



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase II Study to Evaluate the Safety and Efficacy of RO7123520 as Adjunct Treatment in Patients with Moderately to Severely Active Rheumatoid Arthritis

Summary

EudraCT number	2016-002126-36
Trial protocol	AT DE ES IT
Global end of trial date	06 November 2018

Results information

Result version number	v1 (current)
This version publication date	20 November 2019
First version publication date	20 November 2019

Trial information

Trial identification

Sponsor protocol code	BP39261
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03001219
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	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	06 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of RO7123520 as adjunctive therapy in patients with RA who were inadequately responding to standard-of-care (methotrexate (MTX) and anti-TNF-a therapy).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 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	Argentina: 9
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Guatemala: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	118
EEA total number of subjects	16

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	92
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult men and women with moderate to severe active rheumatoid arthritis (RA) who experience an inadequate response to disease-modifying anti-rheumatic drug (DMARD) therapy with MTX plus anti-TNF- α therapy.

Pre-assignment

Screening details:

Proof of Concept: Subjects received either placebo or 810 mg/dose of RO7123520. Extension Period Analysis: Subjects were given the option to continue in an optional extension period. Subjects received either 360 mg/dose or 810 mg/dose of RO7123520. Part 3 was not conducted due to early study termination.

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?	No
Arm title	Proof of Concept: Placebo

Arm description:

Participants received placebo (IV saline matched to RO7123520) on Days 1, 14, 28, and 56 with pre-trial anti-TNF- α and methotrexate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously (IV) on Days 1, 14, 28, and 56.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Tablet, Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Oral use, Subcutaneous use, Intramuscular use

Dosage and administration details:

Subjects must have been on stable regimens of MTX (i.e. 5.0-25 mg/wk) for at least 4 weeks prior to randomization.

Investigational medicinal product name	Anti-TNF- α
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects must have been on stable regimens of anti-TNF- α therapy at the recommended dose for at least 12 weeks prior to randomization.

Arm title	Proof of Concept: RO7123520 810mg/dose
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Arm description:

Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Arm type	Experimental
Investigational medicinal product name	RO7123520
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Tablet, Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Oral use, Subcutaneous use, Intramuscular use

Dosage and administration details:

Subjects must have been on stable regimens of MTX (i.e. 5.0-25 mg/wk) for at least 4 weeks prior to randomization.

Investigational medicinal product name	Anti-TNF-alpha
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects must have been on stable regimens of anti-TNF-alpha therapy at the recommended dose for at least 12 weeks prior to randomization.

Arm title	Extension Period Analysis: RO7123520 360mg/dose
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Arm description:

Participants received 360mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Arm type	Experimental
Investigational medicinal product name	RO7123520
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 360mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Tablet, Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Oral use, Subcutaneous use, Intramuscular use

Dosage and administration details:

Subjects must have been on stable regimens of MTX (i.e. 5.0-25 mg/wk) for at least 4 weeks prior to randomization.

Investigational medicinal product name	Anti-TNF-alpha
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects must have been on stable regimens of anti-TNF-alpha therapy at the recommended dose for at least 12 weeks prior to randomization.

Arm title	Extension Period Analysis: RO7123520 810mg/dose
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Arm description:

Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Arm type	Experimental
Investigational medicinal product name	RO7123520
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Solution for injection/infusion, Tablet, Powder for solution for injection/infusion
Routes of administration	Oral use, Subcutaneous use, Intramuscular use

Dosage and administration details:

Subjects must have been on stable regimens of MTX (i.e. 5.0-25 mg/wk) for at least 4 weeks prior to randomization.

Investigational medicinal product name	Anti-TNF-alpha
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Subjects must have been on stable regimens of anti-TNF-alpha therapy at the recommended dose for at least 12 weeks prior to randomization.

Number of subjects in period 1	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose
Started	37	72	9
Completed	35	65	4
Not completed	2	7	5
Physician decision	1	-	-
Consent withdrawn by subject	-	4	4
Participant Non-Compliance	-	-	-
Adverse event, non-fatal	1	1	1
Protocol Deviation	-	1	-

Study Termination by Sponsor	-	1	-
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Number of subjects in period 1	Extension Period Analysis: R07123520 810mg/dose
Started	97
Completed	52
Not completed	45
Physician decision	1
Consent withdrawn by subject	5
Participant Non-Compliance	1
Adverse event, non-fatal	1
Protocol Deviation	1
Study Termination by Sponsor	36

Baseline characteristics

Reporting groups

Reporting group title	Proof of Concept: Placebo
Reporting group description: Participants received placebo (IV saline matched to RO7123520) on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Proof of Concept: RO7123520 810mg/dose
Reporting group description: Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Extension Period Analysis: RO7123520 360mg/dose
Reporting group description: Participants received 360mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Extension Period Analysis: RO7123520 810mg/dose
Reporting group description: Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	

Reporting group values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose
Number of subjects	37	72	9
Age categorical Units: Subjects			
Adults (18-64 years)	28	59	5
From 65-84 years	9	13	4
Age Continuous Units: Years			
arithmetic mean	54.7	52.3	56.6
standard deviation	± 14.1	± 12.3	± 14.3
Sex: Female, Male Units: Subjects			
Female	32	66	6
Male	5	6	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	27	54	1
Not Hispanic or Latino	10	18	8
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	7	12	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	25	52	7
More than one race	2	4	0
Unknown or Not Reported	2	3	0

Reporting group values	Extension Period Analysis: RO7123520 810mg/dose	Total	
Number of subjects	97	118	
Age categorical Units: Subjects			
Adults (18-64 years)	78	92	
From 65-84 years	19	26	
Age Continuous Units: Years			
arithmetic mean	53.4		
standard deviation	± 12.8	-	
Sex: Female, Male Units: Subjects			
Female	87	104	
Male	10	14	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	73	82	
Not Hispanic or Latino	24	36	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	16	19	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	4	
White	68	84	
More than one race	6	6	
Unknown or Not Reported	5	5	

End points

End points reporting groups

Reporting group title	Proof of Concept: Placebo
Reporting group description: Participants received placebo (IV saline matched to RO7123520) on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Proof of Concept: RO7123520 810mg/dose
Reporting group description: Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Extension Period Analysis: RO7123520 360mg/dose
Reporting group description: Participants received 360mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	
Reporting group title	Extension Period Analysis: RO7123520 810mg/dose
Reporting group description: Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.	

Primary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events ^[1]
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	Primary
End point timeframe: Baseline to end of study (approximately 2 years)	

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: Numbers provided are the percentage. No statistical analysis is performed on numbers/percentage of AEs.

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	70	9	97
Units: Percent				
number (not applicable)	48.6	60.0	66.7	60.8

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of Participants Achieving an American College of Rheumatology (ACR) 50 Response at Week 12

End point title	Proportion of Participants Achieving an American College of Rheumatology (ACR) 50 Response at Week 12 ^[2]
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End point description:

The ACR50 is a composite measure defined as both improvement of 50% in the number of tender and number of swollen joints, and a 50% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). The ACR is reported as percent improvement at discrete time points.

End point type	Primary
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End point timeframe:

Week 12

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: Numbers provided are a proportion. No statistical analysis is performed on proportions for this endpoint.

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: Percent				
number (confidence interval 90%)	16.2 (7.67 to 29.95)	11.1 (5.86 to 19.48)	0 (0 to 30.89)	1.0 (0.07 to 5.28)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Anti-Drug Antibodies

End point title	Percentage of Participants With Anti-Drug Antibodies ^{[3][4]}
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End point description:

The immunogenicity population included participants with at least 1 pre-dose ADA assessment, grouped by treatment and dose level.

End point type	Primary
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End point timeframe:

Baseline

Notes:

[3] - 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: Numbers provided are the percentage. No statistical analysis is performed on numbers/percentage of AEs.

[4] - 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: Numbers provided are the percentage. No statistical analysis is performed on numbers/percentage of ADAs.

End point values	Extension Period Analysis: RO7123520 810mg/dose			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Percent	0			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Bone Mineral Density Lumbar Spine L1-L4 as Assessed by Dual Energy X-ray Absorptiometry (DEXA) Scans

End point title	Change From Baseline in Bone Mineral Density Lumbar Spine L1-L4 as Assessed by Dual Energy X-ray Absorptiometry (DEXA) Scans ^[5]
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End point description:

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

[5] - 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 formal statistical analyses were planned due to early study termination due to futility (not due to safety issues).

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	67 ^[6]	9 ^[7]	94 ^[8]
Units: g/cm ²				
arithmetic mean (standard deviation)				
Baseline	1.02 (± 0.21)	2.51 (± 12.46)	1.17 (± 0.20)	2.06 (± 10.53)
Week 12	-0.06 (± 0.20)	0.71 (± 5.50)	-0.01 (± 0.04)	0.58 (± 4.98)

Notes:

[6] - Week 12 n=59

[7] - Week 12 n=6

[8] - Week 12 n=72

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) Score at Week 12

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) Score at Week 12
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End point description:

The CDAI for Rheumatoid Arthritis (RA) assesses the severity of the disease using clinical data. It consists of the Patient Global disease Activity (PGA) estimate and the Evaluator Global disease Activity (EGA) estimate, each of which represent assessments of disease activity on a scale of 1-10, with 10 being maximum activity.

-9999 = Data was not reported for this arm at the specified time point.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	69 ^[9]	9	96 ^[10]
Units: No Units				
arithmetic mean (standard deviation)				
Baseline	37.05 (± 10.99)	37.38 (± 13.14)	30.89 (± 15.31)	32.17 (± 15.91)
Week 12	-17.44 (± 15.11)	-14.44 (± 13.96)	-9999 (± 0)	-9999 (± 0)

Notes:

[9] - Week 12 n=65

[10] - Week 12 n=97

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score 28 (DAS28) at Week 12

End point title	Change From Baseline in Disease Activity Score 28 (DAS28) at Week 12
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End point description:

The DAS28 is a combined index for measuring disease activity in RA; the "28" refers to the number of joints included in the assessment. The index includes swollen and tender joint counts, acute phase response, and general arthritis disease activity status. An overall disease activity score of 5.1 or greater implies active disease, less than 3.2 implies low disease activity, and less than 2.6 implies disease remission.

-9999 = Data was not reported for this arm at the specified time point.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: No Units				
arithmetic mean (standard deviation)				
Baseline	6.29 (± 0.78)	6.28 (± 1.03)	5.42 (± 1.63)	5.82 (± 1.28)
Week 12	-1.62 (± 1.28)	-1.15 (± 1.06)	-9999 (± 0)	-9999 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving DAS28 Remission at Week 12

End point title	Percentage of Participants Achieving DAS28 Remission at Week 12
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End point description:

The DAS28 is a combined index for measuring disease activity in RA; the "28" refers to the number of joints included in the assessment. The index includes swollen and tender joint counts, acute phase response, and general arthritis disease activity status. An overall disease activity score of 5.1 or greater implies active disease, less than 3.2 implies low disease activity, and less than 2.6 implies disease remission.

-9999 = Data was not reported for this arm at the specified time point.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: Percent				
number (not applicable)	0	1.4	-9999	-9999

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving CDAI Remission at Week 12

End point title	Percentage of Participants Achieving CDAI Remission at Week 12
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End point description:

The CDAI for Rheumatoid Arthritis (RA) assesses the severity of the disease using clinical data. It consists of the Patient Global disease Activity (PGA) estimate and the Evaluator Global disease Activity (EGA) estimate, each of which represent assessments of disease activity on a scale of 1-10, with 10 being maximum activity. CDAI remission is defined as a score of less than or equal to 2.8.

-9999 = Data was not reported for this arm at the specified time point.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: Percent				
number (not applicable)	0	1.4	-9999	-9999

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR20 Response at Week 12

End point title	Percentage of Participants Achieving ACR20 Response at Week 12
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End point description:

The ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). The ACR is reported as percent improvement at discrete time points.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: Percent				
number (confidence interval 90%)	43.2 (29.55 to 57.94)	27.8 (19.42 to 37.88)	0 (0.00 to 30.89)	11.3 (6.66 to 18.32)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ACR70 Response at Week 12

End point title	Percentage of Participants Achieving ACR70 Response at Week 12
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End point description:

The ACR70 is a composite measure defined as both improvement of 70% in the number of tender and number of swollen joints, and a 70% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP). The ACR is reported as percent improvement at discrete time points.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	72	9	97
Units: Percent				
number (confidence interval 90%)	0 (0.00 to 9.15)	1.4 (0.10 to 7.04)	0 (0.00 to 30.89)	0 (0.00 to 3.65)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Simple Disease Activity Index (SDAI) Score at Week 12

End point title	Change From Baseline in Simple Disease Activity Index (SDAI) Score at Week 12
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End point description:

The SDAI consists of 5 parameters used to assess RA disease activity: 28-joint count assessments of tenderness and swelling, participant and investigator global assessments, and CRP levels. A composite score is produced, with remission defined as an SDAI of <3.3, low disease activity as ≤ 11 , moderate disease activity as ≤ 26 and high disease activity as > 26 .

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37 ^[11]	69 ^[12]	9 ^[13]	96 ^[14]
Units: No Units				
arithmetic mean (standard deviation)				
Baseline	38.84 (± 10.58)	39.02 (± 14.55)	31.23 (± 15.25)	34.08 (± 16.69)
Week 12	-17.48 (± 14.48)	-14.99 (± 15.19)	-15.33 (± 18.24)	-13.15 (± 14.56)

Notes:

[11] - Week 12 n=34

[12] - Week 12 n=65

[13] - Week 12 n=6

[14] - Week 12 n=80

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

End point title	Change From Baseline in the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12
End point description:	The HAQ-DI is a 20-item, validated questionnaire used to assess difficulty in performing activities of daily living. The questionnaire assesses eight domains of physical functioning: Dressing and Grooming (2 items), Hygiene (3 items), Arising (2 items), Reach (2 items), Eating (3 items), Grip (3 items), Walking (2 items), Common Daily Activities (3 items). The questions assess usual abilities ranging from 0 "without any difficulty" to 3 "unable to do." A lower HAQ-DI score indicates better quality of life.
End point type	Secondary
End point timeframe:	Baseline, Week 12

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	70 ^[15]	9 ^[16]	96 ^[17]
Units: No Units				
arithmetic mean (standard deviation)				
Baseline	1.63 (± 0.64)	1.61 (± 0.76)	1.29 (± 0.70)	1.59 (± 0.71)
Week 12	-0.15 (± 0.52)	-0.24 (± 0.51)	-0.21 (± 0.74)	-0.21 (± 0.49)

Notes:

[15] - Week 12 n=65

[16] - Week 12 n=6

[17] - Week 12 n=81

Statistical analyses

No statistical analyses for this end point

Secondary: Serum RO7123520 Concentration

End point title	Serum RO7123520 Concentration
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End point description:

All enrolled participants were included in the PK population.

End point type	Secondary
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End point timeframe:

Pre-dose (0 hour), 1 hour post infusion (duration of infusion: approximately 1 hour) on Days 1, 14, 28, 56; Pre-dose (0 hour) on Days 84, 112

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[18]	0 ^[19]	0 ^[20]	0 ^[21]
Units: No Units				

Notes:

[18] - No PK analysis was performed due to an insufficient number of available participant samples.

[19] - No PK analysis was performed due to an insufficient number of available participant samples.

[20] - No PK analysis was performed due to an insufficient number of available participant samples.

[21] - No PK analysis was performed due to an insufficient number of available participant samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Synovial Fluid RO7123520 Concentration

End point title	Synovial Fluid RO7123520 Concentration
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End point description:

All enrolled participants were included in the PK population.

End point type	Secondary
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End point timeframe:

Pre-dose (0 hour) on Days 1, 84

End point values	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose	Extension Period Analysis: RO7123520 810mg/dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[22]	0 ^[23]	0 ^[24]	0 ^[25]
Units: No Units				

Notes:

[22] - No PK analysis was performed due to an insufficient number of available participant samples.

[23] - No PK analysis was performed due to an insufficient number of available participant samples.

[24] - No PK analysis was performed due to an insufficient number of available participant samples.

[25] - No PK analysis was performed due to an insufficient number of available participant samples.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through end of study (approximately 2 years)

Adverse event reporting additional description:

The safety population included participants who received at least one dose of study drug.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Proof of Concept: Placebo
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Reporting group description:

Participants received placebo (IV saline matched to RO7123520) on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Reporting group title	Proof of Concept: RO7123520 810mg/dose
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Reporting group description:

Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Reporting group title	Extension Period Analysis: RO7123520 360mg/dose
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Reporting group description:

Participants received 360mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Reporting group title	Extension Period Analysis: RO7123520 810mg/dose
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Reporting group description:

Participants received 810mg of RO7123520 on Days 1, 14, 28, and 56 with pre-trial anti-TNF-alpha and methotrexate.

Serious adverse events	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	1 / 70 (1.43%)	1 / 9 (11.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 70 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			

subjects affected / exposed	0 / 37 (0.00%)	0 / 70 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 70 (1.43%)	0 / 9 (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
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 37 (2.70%)	0 / 70 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension Period Analysis: R07123520 810mg/dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 97 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsil cancer			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Proof of Concept: Placebo	Proof of Concept: RO7123520 810mg/dose	Extension Period Analysis: RO7123520 360mg/dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 37 (27.03%)	10 / 70 (14.29%)	6 / 9 (66.67%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 37 (5.41%)	0 / 70 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Computerised tomogram abnormal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 70 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 37 (8.11%)	1 / 70 (1.43%)	1 / 9 (11.11%)
occurrences (all)	3	1	1
Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	1 / 70 (1.43%)	1 / 9 (11.11%)
occurrences (all)	2	1	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 70 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 70 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			

Abdominal distension subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Constipation subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Flatulence subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Musculoskeletal and connective tissue disorders Neck mass subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Rheumatoid arthritis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Infections and infestations Chronic tonsillitis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Folliculitis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Laryngitis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1

Urinary tract infection subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	0 / 9 (0.00%) 0
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	4 / 70 (5.71%) 4	0 / 9 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	4 / 70 (5.71%) 4	0 / 9 (0.00%) 0
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 70 (0.00%) 0	1 / 9 (11.11%) 1

Non-serious adverse events	Extension Period Analysis: RO7123520 810mg/dose		
Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 97 (17.53%)		
Investigations			
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Computerised tomogram abnormal subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 2		
Blood and lymphatic system disorders			
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Flatulence subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Musculoskeletal and connective tissue disorders Neck mass subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Rheumatoid arthritis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Infections and infestations Chronic tonsillitis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Folliculitis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Laryngitis			

subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2		
Urinary tract infection subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 12		
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	Modified inclusion/exclusion criteria
09 May 2017	Clarified total study duration, modified safety outcome measures, modified inclusion/exclusion criteria
28 March 2018	Inclusion criteria modified, allowed concomitant treatment with non-biological agents, modified allowed dose range for MTX, expanded age range for eligible population

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was prematurely terminated due to a lack of efficacy of the investigational drug. There were no serious safety issues or adverse events contributing to the decision to terminate early.
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Notes: