/L				
arithmetic mean (standard deviation)				
Baseline in Rheumatoid Factor|	43.00 (± 48.51)	117.84 (± 336.82)		
Change from Baseline at Week 6|	-1.50 (± 10.74)	-28.03 (± 70.04)		
Change from Baseline at Week 12|	-0.68 (± 9.97)	-57.77 (± 173.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Immunoglobulin G (IgG) at Weeks 6, and

12

End point title	Change From Baseline in Total Immunoglobulin G (IgG) at Weeks 6, and 12

End point description:

Total IgG is a type of auto-antibody found in the auto-antibody titers.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline in Total IgG|	15.74 (± 6.77)	13.59 (± 4.92)		
Change from Baseline at Week 6|	0.11 (± 1.51)	-0.30 (± 1.21)		
Change from Baseline at Week 12|	0.48 (± 1.78)	-0.50 (± 1.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Immunoglobulin M (IgM) at Weeks 6, and 12

End point title	Change From Baseline in Total Immunoglobulin M (IgM) at Weeks 6, and 12

End point description:

Total IgM is a type of auto-antibody found in the auto-antibody titers.

End point type	Secondary

End point timeframe:

Baseline, Week 6, and Week 12

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: g/L				
arithmetic mean (standard deviation)				
Baseline in Total IgM|	1.24 (± 0.82)	1.26 (± 0.75)		
Change from Baseline at Week 6|	0.03 (± 0.20)	-0.10 (± 0.17)		
Change from Baseline at Week 12|	0.06 (± 0.25)	-0.17 (± 0.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Concentration (Cmin) of RO5459072

End point title	Minimum Concentration (Cmin) of RO5459072[1]

End point description:

Minimum observed plasma concentration (mass/volume)

End point type	Secondary

End point timeframe:

Week 2, Week 6, and Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only analyzing the minimum concentration of RO5459072

End point values	RO5459072			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: ng/mL				
median (confidence interval 90%)	1340 (2.68 to 2900)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of RO5459072

End point title	Maximum Concentration (Cmax) of RO5459072[2]

End point description:

Maximum observed plasma concentration (mass/volume)

End point type	Secondary

End point timeframe:

Week 2, Week 6, and Week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only analyzing the max concentration of RO5459072

End point values	RO5459072			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: ng/mL				
median (confidence interval 90%)	2350 (1140 to 3610)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Concentration (Caverage) of RO5459072

End point title	Average Concentration (Caverage) of RO5459072[3]

End point description:

Average observed plasma concentration (mass/volume)

End point type	Secondary

End point timeframe:

Week 2, Week 6, and Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was only analyzing the average concentration of RO5459072

End point values	RO5459072			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: ng/mL				
median (confidence interval 90%)	1740 (816 to 3187)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary

End point timeframe:

Baseline up to Week 14

End point values	Placebo	RO5459072		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Participants				
number (not applicable)	78.4	76.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The total duration of the study for each patient was (up to) 19 weeks.	
Adverse event reporting additional description:	
The safety population is defined as all patients who received at least one dose of the study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching-placebo capsules was administered orally, 2 times a day, for up to 12 weeks.	
Reporting group title	RO5459072
Reporting group description:	
RO5459072 at a dose of 100 milligrams (as capsules) was administered orally, 2 times a day, for up to 12 weeks.	

Serious adverse events	Placebo	RO5459072	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Metabolic Acidosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (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	RO5459072	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 37 (51.35%)	25 / 38 (65.79%)	
Investigations			
Blood Thyroid Stimulating Hormone Decreased			
subjects affected / exposed	0 / 37 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 37 (10.81%)	5 / 38 (13.16%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 37 (2.70%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 37 (2.70%)	3 / 38 (7.89%)	
occurrences (all)	1	5	
Diarrhoea			
subjects affected / exposed	2 / 37 (5.41%)	2 / 38 (5.26%)	
occurrences (all)	2	2	
Dyspepsia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	

Nausea			
subjects affected / exposed	0 / 37 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	6	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 37 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	2 / 37 (5.41%)	2 / 38 (5.26%)	
occurrences (all)	2	3	
Rash			
subjects affected / exposed	1 / 37 (2.70%)	5 / 38 (13.16%)	
occurrences (all)	1	5	
Urticaria			
subjects affected / exposed	0 / 37 (0.00%)	5 / 38 (13.16%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 38 (7.89%)	
occurrences (all)	1	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	1 / 37 (2.70%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Sinusitis			
subjects affected / exposed	3 / 37 (8.11%)	1 / 38 (2.63%)	
occurrences (all)	4	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 37 (5.41%)	5 / 38 (13.16%)	
occurrences (all)	2	8	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 37 (5.41%)	6 / 38 (15.79%)	
occurrences (all)	2	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2016	The instructions that the patients need to be fasted prior to safety laboratory tests was added to laboratory assessments. The list of MDR1 (P-gp) inhibitors was updated and restricted to only those medications which are potent inhibitors in vivo.
30 October 2016	The eligibility criteria of the protocol was amended to mandate testing for tuberculosis and exclude patients with positive results and excluded women who are breast-feeding or planning to nurse. The eligibility criteria was amended to explicitly exclude patients who are using strong inhibitors of CYP3A4 and P-glycoprotein (P-gp), as well as compounds inducing CYP3A4. Measurement of bicarbonate was added to the laboratory test panel. Total IgM was added to the list of antibody titres to be measured. As samples for the above were not collected at all visits where ESSDAI was evaluated, additional assessment time points for cryoglobulin, IgG and IgM was added to the Schedule of Assessment and the complement C3/4 assessment was moved to the blood biochemistry panel. A section on interpretation and reporting of abnormal liver function tests was inserted to provide more specific guidance for investigators. The alpha level for any hypothesis testing was clarified as 2-sided at the 0.05 level to align with the use of 95% confidence intervals. Additionally the primary analysis used a non-responder approach for missing data and an exploratory analysis was pre-specified adjusting for baseline ESSDAI score.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported