



## 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 |
|-----------------------|---------|

##### 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- $\alpha$  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                        |
| <b>Arm title</b>             | 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- $\alpha$  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- $\alpha$                |
| 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.

|                  |                                        |
|------------------|----------------------------------------|
| <b>Arm title</b> | Proof of Concept: RO7123520 810mg/dose |
|------------------|----------------------------------------|

**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.

|                  |                                                 |
|------------------|-------------------------------------------------|
| <b>Arm title</b> | Extension Period Analysis: RO7123520 360mg/dose |
|------------------|-------------------------------------------------|

**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.

|                  |                                                 |
|------------------|-------------------------------------------------|
| <b>Arm title</b> | Extension Period Analysis: RO7123520 810mg/dose |
|------------------|-------------------------------------------------|

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 | - |
|------------------------------|---|---|---|

| <b>Number of subjects in period 1</b> | Extension Period<br>Analysis:<br>R07123520<br>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:<br>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:<br>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:<br>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:<br>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<br>Units: Subjects        |                           |                                        |                                                 |
| Adults (18-64 years)                      | 28                        | 59                                     | 5                                               |
| From 65-84 years                          | 9                         | 13                                     | 4                                               |
| Age Continuous<br>Units: Years            |                           |                                        |                                                 |
| arithmetic mean                           | 54.7                      | 52.3                                   | 56.6                                            |
| standard deviation                        | ± 14.1                    | ± 12.3                                 | ± 14.3                                          |
| Sex: Female, Male<br>Units: Subjects      |                           |                                        |                                                 |
| Female                                    | 32                        | 66                                     | 6                                               |
| Male                                      | 5                         | 6                                      | 3                                               |
| Ethnicity (NIH/OMB)<br>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)<br>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<br>Analysis:<br>RO7123520<br>810mg/dose | Total |  |
|----------------------------------------------|----------------------------------------------------------|-------|--|
| Number of subjects                           | 97                                                       | 118   |  |
| Age categorical<br>Units: Subjects           |                                                          |       |  |
| Adults (18-64 years)                         | 78                                                       | 92    |  |
| From 65-84 years                             | 19                                                       | 26    |  |
| Age Continuous<br>Units: Years               |                                                          |       |  |
| arithmetic mean                              | 53.4                                                     |       |  |
| standard deviation                           | ± 12.8                                                   | -     |  |
| Sex: Female, Male<br>Units: Subjects         |                                                          |       |  |
| Female                                       | 87                                                       | 104   |  |
| Male                                         | 10                                                       | 14    |  |
| Ethnicity (NIH/OMB)<br>Units: Subjects       |                                                          |       |  |
| Hispanic or Latino                           | 73                                                       | 82    |  |
| Not Hispanic or Latino                       | 24                                                       | 36    |  |
| Unknown or Not Reported                      | 0                                                        | 0     |  |
| Race (NIH/OMB)<br>Units: Subjects            |                                                          |       |  |
| American Indian or Alaska Native             | 16                                                       | 19    |  |
| Asian                                        | 0                                                        | 0     |  |
| Native Hawaiian or Other Pacific<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>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:<br>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 <sup>[2]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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: 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 <sup>[3]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 12

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: 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:<br>Placebo | Proof of Concept:<br>RO7123520<br>810mg/dose | Extension Period<br>Analysis:<br>RO7123520<br>360mg/dose | Extension Period<br>Analysis:<br>RO7123520<br>810mg/dose |
|--------------------------------------|------------------------------|----------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Subject group type                   | Reporting group              | Reporting group                              | Reporting group                                          | Reporting group                                          |
| Number of subjects analysed          | 37                           | 67 <sup>[4]</sup>                            | 9 <sup>[5]</sup>                                         | 94 <sup>[6]</sup>                                        |
| Units: g/cm <sup>2</sup>             |                              |                                              |                                                          |                                                          |
| 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:

[4] - Week 12 n=59

[5] - Week 12 n=6

[6] - Week 12 n=72

## 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 <sup>[7][8]</sup> |
| End point description:<br>The immunogenicity population included participants with at least 1 pre-dose ADA assessment, grouped by treatment and dose level. |                                                                        |
| End point type                                                                                                                                              | Primary                                                                |
| End point timeframe:<br>Baseline                                                                                                                            |                                                                        |

Notes:

[7] - 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.

[8] - 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<br>Analysis:<br>RO7123520<br>810mg/dose |  |  |  |
|-----------------------------|----------------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                          |  |  |  |
| Number of subjects analysed | 69                                                       |  |  |  |
| Units: Percent              | 0                                                        |  |  |  |

## 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) |
|-----------------|----------------------------------------------------------------|

## 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 <sup>[9]</sup>                      | 9                                               | 96 <sup>[10]</sup>                              |
| 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 |
|-----------------|----------------------------------------------------------------------|

## 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 |
|-----------------|-----------------------------------------------------------------|

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:

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 |
|-----------------|----------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|----------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|----------------------------------------------------------------|

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 |
|----------------|-----------|

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 |
|-----------------|-------------------------------------------------------------------------------|

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  $\leq 11$ , moderate disease activity as  $\leq 26$  and high disease activity as  $> 26$ .

|                |           |
|----------------|-----------|
| 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 <sup>[11]</sup>        | 69 <sup>[12]</sup>                     | 9 <sup>[13]</sup>                               | 96 <sup>[14]</sup>                              |
| 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 <sup>[15]</sup>                     | 9 <sup>[16]</sup>                               | 96 <sup>[17]</sup>                              |
| 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 |
|-----------------|-------------------------------|

End point description:

All enrolled participants were included in the PK population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 <sup>[18]</sup>         | 0 <sup>[19]</sup>                      | 0 <sup>[20]</sup>                               | 0 <sup>[21]</sup>                               |
| 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 |
|-----------------|----------------------------------------|

End point description:

All enrolled participants were included in the PK population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| <b>End point values</b>     | Proof of Concept:<br>Placebo | Proof of Concept:<br>RO7123520<br>810mg/dose | Extension Period<br>Analysis:<br>RO7123520<br>360mg/dose | Extension Period<br>Analysis:<br>RO7123520<br>810mg/dose |
|-----------------------------|------------------------------|----------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Subject group type          | Reporting group              | Reporting group                              | Reporting group                                          | Reporting group                                          |
| Number of subjects analysed | 0 <sup>[22]</sup>            | 0 <sup>[23]</sup>                            | 0 <sup>[24]</sup>                                        | 0 <sup>[25]</sup>                                        |
| 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 |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### 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.

| 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          |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                |
| 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          |
| <b>Infections and infestations</b>                     |                |                |                |
| 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          |

|                                                                            |                                                          |  |  |
|----------------------------------------------------------------------------|----------------------------------------------------------|--|--|
| <b>Serious adverse events</b>                                              | Extension Period<br>Analysis:<br>R07123520<br>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                             |                                                          |  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                                                          |  |  |
| 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                                                    |  |  |
| <b>Tonsil cancer</b>                                                       |                                                          |  |  |
| subjects affected / exposed                                                | 0 / 97 (0.00%)                                           |  |  |
| occurrences causally related to treatment / all                            | 0 / 0                                                    |  |  |
| deaths causally related to treatment / all                                 | 0 / 0                                                    |  |  |
| <b>Musculoskeletal and connective tissue disorders</b>                     |                                                          |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Proof of Concept:<br>Placebo | Proof of Concept:<br>RO7123520<br>810mg/dose | Extension Period<br>Analysis:<br>RO7123520<br>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<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                       | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Neck mass<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Rheumatoid arthritis<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Infections and infestations<br>Chronic tonsillitis<br>subjects affected / exposed<br>occurrences (all)           | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 37 (0.00%)<br>0 | 0 / 70 (0.00%)<br>0 | 1 / 9 (11.11%)<br>1 |

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

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



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

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

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### 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: