



## Clinical trial results:

A randomized, double-blind, placebo- and active-controlled study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the safety, tolerability and long term efficacy up to 1 year in patients with active rheumatoid arthritis who have an inadequate response to anti-TNF agents (CAIN457F2309) and A four year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active rheumatoid arthritis (CAIN457F2309E1)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

## Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2012-002760-27       |
| Trial protocol           | CZ HU DE SK IT BG ES |
| Global end of trial date | 14 May 2015          |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 July 2018 |
| First version publication date | 11 July 2018 |

## Trial information

### Trial identification

|                       |                                 |
|-----------------------|---------------------------------|
| Sponsor protocol code | CAIN457F2309 and CAIN457F2309E1 |
|-----------------------|---------------------------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01350804 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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                       | 14 May 2015 |
| Is this the analysis of the primary completion data? | No          |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 14 May 2015 |
| Was the trial ended prematurely? | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

Core: To demonstrate that the efficacy of secukinumab 75 mg or 150 mg at Week 24 is superior to placebo in patients with active RA based on the proportion of patients achieving an ACR20 response.

Extension: To evaluate the long-term efficacy of secukinumab 75 and 150 mg (provided as prefilled syringes) with respect to ACR20, ACR50 and ACR70 response over time up to Month 60 in patients with active rheumatoid arthritis who had previously experienced an inadequate or intolerant response to anti-TNF- $\alpha$  therapy and who completed the core study CAIN457F2309.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 07 September 2011 |
| 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 | Brazil: 37         |
| Country: Number of subjects enrolled | Bulgaria: 35       |
| Country: Number of subjects enrolled | Canada: 3          |
| Country: Number of subjects enrolled | Colombia: 35       |
| Country: Number of subjects enrolled | Czech Republic: 30 |
| Country: Number of subjects enrolled | France: 15         |
| Country: Number of subjects enrolled | Germany: 122       |
| Country: Number of subjects enrolled | Hungary: 14        |
| Country: Number of subjects enrolled | Italy: 17          |
| Country: Number of subjects enrolled | Mexico: 62         |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 1             |
| Country: Number of subjects enrolled | Russian Federation: 22 |
| Country: Number of subjects enrolled | Slovakia: 2            |
| Country: Number of subjects enrolled | Spain: 27              |
| Country: Number of subjects enrolled | United States: 129     |
| Worldwide total number of subjects   | 551                    |
| EEA total number of subjects         | 263                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 435 |
| From 65 to 84 years                       | 115 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

At week 16, placebo responders and non-responders were re-randomized to AIN457 75mg or AIN457 150mg. Abatacept responders at Week 16 continued on abatacept. Abatacept non-responders at Week 16 were re-randomized to AIN457 75mg or AIN457 150mg.

### Pre-assignment

Screening details:

One patient was randomized to AIN457 75mg but instead received placebo up to week 16 and was re-categorized to placebo in the Safety Set for the first 16 weeks. Past week 16, this patient received secukinumab and was included in the "Any AIN457 75mg" for long term safety analyses.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Core Study  |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Investigator, Subject, Monitor, Carer, Data analyst, Assessor |

### Arms

|                              |                        |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes                    |
| <b>Arm title</b>             | AIN457 10mg/kg - 75 mg |

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | AIN457                                     |
| Investigational medicinal product code |  |
| Other name                             | Secukinumab                                |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

Dosage and administration details:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | AIN457 10mg/kg - 150 mg |
|------------------|-------------------------|

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | AIN457                                     |
| Investigational medicinal product code |  |
| Other name                             | Secukinumab                                |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

Dosage and administration details:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$  reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24.

|  |  |
|--|--|
| Arm type                               | Placebo                                    |
| Investigational medicinal product name | Placebo                                    |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

**Dosage and administration details:**

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status treatment at week 16. Responders were switched to active treatment at week 24.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Abatacept |
|------------------|-----------|

**Arm description:**

Participants received abatacept (from 500 to 1000 mg i.v. based on weight). Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | Abatacept  |
| Investigational medicinal product code |  |
| Other name                             | Orencia  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Participants received abatacept (from 500 to 1000 mg i.v. based on weight) up until week 16. At week 16, participants who responded to abatacept maintained treatment with abatacept for the duration of the study. Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).

| <b>Number of subjects in period 1</b> | AIN457 10mg/kg - 75 mg | AIN457 10mg/kg - 150 mg | Placebo           |
|---------------------------------------|------------------------|-------------------------|-------------------|
| Started                               | 138                    | 137                     | 138               |
| Safety set                            | 137                    | 136                     | 138               |
| Treatment switch to AIN457 at week 16 | 0 <sup>[1]</sup>       | 0 <sup>[2]</sup>        | 78 <sup>[3]</sup> |
| Treatment switch to AIN457 at week 24 | 0 <sup>[4]</sup>       | 0 <sup>[5]</sup>        | 45 <sup>[6]</sup> |
| Full Analysis Set                     | 138                    | 137                     | 138               |
| Completed                             | 97                     | 90                      | 91                |
| Not completed                         | 41                     | 47                      | 47                |
| Adverse event, serious fatal          | 1                      | 1                       | 1                 |
| Consent withdrawn by subject          | 11                     | 17                      | 16                |
| Physician decision                    | 1                      | -                       | 1                 |
| Study terminated by Sponsor           | -                      | -                       | -                 |
| Adverse event, non-fatal              | 8                      | 10                      | 8                 |
| Protocol deviation                    | 1                      | -                       | 1                 |
| Lost to follow-up                     | 3                      | -                       | 2                 |
| Lack of efficacy                      | 16                     | 19                      | 18                |

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 1</b> | Abatacept |
| Started                               | 138       |

|                                       |                   |
|---------------------------------------|-------------------|
| Safety set                            | 137               |
| Treatment switch to AIN457 at week 16 | 0 <sup>[7]</sup>  |
| Treatment switch to AIN457 at week 24 | 37 <sup>[8]</sup> |
| Full Analysis Set                     | 138               |
| Completed                             | 112               |
| Not completed                         | 26                |
| Adverse event, serious fatal          | -                 |
| Consent withdrawn by subject          | 7                 |
| Physician decision                    | 3                 |
| Study terminated by Sponsor           | 2                 |
| Adverse event, non-fatal              | 8                 |
| Protocol deviation                    | -                 |
| Lost to follow-up                     | 1                 |
| Lack of efficacy                      | 5                 |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Crossover of placebo non responders arm to active treatment arms in a 1:1 randomized manner

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | Extension Study, weeks 52 - 260                               |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Data analyst, Assessor |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | AIN457 10mg/kg - 75 mg |
|------------------|------------------------|

## Arm description:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | AIN457                                     |
| Investigational medicinal product code |  |
| Other name                             | Secukinumab                                |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

## Dosage and administration details:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | AIN457 10mg/kg - 150 mg |
|------------------|-------------------------|

## Arm description:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                               |
| Investigational medicinal product name | AIN457                                     |
| Investigational medicinal product code |  |
| Other name                             | Secukinumab                                |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

## Dosage and administration details:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

## Arm description:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$  reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24.

|  |  |
|--|--|
| Arm type                               | Placebo                                    |
| Investigational medicinal product name | Placebo                                    |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Intravenous use, Subcutaneous use          |

## Dosage and administration details:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$  reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Abatacept |
|------------------|-----------|

## Arm description:

Participants received abatacept (from 500 to 1000 mg i.v. based on weight). Participants who did not

respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | Abatacept  |
| Investigational medicinal product code |  |
| Other name                             | Orencia  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Participants received abatacept (from 500 to 1000 mg i.v. based on weight) up until week 16. At week 16, participants who responded to abatacept maintained treatment with abatacept for the duration of the study. Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).

| <b>Number of subjects in period 2<sup>[9]</sup></b> | AIN457 10mg/kg - 75 mg | AIN457 10mg/kg - 150 mg | Placebo |
|---|------------------------|-------------------------|---------|
| Started   | 80                     | 79                      | 72      |
| Completed   | 0                      | 0                       | 0       |
| Not completed                                       | 80                     | 79                      | 72      |
| Consent withdrawn by subject                        | 5                      | 6                       | 4       |
| Physician decision                                  | 1                      | -                       | 2       |
| Study terminated by Sponsor                         | 67                     | 67                      | 64      |
| Adverse event, non-fatal                            | 3                      | 1                       | 2       |
| Lost to follow-up                                   | -                      | 1                       | -       |
| Lack of efficacy                                    | 4                      | 4                       | -       |

| <b>Number of subjects in period 2<sup>[9]</sup></b> | Abatacept |
|---|-----------|
| Started   | 23        |
| Completed   | 0         |
| Not completed                                       | 23        |
| Consent withdrawn by subject                        | 3         |
| Physician decision                                  | -         |
| Study terminated by Sponsor                         | 16        |
| Adverse event, non-fatal                            | 3         |
| Lost to follow-up                                   | -         |
| Lack of efficacy                                    | 1         |

Notes:

[9] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all patients completing the previous milestone continued on in the extension study

## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | AIN457 10mg/kg - 75 mg  |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.  |                         |
| Reporting group title   | AIN457 10mg/kg - 150 mg |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.  |                         |
| Reporting group title   | Placebo                 |
| Reporting group description:<br>Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$ reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24. |                         |
| Reporting group title   | Abatacept               |
| Reporting group description:<br>Participants received abatacept (from 500 to 1000 mg i.v. based on weight). Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).  |                         |

| Reporting group values                     | AIN457 10mg/kg - 75 mg | AIN457 10mg/kg - 150 mg | Placebo             |
|--|------------------------|-------------------------|---------------------|
| Number of subjects                         | 138                    | 137                     | 138                 |
| Age Categorical<br>Units: Participants     |                        |                         |                     |
| $\leq 18$ years                            | 0                      | 0                       | 0                   |
| Between 18 and 65 years                    | 111                    | 103                     | 106                 |
| $\geq 65$ years                            | 27                     | 34                      | 32                  |
| Age continuous<br>Units:                   |                        |                         |                     |
|  | 54.9<br>$\pm 11.32$    | 55.9<br>$\pm 12.27$     | 55.5<br>$\pm 12.05$ |
| Gender, Male/Female<br>Units: Participants |                        |                         |                     |
| Female                                     | 119                    | 109                     | 115                 |
| Male                                       | 19                     | 28                      | 23                  |

| Reporting group values                 | Abatacept           | Total |  |
|--|---------------------|-------|--|
| Number of subjects                     | 138                 | 551   |  |
| Age Categorical<br>Units: Participants |                     |       |  |
| $\leq 18$ years                        | 0                   | 0     |  |
| Between 18 and 65 years                | 115                 | 435   |  |
| $\geq 65$ years                        | 23                  | 116   |  |
| Age continuous<br>Units:               |                     |       |  |
|  | 51.6<br>$\pm 12.39$ | -     |  |

|                     |     |     |  |
|---------------------|-----|-----|--|
| Gender, Male/Female |     |     |  |
| Units: Participants |     |     |  |
| Female              | 107 | 450 |  |
| Male                | 31  | 101 |  |

## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | AIN457 10mg/kg - 75 mg               |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.  |                                      |
| Reporting group title   | AIN457 10mg/kg - 150 mg              |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.  |                                      |
| Reporting group title   | Placebo                              |
| Reporting group description:<br>Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$ reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24. |                                      |
| Reporting group title   | Abatacept                            |
| Reporting group description:<br>Participants received abatacept (from 500 to 1000 mg i.v. based on weight). Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).  |                                      |
| Reporting group title   | AIN457 10mg/kg - 75 mg               |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks.  |                                      |
| Reporting group title   | AIN457 10mg/kg - 150 mg              |
| Reporting group description:<br>Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks.  |                                      |
| Reporting group title   | Placebo                              |
| Reporting group description:<br>Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status ( $\geq 20\%$ reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24. |                                      |
| Reporting group title   | Abatacept                            |
| Reporting group description:<br>Participants received abatacept (from 500 to 1000 mg i.v. based on weight). Participants who did not respond to abatacept at Week 16 were re-randomized 1:1 to AIN457 75mg or 150mg at week 24 (after an 8 week washout period).  |                                      |
| Subject analysis set title  | Placebo non-responder - AIN457 75mg  |
| Subject analysis set type   | Full analysis                        |
| Subject analysis set description:<br>Participants switched from placebo to AIN457 75 mg starting at week 16.  |                                      |
| Subject analysis set title  | Placebo non-responder - AIN457 150mg |
| Subject analysis set type   | Full analysis                        |
| Subject analysis set description:<br>Participants switched from placebo to AIN457 150 mg starting at week 16.   |                                      |
| Subject analysis set title  | Placebo responder - AIN457 75mg      |
| Subject analysis set type   | Full analysis                        |
| Subject analysis set description:<br>Participants switched from placebo to AIN457 75 mg starting at week 24.  |                                      |
| Subject analysis set title  | Placebo responder - AIN457 150mg     |
| Subject analysis set type   | Full analysis                        |

Subject analysis set description:

Participants switched from placebo to AIN457 150 mg starting at week 24.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Abatacept responders |
| Subject analysis set type  | Full analysis        |

Subject analysis set description:

Abatacept responders remained on abatacept (from 500 to 1000 mg iv based on weight).

|                            |  |
|----------------------------|--|
| Subject analysis set title | Abatacept non-responders - AIN457 75mg |
| Subject analysis set type  | Full analysis                          |

Subject analysis set description:

Participants switched from abatacept to AIN457 75 mg starting at week 24.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Abatacept non-responders - AIN457 150mg |
| Subject analysis set type  | Full analysis                           |

Subject analysis set description:

Participants switched from abatacept to AIN457 150 mg starting at week 24.

### **Primary: Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20).**

|                 |   |
|-----------------|---|
| End point title | Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20). |
|-----------------|---|

End point description:

ACR20 response was defined as having a positive clinical response to treatment (individual improvement) in disease activity if the participant had at least 20% improvement in tender 68-joint count, swollen 66-joint count and at least 3 of the following 5 measures: patient's assessment of RA pain, patient's global assessment of disease activity, physician's global assessment of disease activity, subject self-assessed disability (Health Assessment Questionnaire [HAQ-DI] score), and/or acute phase reactant (high sensitivity c-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR). The ACR20 response results at week 24 used non-responder imputation.

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

End point timeframe:

week 24

| <b>End point values</b>           | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|-----------------------------------|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed       | 138                          | 137                           | 138             | 138             |
| Units: Percentage of participants |                              |                               |                 |                 |
| number (not applicable)           | 28.3                         | 30.7                          | 18.1            | 42.8            |

### **Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | ACR20 in AIN457 10mg/kg - 75 mg versus placebo |
| Comparison groups                 | AIN457 10mg/kg - 75 mg v Placebo               |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 276                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           |                      |
| P-value                                 | = 0.0458             |
| Method                                  | Regression, Logistic |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 1.79                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 1                    |
| upper limit                             | 3.2                  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | ACR20 in AIN457 10mg/kg - 150 mg versus placebo |
| Comparison groups                       | AIN457 10mg/kg - 150 mg v Placebo               |
| Number of subjects included in analysis | 275   |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           |   |
| P-value                                 | = 0.0152  |
| Method                                  | Regression, Logistic                            |
| Parameter estimate                      | Odds ratio (OR)                                 |
| Point estimate                          | 2.02  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 1.1   |
| upper limit                             | 3.5   |

## Secondary: Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP)

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP) |
|-----------------|--|

End point description:

The DAS28 is a measure of disease activity in RA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission. A negative change from baseline indicates improvement.

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

End point timeframe:

baseline, week 24

| End point values                    | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo                 | Abatacept               |
|-------------------------------------|------------------------------|-------------------------------|-------------------------|-------------------------|
| Subject group type                  | Reporting group              | Reporting group               | Reporting group         | Reporting group         |
| Number of subjects analysed         | 116                          | 108                           | 44                      | 84                      |
| Units: score on a scale             |                              |                               |                         |                         |
| least squares mean (standard error) | -1.47 ( $\pm$<br>0.115)      | -1.47 ( $\pm$<br>0.119)       | -1.02 ( $\pm$<br>0.163) | -2.07 ( $\pm$<br>0.128) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) |
|-----------------|--|

End point description:

The HAQ-DI assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities. The stem of each item asks 'Over the past week, "are you able to..." perform a particular task'. Each item is scored on a 4 point scale from 0 - 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2) and unable to do (3). The disability index score is calculated as the mean of the available category scores, ranging from 0 to 3. A negative change from baseline indicates improvement.

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

End point timeframe:

baseline, week 24

| End point values                    | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo                 | Abatacept               |
|-------------------------------------|------------------------------|-------------------------------|-------------------------|-------------------------|
| Subject group type                  | Reporting group              | Reporting group               | Reporting group         | Reporting group         |
| Number of subjects analysed         | 117                          | 110                           | 44                      | 86                      |
| Units: score on a scale             |                              |                               |                         |                         |
| least squares mean (standard error) | -0.3 ( $\pm$ 0.049)          | -0.39 ( $\pm$<br>0.051)       | -0.26 ( $\pm$<br>0.065) | -0.61 ( $\pm$<br>0.053) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants achieving ACR50

|                 |  |
|-----------------|--|
| End point title | Percentage of participants achieving ACR50 |
|-----------------|--|

End point description:

ACR50 response was defined as having a positive clinical response to treatment (individual improvement) in disease activity if the participant had at least 50% improvement in tender 68-joint count, swollen 66-joint count and at least 3 of the following 5 measures: patient's assessment of RA

pain, patient's global assessment of disease activity, physician's global assessment of disease activity, subject self-assessed disability (Health Assessment Questionnaire [HAQ-DI] score), and/or acute phase reactant (high sensitivity c-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR). The ACR50 response results at week 24 used non-responder imputation.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| week 24              |           |

| End point values                  | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|-----------------------------------|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed       | 138                          | 137                           | 138             | 138             |
| Units: Percentage of participants |                              |                               |                 |                 |
| number (not applicable)           | 11.6                         | 16.8                          | 9.4             | 27.5            |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants achieving ACR20, ACR 50 and ACR 70 - using non-responder imputation

|                 |  |
|-----------------|--|
| End point title | Percentage of participants achieving ACR20, ACR 50 and ACR 70 - using non-responder imputation |
|-----------------|--|

End point description:

ACR20, ACR 50 and ACR 70 response was defined as having a positive clinical response to treatment (individual improvement) in disease activity if the participant had at least 20%, 50% and/or 70% improvement, respectively, in tender 68-joint count, swollen 66-joint count and at least 3 of the following 5 measures: patient's assessment of RA pain, patient's global assessment of disease activity, physician's global assessment of disease activity, subject self-assessed disability (Health Assessment Questionnaire [HAQ-DI] score), and/or acute phase reactant (high sensitivity c-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR).

|   |           |
|---|-----------|
| End point type                                | Secondary |
| End point timeframe:                          |           |
| baseline, weeks 1, 2, 4, 8, 12, 16, 20 and 24 |           |

| End point values                  | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|-----------------------------------|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed       | 138                          | 137                           | 138             | 138             |
| Units: Percentage of participants |                              |                               |                 |                 |
| number (not applicable)           |                              |                               |                 |                 |
| ACR20, week 1                     | 21                           | 17.5                          | 7.2             | 10.9            |
| ACR20, week 2                     | 24.6                         | 21.2                          | 12.3            | 23.9            |
| ACR20, week 4                     | 34.1                         | 27                            | 21.7            | 31.2            |
| ACR20, week 8                     | 35.5                         | 41.6                          | 21              | 49.3            |
| ACR20, week 12                    | 28.3                         | 33.6                          | 24.6            | 47.1            |

|                |      |      |      |      |
|----------------|------|------|------|------|
| ACR20, week 16 | 34.1 | 39.4 | 23.2 | 51.4 |
| ACR20, week 20 | 26.8 | 38   | 18.1 | 47.8 |
| ACR20, week 24 | 28.3 | 30.7 | 18.1 | 42.8 |
| ACR50, week 1  | 6.5  | 2.9  | 0.7  | 1.4  |
| ACR50, week 2  | 5.1  | 8.8  | 2.9  | 2.9  |
| ACR50, week 4  | 9.4  | 10.2 | 2.9  | 7.2  |
| ACR50, week 8  | 7.2  | 15.3 | 10.1 | 18.8 |
| ACR50, week 12 | 8.7  | 13.1 | 10.1 | 22.5 |
| ACR50, week 16 | 13.8 | 20.4 | 9.4  | 23.9 |
| ACR50, week 20 | 12.3 | 18.2 | 8    | 26.8 |
| ACR50, week 24 | 11.6 | 16.8 | 9.4  | 27.5 |
| ACR70, week 1  | 0.7  | 0.7  | 0    | 0.7  |
| ACR70, week 2  | 1.4  | 0.7  | 1.4  | 0.7  |
| ACR70, week 4  | 4.3  | 2.9  | 1.4  | 1.4  |
| ACR70, week 8  | 1.4  | 4.4  | 2.9  | 5.8  |
| ACR70, week 12 | 2.2  | 2.9  | 2.9  | 9.4  |
| ACR70, week 16 | 5.1  | 8    | 2.9  | 9.4  |
| ACR70, week 20 | 4.3  | 7.3  | 5.8  | 10.1 |
| ACR70, week 24 | 5.1  | 10.2 | 5.1  | 12.3 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants achieving ACR20, ACR 50 and ACR 70 - observed data

|                 |   |
|-----------------|---|
| End point title | Percentage of participants achieving ACR20, ACR 50 and ACR 70 - observed data |
|-----------------|---|

End point description:

ACR20, ACR 50 and ACR 70 response was defined as having a positive clinical response to treatment (individual improvement) in disease activity if the participant had at least 20%, 50% and/or 70% improvement, respectively, in tender 68-joint count, swollen 66-joint count and at least 3 of the following 5 measures: patient's assessment of RA pain, patient's global assessment of disease activity, physician's global assessment of disease activity, subject self-assessed disability (Health Assessment Questionnaire [HAQ-DI] score), and/or acute phase reactant (high sensitivity c-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR). The ACR20, ACR50 and ACR70 response results from baseline up to week 52 were based on observed data, i.e. without imputation.

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

End point timeframe:

baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

| End point values                                 | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|--|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                               | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed                      | 138                          | 137                           | 138             | 138             |
| Units: Percentage of participants                |                              |                               |                 |                 |
| number (not applicable)                          |                              |                               |                 |                 |
| ACR20,wk<br>1,n=132,129,130,130,39,35,21,22,96,1 | 22.7                         | 18.6                          | 7.7             | 11.5            |

|   |      |      |      |      |
|---|------|------|------|------|
| ACR20,wk<br>2,n=131,130,134,134,39,36,23,22,99,1      | 26.7 | 22.3 | 12.7 | 25.4 |
| ACR20,wk<br>4,n=133,132,131,129,39,39,23,21,93,1      | 36.1 | 28   | 22.9 | 34.1 |
| ACR20,wk<br>8,n=132,127,131,131,39,39,23,22,95,1      | 38.6 | 44.9 | 22.1 | 52.7 |
| ACR20,wk<br>12,n=130,115,123,129,39,37,23,21,94,      | 30.8 | 40   | 27.6 | 51.2 |
| ACR20,wk<br>16,n=126,118,116,129,36,37,21,22,94,      | 38.1 | 45.8 | 27.6 | 55.8 |
| ACR20,wk<br>20,n=122,114,119,126,38,37,23,21,91,      | 39.3 | 51.8 | 42.9 | 57.9 |
| ACR20,wk<br>24,n=117,110,117,121,38,36,21,22,87,      | 45.3 | 48.2 | 40.2 | 57.9 |
| ACR20,wk28,n=115,103,na,na,33,35,21<br>,21,86,17,19   | 47.8 | 65   | 9999 | 9999 |
| ACR20,wk32,n=104,97,na,na,33,30,21,<br>19,87,17,17    | 56.7 | 61.9 | 9999 | 9999 |
| ACR20,wk36,n=102,93,na,na,30,30,21,<br>20,85,18,16    | 56.9 | 53.8 | 9999 | 9999 |
| ACR20,wk40,n=96,90,na,na,28,28,21,1<br>9,85,15,17     | 53.1 | 61.1 | 9999 | 9999 |
| ACR20,wk44,n=97,90,na,na,28,27,20,1<br>8,84,15,16     | 56.7 | 61.1 | 9999 | 9999 |
| ACR20,wk48,n=94,89,na,na,28,26,18,1<br>9,77,12,14     | 57.4 | 68.5 | 9999 | 9999 |
| ACR20,wk52,n=92,88,na,na,28,26,20,1<br>8,79,15,15     | 56.5 | 62.5 | 9999 | 9999 |
| ACR50,wk1,n=132,129,130,130,39,35,2<br>1,22,96,17,17  | 6.8  | 3.1  | 0.8  | 1.5  |
| ACR50,wk2,n=131,130,134,134,39,36,2<br>3,22,99,17,18  | 5.3  | 9.2  | 3    | 3    |
| ACR50,wk4,n=133,132,131,129,39,39,2<br>3,21,93,17,19  | 9.8  | 10.6 | 3.1  | 7.8  |
| ACR50,wk8,n=132,127,131,131,39,39,2<br>3,22,95,17,19  | 9.1  | 16.5 | 10.7 | 20.6 |
| ACR50,wk12,n=130,115,123,129,39,37,<br>23,21,94,17,18 | 10   | 15.7 | 11.4 | 24.8 |
| ACR50,wk16,n=126,118,116,129,36,37,<br>21,22,94,16,19 | 15.9 | 23.7 | 11.2 | 26.4 |
| ACR50,wk20,n=122,114,119,126,38,37,<br>23,21,91,16,19 | 15.6 | 21.9 | 12.6 | 31.7 |
| ACR50,wk24,n=117,110,117,121,38,36,<br>21,22,87,16,18 | 14.5 | 22.7 | 14.5 | 33.1 |
| ACR50,wk28,n=115,103,na,na,33,35,21<br>,21,86,17,19   | 13.9 | 31.1 | 9999 | 9999 |
| ACR50,wk32,n=104,97,na,na,33,30,21,<br>19,87,17,17    | 21.2 | 32   | 9999 | 9999 |
| ACR50,wk36,n=102,93,na,na,30,30,21,<br>20,85,18,16    | 23.5 | 24.7 | 9999 | 9999 |
| ACR50,wk40,n=96,90,na,na,28,28,21,1<br>9,85,15,17     | 25   | 25.6 | 9999 | 9999 |
| ACR50,wk44,n=97,90,na,na,28,27,20,1<br>8,84,15,16     | 27.8 | 30   | 9999 | 9999 |
| ACR50,wk48,n=94,89,na,na,28,26,18,1<br>9,77,12,14     | 25.5 | 42.7 | 9999 | 9999 |
| ACR50,wk52,n=92,88,na,na,28,26,20,1<br>8,79,15,15     | 26.1 | 45.5 | 9999 | 9999 |
| ACR70,wk1,n=132,129,130,130,39,35,2<br>1,22,96,17,17  | 0.8  | 0.8  | 0    | 0.8  |
| ACR70,wk2,n=131,130,134,134,39,36,2<br>3,22,99,17,18  | 1.5  | 0.8  | 1.5  | 0.7  |

|   |      |      |      |      |
|---|------|------|------|------|
| ACR70,wk4,n=133,132,131,129,39,39,23,21,93,17,19  | 4.5  | 3    | 1.5  | 1.6  |
| ACR70,wk8,n=132,127,131,131,39,39,23,22,95,17,19  | 1.5  | 4.7  | 3.1  | 6.1  |
| ACR70,wk12,n=130,115,123,129,39,37,23,21,94,17,18 | 3.1  | 3.5  | 3.3  | 10.9 |
| ACR70,wk16,n=126,118,116,129,36,37,21,22,94,16,19 | 6.3  | 9.3  | 3.4  | 10   |
| ACR70,wk20,n=122,114,119,126,38,37,23,21,91,16,19 | 6.6  | 8.8  | 6.7  | 11.1 |
| ACR70,wk24,n=117,110,117,121,38,36,21,22,87,16,18 | 6    | 12.7 | 8.5  | 14.9 |
| ACR70,wk28,n=115,103,na,na,33,35,21,21,86,17,19   | 6.1  | 17.5 | 9999 | 9999 |
| ACR70,wk32,n=104,97,na,na,33,30,21,19,87,17,17    | 4.8  | 10   | 9999 | 9999 |
| ACR70,wk36,n=102,93,na,na,30,30,21,20,85,18,16    | 5.9  | 11.8 | 9999 | 9999 |
| ACR70,wk40,n=96,90,na,na,28,28,21,19,85,15,17     | 8.3  | 11.1 | 9999 | 9999 |
| ACR70,wk44,n=97,90,na,na,28,27,20,18,84,15,16     | 12.4 | 18.9 | 9999 | 9999 |
| ACR70,wk48,n=94,89,na,na,28,26,18,19,77,12,14     | 9.6  | 20.2 | 9999 | 9999 |
| ACR70,wk52,n=92,88,na,na,28,26,20,18,79,15,15     | 6.5  | 19.3 | 9999 | 9999 |

| End point values                                | Placebo non-responder - AIN457 75mg | Placebo non-responder - AIN457 150mg | Placebo responder - AIN457 75mg | Placebo responder - AIN457 150mg |
|---|-------------------------------------|--------------------------------------|---------------------------------|----------------------------------|
| Subject group type                              | Subject analysis set                | Subject analysis set                 | Subject analysis set            | Subject analysis set             |
| Number of subjects analysed                     | 39                                  | 39                                   | 23                              | 22                               |
| Units: Percentage of participants               |                                     |                                      |                                 |                                  |
| number (not applicable)                         |                                     |                                      |                                 |                                  |
| ACR20,wk1,n=132,129,130,130,39,35,21,22,96,1    | 5.1                                 | 5.7                                  | 14.3                            | 13.6                             |
| ACR20,wk2,n=131,130,134,134,39,36,23,22,99,1    | 2.6                                 | 11.1                                 | 34.8                            | 13.6                             |
| ACR20,wk4,n=133,132,131,129,39,39,23,21,93,1    | 15.4                                | 12.8                                 | 43.5                            | 42.9                             |
| ACR20,wk8,n=132,127,131,131,39,39,23,22,95,1    | 17.9                                | 12.8                                 | 39.1                            | 31.8                             |
| ACR20,wk12,n=130,115,123,129,39,37,23,21,94,    | 15.4                                | 16.2                                 | 47.8                            | 52.4                             |
| ACR20,wk16,n=126,118,116,129,36,37,21,22,94,    | 2.8                                 | 2.7                                  | 76.2                            | 63.6                             |
| ACR20,wk20,n=122,114,119,126,38,37,23,21,91,    | 42.1                                | 29.7                                 | 60.9                            | 47.6                             |
| ACR20,wk24,n=117,110,117,121,38,36,21,22,87,    | 26.3                                | 33.3                                 | 57.1                            | 59.1                             |
| ACR20,wk28,n=115,103,na,na,33,35,21,21,86,17,19 | 33.3                                | 37.1                                 | 71.4                            | 90.5                             |
| ACR20,wk32,n=104,97,na,na,33,30,21,19,87,17,17  | 51.5                                | 36.7                                 | 81                              | 68.4                             |
| ACR20,wk36,n=102,93,na,na,30,30,21,20,85,18,16  | 46.7                                | 56.7                                 | 85.7                            | 65                               |
| ACR20,wk40,n=96,90,na,na,28,28,21,19,85,15,17   | 53.6                                | 53.6                                 | 85.7                            | 73.7                             |

|   |      |      |      |      |
|---|------|------|------|------|
| ACR20,wk44,n=97,90,na,na,28,27,20,1<br>8,84,15,16     | 50   | 55.6 | 85   | 77.8 |
| ACR20,wk48,n=94,89,na,na,28,26,18,1<br>9,77,12,14     | 53.6 | 61.5 | 72.2 | 57.9 |
| ACR20,wk52,n=92,88,na,na,28,26,20,1<br>8,79,15,15     | 39.3 | 57.7 | 75   | 88.9 |
| ACR50,wk1,n=132,129,130,130,39,35,2<br>1,22,96,17,17  | 0    | 0    | 4.8  | 0    |
| ACR50,wk2,n=131,130,134,134,39,36,2<br>3,22,99,17,18  | 0    | 0    | 13   | 4.5  |
| ACR50,wk4,n=133,132,131,129,39,39,2<br>3,21,93,17,19  | 0    | 0    | 8.7  | 9.5  |
| ACR50,wk8,n=132,127,131,131,39,39,2<br>3,22,95,17,19  | 5.1  | 5.1  | 34.8 | 9.1  |
| ACR50,wk12,n=130,115,123,129,39,37,<br>23,21,94,17,18 | 2.6  | 8.1  | 21.7 | 23.8 |
| ACR50,wk16,n=126,118,116,129,36,37,<br>21,22,94,16,19 | 0    | 0    | 38.1 | 22.7 |
| ACR50,wk20,n=122,114,119,126,38,37,<br>23,21,91,16,19 | 7.9  | 2.7  | 34.8 | 14.3 |
| ACR50,wk24,n=117,110,117,121,38,36,<br>21,22,87,16,18 | 0    | 11.1 | 38.1 | 22.7 |
| ACR50,wk28,n=115,103,na,na,33,35,21<br>,21,86,17,19   | 6.1  | 8.6  | 33.3 | 33.3 |
| ACR50,wk32,n=104,97,na,na,33,30,21,<br>19,87,17,17    | 6.1  | 13.3 | 42.9 | 31.6 |
| ACR50,wk36,n=102,93,na,na,30,30,21,<br>20,85,18,16    | 16.7 | 16.7 | 28.6 | 20   |
| ACR50,wk40,n=96,90,na,na,28,28,21,1<br>9,85,15,17     | 14.3 | 28.6 | 38.1 | 26.3 |
| ACR50,wk44,n=97,90,na,na,28,27,20,1<br>8,84,15,16     | 7.1  | 29.6 | 35   | 33.3 |
| ACR50,wk48,n=94,89,na,na,28,26,18,1<br>9,77,12,14     | 14.3 | 23.1 | 38.9 | 26.3 |
| ACR50,wk52,n=92,88,na,na,28,26,20,1<br>8,79,15,15     | 10.7 | 26.9 | 40   | 44.4 |
| ACR70,wk1,n=132,129,130,130,39,35,2<br>1,22,96,17,17  | 0    | 0    | 0    | 0    |
| ACR70,wk2,n=131,130,134,134,39,36,2<br>3,22,99,17,18  | 0    | 0    | 4.3  | 4.5  |
| ACR70,wk4,n=133,132,131,129,39,39,2<br>3,21,93,17,19  | 0    | 0    | 4.3  | 4.8  |
| ACR70,wk8,n=132,127,131,131,39,39,2<br>3,22,95,17,19  | 0    | 2.6  | 13   | 0    |
| ACR70,wk12,n=130,115,123,129,39,37,<br>23,21,94,17,18 | 0    | 0    | 13   | 4.8  |
| ACR70,wk16,n=126,118,116,129,36,37,<br>21,22,94,16,19 | 0    | 0    | 14.3 | 4.5  |
| ACR70,wk20,n=122,114,119,126,38,37,<br>23,21,91,16,19 | 0    | 0    | 21.7 | 14.3 |
| ACR70,wk24,n=117,110,117,121,38,36,<br>21,22,87,16,18 | 0    | 8.3  | 23.8 | 9.1  |
| ACR70,wk28,n=115,103,na,na,33,35,21<br>,21,86,17,19   | 0    | 2.9  | 14.3 | 14.3 |
| ACR70,wk32,n=104,97,na,na,33,30,21,<br>19,87,17,17    | 0    | 3.3  | 19   | 0    |
| ACR70,wk36,n=102,93,na,na,30,30,21,<br>20,85,18,16    | 3.3  | 0    | 23.8 | 0    |
| ACR70,wk40,n=96,90,na,na,28,28,21,1<br>9,85,15,17     | 7.1  | 10.7 | 19   | 10.5 |
| ACR70,wk44,n=97,90,na,na,28,27,20,1<br>8,84,15,16     | 0    | 11.1 | 25   | 11.1 |

|   |     |      |      |      |
|---|-----|------|------|------|
| ACR70,wk48,n=94,89,na,na,28,26,18,19,77,12,14 | 3.6 | 15.4 | 33.3 | 10.5 |
| ACR70,wk52,n=92,88,na,na,28,26,20,18,79,15,15 | 0   | 7.7  | 30   | 16.7 |

| End point values                                  | Abatacept responders | Abatacept non-responders - AIN457 75mg | Abatacept non-responders - AIN457 150mg |  |
|---|----------------------|--|---|--|
| Subject group type                                | Subject analysis set | Subject analysis set                   | Subject analysis set                    |  |
| Number of subjects analysed                       | 101                  | 18                                     | 19                                      |  |
| Units: Percentage of participants                 |                      |  |   |  |
| number (not applicable)                           |                      |  |   |  |
| ACR20,wk1,n=132,129,130,130,39,35,21,22,96,1      | 14.6                 | 0                                      | 5.9                                     |  |
| ACR20,wk2,n=131,130,134,134,39,36,23,22,99,1      | 29.3                 | 11.8                                   | 16.7                                    |  |
| ACR20,wk4,n=133,132,131,129,39,39,23,21,93,1      | 41.9                 | 17.6                                   | 10.5                                    |  |
| ACR20,wk8,n=132,127,131,131,39,39,23,22,95,1      | 61.1                 | 29.4                                   | 31.6                                    |  |
| ACR20,wk12,n=130,115,123,129,39,37,23,21,94,      | 62.8                 | 17.6                                   | 22.2                                    |  |
| ACR20,wk16,n=126,118,116,129,36,37,21,22,94,      | 76.6                 | 0                                      | 0                                       |  |
| ACR20,wk20,n=122,114,119,126,38,37,23,21,91,      | 73.6                 | 6.3                                    | 26.3                                    |  |
| ACR20,wk24,n=117,110,117,121,38,36,21,22,87,      | 69                   | 31.3                                   | 27.8                                    |  |
| ACR20,wk28,n=115,103,na,na,33,35,21,21,86,17,19   | 74.4                 | 41.2                                   | 42.1                                    |  |
| ACR20,wk32,n=104,97,na,na,33,30,21,19,87,17,17    | 74.7                 | 23.5                                   | 47.1                                    |  |
| ACR20,wk36,n=102,93,na,na,30,30,21,20,85,18,16    | 77.6                 | 27.8                                   | 56.3                                    |  |
| ACR20,wk40,n=96,90,na,na,28,28,21,19,85,15,17     | 71.8                 | 40                                     | 58.8                                    |  |
| ACR20,wk44,n=97,90,na,na,28,27,20,18,84,15,16     | 77.4                 | 33.3                                   | 31.3                                    |  |
| ACR20,wk48,n=94,89,na,na,28,26,18,19,77,12,14     | 71.4                 | 25                                     | 50                                      |  |
| ACR20,wk52,n=92,88,na,na,28,26,20,18,79,15,15     | 74.7                 | 40                                     | 33.3                                    |  |
| ACR50,wk1,n=132,129,130,130,39,35,21,22,96,17,17  | 1                    | 0                                      | 5.9                                     |  |
| ACR50,wk2,n=131,130,134,134,39,36,23,22,99,17,18  | 3                    | 0                                      | 5.6                                     |  |
| ACR50,wk4,n=133,132,131,129,39,39,23,21,93,17,19  | 10.8                 | 0                                      | 0                                       |  |
| ACR50,wk8,n=132,127,131,131,39,39,23,22,95,17,19  | 25.3                 | 11.8                                   | 5.3                                     |  |
| ACR50,wk12,n=130,115,123,129,39,37,23,21,94,17,18 | 30.9                 | 5.9                                    | 11.1                                    |  |
| ACR50,wk16,n=126,118,116,129,36,37,21,22,94,16,19 | 36.2                 | 0                                      | 0                                       |  |
| ACR50,wk20,n=122,114,119,126,38,37,23,21,91,16,19 | 40.7                 | 0                                      | 15.8                                    |  |
| ACR50,wk24,n=117,110,117,121,38,36,21,22,87,16,18 | 44.8                 | 0                                      | 5.6                                     |  |

|   |      |      |      |  |
|---|------|------|------|--|
| ACR50,wk28,n=115,103,na,na,33,35,21,21,86,17,19   | 41.9 | 23.5 | 0    |  |
| ACR50,wk32,n=104,97,na,na,33,30,21,19,87,17,17    | 47.1 | 5.9  | 0    |  |
| ACR50,wk36,n=102,93,na,na,30,30,21,20,85,18,16    | 47.1 | 16.7 | 18.8 |  |
| ACR50,wk40,n=96,90,na,na,28,28,21,19,85,15,17     | 45.9 | 20   | 5.9  |  |
| ACR50,wk44,n=97,90,na,na,28,27,20,18,84,15,16     | 50   | 13.3 | 6.3  |  |
| ACR50,wk48,n=94,89,na,na,28,26,18,19,77,12,14     | 48.1 | 0    | 0    |  |
| ACR50,wk52,n=92,88,na,na,28,26,20,18,79,15,15     | 51.9 | 20   | 13.3 |  |
| ACR70,wk1,n=132,129,130,130,39,35,21,22,96,17,17  | 1    | 0    | 0    |  |
| ACR70,wk2,n=131,130,134,134,39,36,23,22,99,17,18  | 1    | 0    | 0    |  |
| ACR70,wk4,n=133,132,131,129,39,39,23,21,93,17,19  | 2.2  | 0    | 0    |  |
| ACR70,wk8,n=132,127,131,131,39,39,23,22,95,17,19  | 7.4  | 5.9  | 0    |  |
| ACR70,wk12,n=130,115,123,129,39,37,23,21,94,17,18 | 14.9 | 0    | 0    |  |
| ACR70,wk16,n=126,118,116,129,36,37,21,22,94,16,19 | 13.8 | 0    | 0    |  |
| ACR70,wk20,n=122,114,119,126,38,37,23,21,91,16,19 | 15.4 | 0    | 0    |  |
| ACR70,wk24,n=117,110,117,121,38,36,21,22,87,16,18 | 19.5 | 0    | 5.6  |  |
| ACR70,wk28,n=115,103,na,na,33,35,21,21,86,17,19   | 17.4 | 5.9  | 0    |  |
| ACR70,wk32,n=104,97,na,na,33,30,21,19,87,17,17    | 21.8 | 0    | 0    |  |
| ACR70,wk36,n=102,93,na,na,30,30,21,20,85,18,16    | 23.5 | 11.1 | 0    |  |
| ACR70,wk40,n=96,90,na,na,28,28,21,19,85,15,17     | 21.2 | 13.3 | 0    |  |
| ACR70,wk44,n=97,90,na,na,28,27,20,18,84,15,16     | 26.2 | 6.7  | 0    |  |
| ACR70,wk48,n=94,89,na,na,28,26,18,19,77,12,14     | 27.3 | 0    | 0    |  |
| ACR70,wk52,n=92,88,na,na,28,26,20,18,79,15,15     | 22.8 | 13.3 | 0    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in HAQ-DI - using mixed model repeated measures (MMRM)

|                 |   |
|-----------------|---|
| End point title | Change from baseline in HAQ-DI - using mixed model repeated measures (MMRM) |
|-----------------|---|

End point description:

The HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities. The stem of each item asks 'Over the past

week, "are you able to..." perform a particular task'. Each item is scored on a 4 point scale from 0 - 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2) and unable to do (3). The disability index score is calculated as the mean of the available category scores, ranging from 0 to 3. A negative change from baseline indicates improvement.

|   |           |
|---|-----------|
| End point type                                | Secondary |
| End point timeframe:                          |           |
| baseline, weeks 1, 2, 4, 8, 12, 16, 20 and 24 |           |

| End point values                    | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo            | Abatacept          |
|-------------------------------------|------------------------------|-------------------------------|--------------------|--------------------|
| Subject group type                  | Reporting group              | Reporting group               | Reporting group    | Reporting group    |
| Number of subjects analysed         | 138                          | 137                           | 138                | 138                |
| Units: score on a scale             |                              |                               |                    |                    |
| least squares mean (standard error) |                              |                               |                    |                    |
| week 1, n=132,129,130,129           | -0.22 (±<br>0.032)           | -0.21 (±<br>0.032)            | -0.08 (±<br>0.032) | -0.19 (±<br>0.032) |
| week 2, n=131,130,134,133           | -0.22 (±<br>0.036)           | -0.25 (±<br>0.036)            | -0.16 (±<br>0.036) | -0.26 (±<br>0.036) |
| week 4, n=133,133,131,130           | -0.3 (± 0.039)               | -0.31 (± 0.04)                | -0.17 (± 0.04)     | -0.36 (± 0.04)     |
| week 8, n=132,127,131,130           | -0.29 (±<br>0.042)           | -0.32 (±<br>0.043)            | -0.17 (±<br>0.043) | -0.46 (±<br>0.043) |
| week 12, n=130,114,123,129          | -0.31 (±<br>0.046)           | -0.33 (±<br>0.047)            | -0.18 (±<br>0.047) | -0.51 (±<br>0.046) |
| week 16, n=127,118,116,129          | -0.3 (± 0.048)               | -0.37 (±<br>0.049)            | -0.22 (±<br>0.049) | -0.52 (±<br>0.048) |
| week 20, n=122,114,47,92            | -0.36 (±<br>0.051)           | -0.42 (±<br>0.052)            | -0.21 (±<br>0.066) | -0.57 (±<br>0.054) |
| week 24, n=117,110,44,86            | -0.3 (± 0.049)               | -0.39 (±<br>0.051)            | -0.26 (±<br>0.065) | -0.61 (±<br>0.053) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in HAQ-DI - observed data

|   |  |
|---|--|
| End point title   | Change from baseline in HAQ-DI - observed data |
| End point description:  |  |
| <p>The HAQ-DI assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities. The stem of each item asks 'Over the past week, "are you able to..." perform a particular task'. Each item is scored on a 4 point scale from 0 - 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2) and unable to do (3). The disability index score is calculated as the mean of the available category scores, ranging from 0 to 3. A negative change from baseline indicates improvement. The HAQ-DI results from baseline up to week 52 were based on observed data, i.e. without imputation.</p> |  |
| End point type  | Secondary                                      |
| End point timeframe:  |  |
| baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52   |  |

| End point values                                   | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo              | Abatacept            |
|--|------------------------------|-------------------------------|----------------------|----------------------|
| Subject group type                                 | Reporting group              | Reporting group               | Reporting group      | Reporting group      |
| Number of subjects analysed                        | 138                          | 137                           | 138                  | 138                  |
| Units: score on a scale                            |                              |                               |                      |                      |
| arithmetic mean (standard deviation)               |                              |                               |                      |                      |
| wk1,n=132,129,130,129,39,35,21,22,9<br>5,17,17     | -0.225 (±<br>0.3766)         | -0.215 (±<br>0.4095)          | -0.101 (±<br>0.3186) | -0.194 (±<br>0.429)  |
| Wk2,n=131,130,134,133,39,36,23,22,1<br>33,98,17,18 | -0.215 (±<br>0.3877)         | -0.239 (±<br>0.4885)          | -0.191 (±<br>0.434)  | -0.254 (±<br>0.452)  |
| Wk4,n=133,133,131,130,39,39,23,21,9<br>4,17,19     | -0.299 (±<br>0.4551)         | -0.3 (±<br>0.5184)            | -0.214 (±<br>0.4492) | -0.368 (±<br>0.513)  |
| Wk8,n=132,127,131,130,39,39,23,22,9<br>4,17,19     | -0.277 (±<br>0.5062)         | -0.309 (±<br>0.5175)          | -0.217 (±<br>0.5457) | -0.463 (±<br>0.5182) |
| wk12,n=130,114,123,129,39,37,23,21,<br>94,17,18    | -0.287 (±<br>0.5384)         | -0.307 (±<br>0.5488)          | -0.241 (±<br>0.5152) | -0.508 (±<br>0.6369) |
| Wk16,n=127,118,116,129,36,37,21,22,<br>94,16,19    | -0.294 (±<br>0.5236)         | -0.355 (±<br>0.6217)          | -0.279 (±<br>0.5493) | -0.535 (±<br>0.6418) |
| Wk20,n=122,114,119,125,38,37,23,21,<br>90,16,19    | -0.333 (±<br>0.5111)         | -0.402 (±<br>0.6429)          | -0.319 (±<br>0.5637) | -0.583 (±<br>0.6654) |
| Wk24,n=117,110,117,120,38,36,21,22,<br>86,16,18    | -0.268 (±<br>0.493)          | -0.405 (±<br>0.5767)          | 0.346 (±<br>0.5941)  | -0.59 (±<br>0.6872)  |
| Wk28,n=115,102,na,na,33,35,21,21,86,<br>17,19      | -0.304 (±<br>0.5342)         | -0.439 (±<br>0.578)           | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk32,n=104,97,na,na,33,30,21,19,87,1<br>7,17       | -0.358 (±<br>0.4964)         | -0.505 (±<br>0.5759)          | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk36,n=102,93,na,na,30,30,21,19,84,1<br>8,16,      | -0.339 (±<br>0.5687)         | -0.43 (±<br>0.5573)           | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk40,n=96,89,na,na,28,28,21,19,84,15<br>,17        | -0.424 (±<br>0.5967)         | -0.44 (±<br>0.5416)           | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk44,n=97,90,na,na,28,27,20,18,84,15<br>,16        | -0.331 (±<br>0.5871)         | -0.449 (±<br>0.5427)          | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk48,n-<br>94,89,na,na,28,26,19,19,76,12,14        | -0.303 (±<br>0.5062)         | -0.483 (±<br>0.5459)          | 9999 (± 9999)        | 9999 (± 9999)        |
| Wk52,n=92,87,na,na,28,26,20,18,79,15<br>,15        | -0.341 (±<br>0.5428)         | -0.516 (±<br>0.6036)          | 9999 (± 9999)        | 9999 (± 9999)        |

| End point values                                   | Placebo non-<br>responder -<br>AIN457 75mg | Placebo non-<br>responder -<br>AIN457 150mg | Placebo<br>responder -<br>AIN457 75mg | Placebo<br>responder -<br>AIN457 150mg |
|--|--|---|---------------------------------------|--|
| Subject group type                                 | Subject analysis set                       | Subject analysis set                        | Subject analysis set                  | Subject analysis set                   |
| Number of subjects analysed                        | 39   | 39  | 23                                    | 22                                     |
| Units: score on a scale                            |  |   |                                       |  |
| arithmetic mean (standard deviation)               |  |   |                                       |  |
| wk1,n=132,129,130,129,39,35,21,22,9<br>5,17,17     | -0.119 (±<br>0.2896)                       | -0.079 (±<br>0.3093)                        | -0.125 (±<br>0.4257)                  | -0.153 (±<br>0.2468)                   |
| Wk2,n=131,130,134,133,39,36,23,22,1<br>33,98,17,18 | -0.122 (±<br>0.2605)                       | -0.176 (±<br>0.4631)                        | -0.38 (±<br>0.5063)                   | -0.25 (±<br>0.5015)                    |
| Wk4,n=133,133,131,130,39,39,23,21,9<br>4,17,19     | -0.077 (±<br>0.3634)                       | -0.224 (±<br>0.4968)                        | -0.364 (±<br>0.5627)                  | -0.31 (±<br>0.3103)                    |
| Wk8,n=132,127,131,130,39,39,23,22,9<br>4,17,19     | -0.186 (±<br>0.5097)                       | -0.128 (±<br>0.5077)                        | -0.543 (±<br>0.6313)                  | -0.176 (±<br>0.4782)                   |

|   |                   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|-------------------|
| wk12,n=130,114,123,129,39,37,23,21,94,17,18 | -0.109 (± 0.4783) | -0.179 (± 0.5133) | -0.451 (± 0.6167) | -0.381 (± 0.3982) |
| Wk16,n=127,118,116,129,36,37,21,22,94,16,19 | -0.167 (± 0.5295) | -0.111 (± 0.4591) | -0.565 (± 0.5356) | -0.472 (± 0.5988) |
| Wk20,n=122,114,119,125,38,37,23,21,90,16,19 | -0.237 (± 0.4756) | -0.179 (± 0.5158) | -0.543 (± 0.5325) | -0.47 (± 0.7309)  |
| Wk24,n=117,110,117,120,38,36,21,22,86,16,18 | -0.257 (± 0.473)  | -0.253 (± 0.6502) | -0.589 (± 0.5648) | -0.42 (± 0.6732)  |
| Wk28,n=115,102,na,na,33,35,21,21,86,17,19   | -0.345 (± 0.588)  | -0.336 (± 0.5846) | -0.625 (± 0.4809) | -0.601 (± 0.5571) |
| Wk32,n=104,97,na,na,33,30,21,19,87,17,17    | -0.284 (± 0.4627) | -0.3 (± 0.5039)   | -0.679 (± 0.5414) | -0.546 (± 0.5998) |
| Wk36,n=102,93,na,na,30,30,21,19,84,18,16,   | -0.368 (± 0.5397) | -0.383 (± 0.45)   | -0.607 (± 0.5538) | -0.474 (± 0.6032) |
| Wk40,n=96,89,na,na,28,28,21,19,84,15,17     | -0.522 (± 0.6805) | -0.391 (± 0.5446) | -0.571 (± 0.5736) | -0.539 (± 0.6998) |
| Wk44,n=97,90,na,na,28,27,20,18,84,15,16     | -0.277 (± 0.6377) | -0.523 (± 0.6587) | -0.638 (± 0.5144) | -0.514 (± 0.7752) |
| Wk48,n-94,89,na,na,28,26,19,19,76,12,14     | -0.348 (± 0.5886) | -0.413 (± 0.5698) | -0.605 (± 0.6113) | -0.454 (± 0.5547) |
| Wk52,n=92,87,na,na,28,26,20,18,79,15,15     | -0.402 (± 0.5436) | -0.351 (± 0.6335) | -0.606 (± 0.6492) | -0.569 (± 0.7126) |

| End point values                               | Abatacept responders | Abatacept non-responders - AIN457 75mg | Abatacept non-responders - AIN457 150mg |  |
|--|----------------------|--|---|--|
| Subject group type                             | Subject analysis set | Subject analysis set                   | Subject analysis set                    |  |
| Number of subjects analysed                    | 101                  | 18                                     | 19                                      |  |
| Units: score on a scale                        |                      |  |   |  |
| arithmetic mean (standard deviation)           |                      |  |   |  |
| wk1,n=132,129,130,129,39,35,21,22,95,17,17     | -0.232 (± 0.4551)    | -0.081 (± 0.3616)                      | -0.096 (± 0.3047)                       |  |
| Wk2,n=131,130,134,133,39,36,23,22,133,98,17,18 | -0.3 (± 0.4693)      | -0.132 (± 0.363)                       | -0.118 (± 0.3987)                       |  |
| Wk4,n=133,133,131,130,39,39,23,21,94,17,19     | -0.445 (± 0.5245)    | -0.11 (± 0.3505)                       | -0.217 (± 0.4874)                       |  |
| Wk8,n=132,127,131,130,39,39,23,22,94,17,19     | -0.543 (± 0.5289)    | -0.206 (± 0.49)                        | -0.303 (± 0.378)                        |  |
| wk12,n=130,114,123,129,39,37,23,21,94,17,18    | -0.622 (± 0.652)     | -0.221 (± 0.4274)                      | -0.181 (± 0.5376)                       |  |
| Wk16,n=127,118,116,129,36,37,21,22,94,16,19    | -0.66 (± 0.659)      | -0.195 (± 0.4281)                      | -0.204 (± 0.4827)                       |  |
| Wk20,n=122,114,119,125,38,37,23,21,90,16,19    | -0.699 (± 0.6849)    | -0.086 (± 0.3972)                      | -0.454 (± 0.5436)                       |  |
| Wk24,n=117,110,117,120,38,36,21,22,86,16,18    | -0.744 (± 0.6787)    | -0.18 (± 0.4257)                       | -0.215 (± 0.6443)                       |  |
| Wk28,n=115,102,na,na,33,35,21,21,86,17,19      | -0.689 (± 0.6428)    | -0.309 (± 0.5522)                      | -0.303 (± 0.5882)                       |  |
| Wk32,n=104,97,na,na,33,30,21,19,87,17,17       | -0.741 (± 0.6909)    | -0.228 (± 0.5612)                      | -0.375 (± 0.7315)                       |  |
| Wk36,n=102,93,na,na,30,30,21,19,84,18,16,      | -0.756 (± 0.6844)    | -0.285 (± 0.5891)                      | -0.43 (± 0.6723)                        |  |
| Wk40,n=96,89,na,na,28,28,21,19,84,15,17        | -0.763 (± 0.675)     | -0.242 (± 0.6312)                      | -0.39 (± 0.6523)                        |  |
| Wk44,n=97,90,na,na,28,27,20,18,84,15,16        | -0.781 (± 0.7252)    | -0.308 (± 0.6319)                      | -0.203 (± 0.7917)                       |  |
| Wk48,n-94,89,na,na,28,26,19,19,76,12,14        | -0.798 (± 0.6481)    | -0.229 (± 0.6546)                      | -0.286 (± 0.7618)                       |  |

|  |                   |                   |                   |  |
|--|-------------------|-------------------|-------------------|--|
| Wk52, n=92,87,na,na,28,26,20,18,79,15,15 | -0.788 (± 0.6853) | -0.392 (± 0.5216) | -0.258 (± 0.8298) |  |
|--|-------------------|-------------------|-------------------|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP) - using MMRM

|   |   |
|---|---|
| End point title   | Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP) - using MMRM |
| End point description:<br>The DAS28 is a measure of disease activity in RA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission. A negative change from baseline indicates improvement. |   |
| End point type  | Secondary   |
| End point timeframe:<br>baseline, weeks 1, 2, 4, 8, 12, 16, 20 and 24   |   |

| End point values                    | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|-------------------------------------|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                  | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed         | 138                          | 137                           | 138             | 39              |
| Units: score on a scale             |                              |                               |                 |                 |
| least squares mean (standard error) |                              |                               |                 |                 |
| week 1, n=131,129,130,129           | -0.89 (± 0.069)              | -0.73 (± 0.069)               | -0.22 (± 0.069) | -0.5 (± 0.069)  |
| week 2, n=131,127,132,133           | -0.96 (± 0.08)               | -0.9 (± 0.081)                | -0.35 (± 0.08)  | -0.78 (± 0.08)  |
| week 4, n=130,131,138,138           | -1.2 (± 0.09)                | -1.11 (± 0.09)                | -0.48 (± 0.09)  | -1.11 (± 0.091) |
| week 8, n=130,126,130,130           | -1.21 (± 0.093)              | -1.23 (± 0.094)               | -0.61 (± 0.093) | -1.55 (± 0.093) |
| week 12, n=130,114,123,128          | -1.23 (± 0.097)              | -1.36 (± 0.102)               | -0.73 (± 0.1)   | -1.78 (± 0.098) |
| week 16, n=126,116,114,127          | -1.23 (± 0.108)              | -1.4 (± 0.112)                | -0.57 (± 0.112) | -1.71 (± 0.108) |
| week 20, n=121,114,47,92            | -1.44 (± 0.108)              | -1.49 (± 0.111)               | -0.89 (± 0.146) | -1.96 (± 0.117) |
| week 24, n=116,108,44,84            | -1.47 (± 0.115)              | -1.47 (± 0.119)               | -1.02 (± 0.163) | -2.07 (± 0.128) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP) - observed data

|   |  |
|---|--|
| End point title   | Change from baseline in Disease Activity Score utilizing CRP (DAS28-CRP) - observed data |
| End point description:  |  |
| The DAS28 is a measure of disease activity in RA based on Swollen and Tender Joint Counts (out of a total of 28), hsCRP and the Patient's Global Assessment of Disease Activity. A DAS28 score greater than 5.1 implies active disease, equal to or less than 3.2 low disease activity, and less than 2.6 remission. A negative change from baseline indicates improvement. The DAS28-CRP results from baseline up to week 52 were based on observed data, i.e. without imputation. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52   |  |

| End point values                             | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo           | Abatacept         |
|--|------------------------------|-------------------------------|-------------------|-------------------|
| Subject group type                           | Reporting group              | Reporting group               | Reporting group   | Reporting group   |
| Number of subjects analysed                  | 138                          | 137                           | 138               | 138               |
| Units: score on a scale                      |                              |                               |                   |                   |
| arithmetic mean (standard deviation)         |                              |                               |                   |                   |
| Wk1,n=131,129,130,129,39,35,21,22,95,17,17   | -0.886 (± 0.9784)            | -0.759 (± 0.8654)             | -0.211 (± 0.6877) | -0.502 (± 0.7539) |
| Wk2,n=131,127,132,133,39,36,23,21,98,17,18   | -0.909 (± 1.0331)            | -0.9 (± 1.0284)               | -0.363 (± 0.8388) | -0.755 (± 0.9234) |
| Wk4,n=130,131,129,128,39,38,23,21,92,17,19   | -1.163 (± 1.1656)            | -1.15 (± 1.1942)              | -0.492 (± 0.8876) | -1.095 (± 1.0483) |
| Wk8,n=130,126,130,130,39,39,23,22,94,17,19   | -1.181 (± 1.1821)            | -1.283 (± 1.1678)             | -0.644 (± 1.1356) | -1.541 (± 1.1172) |
| Wk12,n=130,114,123,128,39,37,23,21,93,17,18  | -1.229 (± 1.1782)            | -1.402 (± 1.2182)             | -0.742 (± 1.233)  | -1.79 (± 1.2356)  |
| Wk16,n=126,116,114,128,36,36,21,21,94,15,19  | -1.225 (± 1.2866)            | -1.455 (± 1.3489)             | -0.592 (± 1.2557) | -1.691 (± 1.2979) |
| Wk20,n=121,114,,119,125,38,37,23,21,90,16,19 | -1.427 (± 1.3266)            | -1.569 (± 1.2361)             | -1.164 (± 1.2087) | -1.84 (± 1.4144)  |
| Wk24,n=116,108,116,117,37,36,21,22,84,15,18  | -1.467 (± 1.3116)            | -1.579 (± 1.3221)             | -1.248 (± 1.2915) | -1.989 (± 1.4717) |
| Wk28,n=115,103,na,na,33,35,21,21,86,17,18    | -1.484 (± 1.3216)            | -1.819 (± 1.3434)             | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk32,n=103,97,na,na,33,39,23,22,87,17,16     | -1.738 (± 1.2783)            | -1.966 (± 1.177)              | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk36,n=101,92,na,na,30,30,21,20,84,18,15     | -1.737 (± 1.4592)            | -1.82 (± 1.25)                | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk40,n=96,90,na,na,28,28,21,19,84,15,17      | -1.742 (± 1.3259)            | -1.788 (± 1.1333)             | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk44,n=96,88,na,na,28,27,20,18,84,15,16      | -1.764 (± 1.3227)            | -1.932 (± 1.285)              | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk48,n=94,88,na,na,28,26,18,19,76,12,14      | -1.761 (± 1.3152)            | -2.2 (± 1.3293)               | 9999 (± 9999)     | 9999 (± 9999)     |
| Wk52,n=92,86,na,na,28,26,20,18,79,15,15      | -1.839 (± 1.3755)            | -2.109 (± 1.4)                | 9999 (± 9999)     | 9999 (± 9999)     |

| End point values | Placebo non- | Placebo non- | Placebo | Placebo |
|------------------|--------------|--------------|---------|---------|
|------------------|--------------|--------------|---------|---------|

|  | responder -<br>AIN457 75mg | responder -<br>AIN457 150mg | responder -<br>AIN457 75mg | responder -<br>AIN457 150mg |
|--|----------------------------|-----------------------------|----------------------------|-----------------------------|
| Subject group type                           | Subject analysis set       | Subject analysis set        | Subject analysis set       | Subject analysis set        |
| Number of subjects analysed                  | 39                         | 39                          | 23                         | 22                          |
| Units: score on a scale                      |                            |                             |                            |                             |
| arithmetic mean (standard deviation)         |                            |                             |                            |                             |
| Wk1,n=131,129,130,129,39,35,21,22,95,17,17   | -0.147 (± 0.5527)          | -0.141 (± 0.7095)           | -0.572 (± 0.7856)          | -0.235 (± 0.7699)           |
| Wk2,n=131,127,132,133,39,36,23,21,98,17,18   | -0.191 (± 0.7331)          | -0.368 (± 0.717)            | -0.835 (± 0.9466)          | -0.292 (± 0.7448)           |
| Wk4,n=130,131,129,128,39,38,23,21,92,17,19   | -0.252 (± 0.8116)          | -0.352 (± 0.7471)           | -1.034 (± 0.9119)          | -0.767 (± 0.9661)           |
| Wk8,n=130,126,130,130,39,39,23,22,94,17,19   | -0.546 (± 1.1597)          | -0.312 (± 0.9151)           | -1.403 (± 1.206)           | -0.613 (± 0.9772)           |
| Wk12,n=130,114,123,128,39,37,23,21,93,17,18  | -0.311 (± 0.9514)          | -0.383 (± 1.1765)           | -1.588 (± 0.9714)          | -1.33 (± 1.4721)            |
| Wk16,n=126,116,114,128,36,36,21,21,94,15,19  | 0.128 (± 0.8579)           | 0.045 (± 0.9145)            | -2.008 (± 0.8675)          | -1.503 (± 0.8746)           |
| Wk20,n=121,114,,119,125,38,37,23,21,90,16,19 | -0.683 (± 1.1231)          | -0.937 (± 1.0966)           | -2.108 (± 1.0368)          | -1.399 (± 1.1487)           |
| Wk24,n=116,108,116,117,37,36,21,22,84,15,18  | -0.666 (± 0.9983)          | -1.14 (± 1.1954)            | -2.343 (± 1.2649)          | -1.362 (± 1.2999)           |
| Wk28,n=115,103,na,na,33,35,21,21,86,17,18    | -1.172 (± 1.1602)          | -1.244 (± 1.2433)           | -2.117 (± 0.8573)          | -1.782 (± 1.0655)           |
| Wk32,n=103,97,na,na,33,39,23,22,87,17,16     | -1.408 (± 1.3855)          | -1.475 (± 1.1846)           | -2.363 (± 1.0711)          | -1.875 (± 0.9807)           |
| Wk36,n=101,92,na,na,30,30,21,20,84,18,15     | -1.271 (± 1.4949)          | -1.444 (± 1.1949)           | -2.269 (± 1.0688)          | -1.784 (± 0.9029)           |
| Wk40,n=96,90,na,na,28,28,21,19,84,15,17      | -1.354 (± 1.359)           | -1.494 (± 1.3243)           | -2.315 (± 1.0773)          | -2.134 (± 1.0405)           |
| Wk44,n=96,88,na,na,28,27,20,18,84,15,16      | -1.168 (± 1.2638)          | -1.858 (± 1.2373)           | -2.155 (± 0.9488)          | -2.121 (± 1.1347)           |
| Wk48,n=94,88,na,na,28,26,18,19,76,12,14      | -1.516 (± 1.0635)          | -1.66 (± 1.1805)            | -2.259 (± 1.1813)          | -1.964 (± 1.3404)           |
| Wk52,n=92,86,na,na,28,26,20,18,79,15,15      | -1.487 (± 1.0729)          | -1.69 (± 1.2093)            | -2.07 (± 0.9984)           | -2.334 (± 1.1428)           |

| End point values                            | Abatacept<br>responders | Abatacept non-<br>responders -<br>AIN457 75mg | Abatacept non-<br>responders -<br>AIN457 150mg |  |
|---|-------------------------|---|--|--|
| Subject group type                          | Subject analysis set    | Subject analysis set                          | Subject analysis set                           |  |
| Number of subjects analysed                 | 101                     | 18  | 19   |  |
| Units: score on a scale                     |                         |   |  |  |
| arithmetic mean (standard deviation)        |                         |   |  |  |
| Wk1,n=131,129,130,129,39,35,21,22,95,17,17  | -0.577 (± 0.7924)       | -0.361 (± 0.3578)                             | -0.222 (± 0.7695)                              |  |
| Wk2,n=131,127,132,133,39,36,23,21,98,17,18  | -0.755 (± 0.9234)       | -0.882 (± 0.9526)                             | -0.359 (± 0.898)                               |  |
| Wk4,n=130,131,129,128,39,38,23,21,92,17,19  | -1.268 (± 1.0533)       | -0.595 (± 1.116)                              | -0.706 (± 0.6999)                              |  |
| Wk8,n=130,126,130,130,39,39,23,22,94,17,19  | -1.816 (± 1.0708)       | -0.834 (± 1.1469)                             | -0.808 (± 0.6444)                              |  |
| Wk12,n=130,114,123,128,39,37,23,21,93,17,18 | -2.144 (± 1.1028)       | -0.749 (± 1.0757)                             | -0.945 (± 1.1008)                              |  |
| Wk16,n=126,116,114,128,36,36,21,21,94,15,19 | -2.159 (± 1.0767)       | -0.49 (± 0.817)                               | -0.322 (± 1.0262)                              |  |

|  |                   |                   |                   |  |
|--|-------------------|-------------------|-------------------|--|
| Wk20,n=121,114,,119,125,38,37,23,21,90,16,19 | -2.317 (± 1.2549) | -0.402 (± 0.982)  | -0.792 (± 1.0272) |  |
| Wk24,n=116,108,116,117,37,36,21,22,84,15,18  | -2.435 (± 1.3266) | -0.772 (± 1.1656) | -0.923 (± 1.256)  |  |
| Wk28,n=115,103,na,na,33,35,21,21,86,17,18    | -2.47 (± 1.2153)  | -1.137 (± 1.205)  | -0.973 (± 1.1034) |  |
| Wk32,n=103,97,na,na,33,39,23,22,87,17,16     | -2.629 (± 1.3104) | -0.961 (± 1.0043) | -1.464 (± 1.2025) |  |
| Wk36,n=101,92,na,na,30,30,21,20,84,18,15     | -2.642 (± 1.4305) | -1.2 (± 1.3228)   | -1.425 (± 0.9247) |  |
| Wk40,n=96,90,na,na,28,28,21,19,84,15,17      | -2.549 (± 1.3305) | -1.201 (± 1.5293) | -1.612 (± 1.1839) |  |
| Wk44,n=96,88,na,na,28,27,20,18,84,15,16      | -2.697 (± 1.2117) | -0.881 (± 1.3337) | -1.528 (± 1.2973) |  |
| Wk48,n=94,88,na,na,28,26,18,19,76,12,14      | -2.634 (± 1.2189) | -1.013 (± 1.1738) | -1.4 (± 1.1985)   |  |
| Wk52,n=92,86,na,na,28,26,20,18,79,15,15      | -2.676 (± 1.3593) | -1.39 (± 1.1884)  | -0.982 (± 1.1943) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in hsCRP - observed data

|  |   |
|--|---|
| End point title  | Change from baseline in hsCRP - observed data |
| End point description:   |   |
| Blood samples were obtained to identify the presence of inflammation, to determine its severity and to monitor response to treatment. A negative change from baseline indicates improvement. The hsCRP results from baseline up to week 52 were based on observed data, i.e. without imputation. |   |
| End point type   | Secondary                                     |
| End point timeframe:   |   |
| baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52   |   |

| End point values                            | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo          | Abatacept        |
|---|------------------------------|-------------------------------|------------------|------------------|
| Subject group type                          | Reporting group              | Reporting group               | Reporting group  | Reporting group  |
| Number of subjects analysed                 | 138                          | 137                           | 138              | 138              |
| Units: mg/L                                 |                              |                               |                  |                  |
| arithmetic mean (standard deviation)        |                              |                               |                  |                  |
| Wk1,n=134,130,131,131,39,36,21,22,97,17,17  | -10.91 (± 30.815)            | -10.31 (± 27.754)             | -0.69 (± 15.521) | -5.64 (± 18.55)  |
| Wk2,n=133,129,133,135,39,36,23,21,100,17,18 | -10.24 (± 33.209)            | -11.51 (± 32.139)             | -2.21 (± 14.501) | -6.36 (± 19.416) |
| Wk4,n=131,134,129,133,39,38,23,21,97,17,19  | -9.1 (± 20.514)              | -10.76 (± 33.376)             | -1.53 (± 19.311) | -6.7 (± 20.732)  |
| Wk8,n=134,128,130,132,39,39,23,22,96,17,19  | -10.18 (± 33.4)              | -12.94 (± 30.854)             | -2.94 (± 20.601) | -8.48 (± 21.134) |
| Wk12,n=133,119,128,131,39,39,23,22,96,17,18 | -9.41 (± 31.859)             | -9.66 (± 24.298)              | -0.69 (± 18.908) | -9.72 (± 25.787) |
| Wk16,n=129,120,121,131,36,38,21,21,96,16,19 | -9.97 (± 33.291)             | -5.78 (± 25.418)              | -1.82 (± 20.849) | -8.37 (± 22.571) |

|   |                  |                  |                  |                  |
|---|------------------|------------------|------------------|------------------|
| Wk20,n=124,116,120,127,38,37,23,21,91,17,19 | -9.19 (± 32.876) | -8.05 (± 22.394) | -3.75 (± 29.301) | -9.43 (± 23.212) |
| Wk24,n=121,113,116,120,37,36,21,22,86,16,18 | -6.9 (± 22.098)  | -4.92 (± 23.075) | -6.88 (± 21.014) | -8.66 (± 21.574) |
| Wk28,n=119,110,na,na,34,35,21,21,89,17,18   | -4.94 (± 23.155) | -5.87 (± 25.885) | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk32,n=107,101,na,na,34,32,20,21,87,17,16   | -8.57 (± 20.826) | 7.37 (± 24.564)  | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk36,n=107,98,na,na,32,31,21,20,85,18,15    | -6.6 (± 25.895)  | -6.36 (± 22.571) | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk40,n=101,96,na,na,29,29,22,20,86,15,17    | -8.74 (± 22.257) | -7.09 (± 24.325) | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk44,n=97,92,na,na,,28,28,20,19,85,15,16    | -6.59 (± 20.975) | -7.25 (± 24.681) | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk48,n=97,91,na,na,28,29,20,19,79,13,14     | -6.19 (± 18.912) | -7.63 (± 21.682) | 9999 (± 9999)    | 9999 (± 9999)    |
| Wk52,n=95,92,na,na,29,28,20,18,83,16,16     | -6.68 (± 26.24)  | -8.14 (± 22.149) | 9999 (± 9999)    | 9999 (± 9999)    |

| End point values                            | Placebo non-responder - AIN457 75mg | Placebo non-responder - AIN457 150mg | Placebo responder - AIN457 75mg | Placebo responder - AIN457 150mg |
|---|-------------------------------------|--------------------------------------|---------------------------------|----------------------------------|
| Subject group type                          | Subject analysis set                | Subject analysis set                 | Subject analysis set            | Subject analysis set             |
| Number of subjects analysed                 | 39                                  | 39                                   | 23                              | 22                               |
| Units: mg/L                                 |                                     |                                      |                                 |                                  |
| arithmetic mean (standard deviation)        |                                     |                                      |                                 |                                  |
| Wk1,n=134,130,131,131,39,36,21,22,97,17,17  | -0.33 (± 10.43)                     | -0.84 (± 24.777)                     | -0.4 (± 12.244)                 | -1.5 (± 7.541)                   |
| Wk2,n=133,129,133,135,39,36,23,21,100,17,18 | 0.43 (± 15.333)                     | -5.48 (± 17.301)                     | -1.7 (± 11.17)                  | -4.78 (± 10.515)                 |
| Wk4,n=131,134,129,133,39,38,23,21,97,17,19  | 2.23 (± 23.317)                     | -1.94 (± 21.927)                     | -6.47 (± 12.458)                | -1.95 (± 12.09)                  |
| Wk8,n=134,128,130,132,39,39,23,22,96,17,19  | -4.72 (± 18.766)                    | -3.28 (± 25.501)                     | 0.13 (± 18.061)                 | -1.5 (± 12.839)                  |
| Wk12,n=133,119,128,131,39,39,23,22,96,17,18 | 2.11 (± 18.312)                     | -2.89 (± 20.763)                     | -2.74 (± 12.899)                | 2.1 (± 22.545)                   |
| Wk16,n=129,120,121,131,36,38,21,21,96,16,19 | 3.92 (± 23.403)                     | -2.13 (± 24.422)                     | -5.67 (± 9.583)                 | -4.29 (± 13.497)                 |
| Wk20,n=124,116,120,127,38,37,23,21,91,17,19 | -5.33 (± 20.645)                    | -7.77 (± 27.581)                     | 3.23 (± 48.634)                 | -1.06 (± 15.737)                 |
| Wk24,n=121,113,116,120,37,36,21,22,86,16,18 | -7.06 (± 20.298)                    | -11.46 (± 26.373)                    | -6.4 (± 11.562)                 | 0.45 (± 18.244)                  |
| Wk28,n=119,110,na,na,34,35,21,21,89,17,18   | -4.43 (± 21.777)                    | -11.1 (± 27.186)                     | -7.97 (± 18.018)                | 0.09 (± 24.933)                  |
| Wk32,n=107,101,na,na,34,32,20,21,87,17,16   | -4.34 (± 23.742)                    | -9.08 (± 25.867)                     | -5.02 (± 10.3)                  | -5.51 (± 14.279)                 |
| Wk36,n=107,98,na,na,32,31,21,20,85,18,15    | -4.21 (± 27.424)                    | -2.35 (± 37.226)                     | -2.73 (± 21.272)                | -6.78 (± 13.94)                  |
| Wk40,n=101,96,na,na,29,29,22,20,86,15,17    | -7.07 (± 26.156)                    | 2.39 (± 32.966)                      | -4.46 (± 22.808)                | -4.73 (± 13.502)                 |
| Wk44,n=97,92,na,na,,28,28,20,19,85,15,16    | -6.66 (± 23.396)                    | -8.53 (± 19.97)                      | -6.5 (± 19.968)                 | -7.27 (± 13.887)                 |
| Wk48,n=97,91,na,na,28,29,20,19,79,13,14     | -10.49 (± 25.564)                   | -4.76 (± 15.784)                     | -1.43 (± 33.122)                | -6.97 (± 13.68)                  |
| Wk52,n=95,92,na,na,29,28,20,18,83,16,16     | -4.63 (± 25.795)                    | -4.79 (± 22.882)                     | 2.95 (± 9.88)                   | -4.88 (± 11.707)                 |

| End point values                            | Abatacept responders | Abatacept non-responders - AIN457 75mg | Abatacept non-responders - AIN457 150mg |  |
|---|----------------------|--|---|--|
| Subject group type                          | Subject analysis set | Subject analysis set                   | Subject analysis set                    |  |
| Number of subjects analysed                 | 101                  | 18                                     | 19                                      |  |
| Units: mg/L                                 |                      |  |   |  |
| arithmetic mean (standard deviation)        |                      |  |   |  |
| Wk1,n=134,130,131,131,39,36,21,22,97,17,17  | -6.4 (± 20.458)      | -2.92 (± 12.405)                       | -4.07 (± 10.811)                        |  |
| Wk2,n=133,129,133,135,39,36,23,21,100,17,18 | -7.52 (± 20.301)     | -3.84 (± 13.737)                       | -2.3 (± 19.035)                         |  |
| Wk4,n=131,134,129,133,39,38,23,21,97,17,19  | -7.53 (± 22.982)     | -4.42 (± 14.991)                       | -4.5 (± 11.029)                         |  |
| Wk8,n=134,128,130,132,39,39,23,22,96,17,19  | -10.13 (± 22.724)    | -0.54 (± 14.849)                       | -4.59 (± 16.603)                        |  |
| Wk12,n=133,119,128,131,39,39,23,22,96,17,18 | -12.17 (± 25.813)    | -4.18 (± 16.024)                       | -1.94 (± 31.483)                        |  |
| Wk16,n=129,120,121,131,36,38,21,21,96,16,19 | -11.25 (± 23.692)    | -1.41 (± 8.81)                         | 0.32 (± 22.024)                         |  |
| Wk20,n=124,116,120,127,38,37,23,21,91,17,19 | -11.59 (± 24.271)    | -3.94 (± 15.716)                       | -3.99 (± 32.871)                        |  |
| Wk24,n=121,113,116,120,37,36,21,22,86,16,18 | -11.72 (± 22.198)    | -4.94 (± 13.605)                       | 2.63 (± 20.875)                         |  |
| Wk28,n=119,110,na,na,34,35,21,21,89,17,18   | -12.08 (± 22.791)    | -4.51 (± 14.144)                       | -1.7 (± 22.671)                         |  |
| Wk32,n=107,101,na,na,34,32,20,21,87,17,16   | -12.83 (± 23.33)     | -4.26 (± 15.329)                       | -7.14 (± 17.446)                        |  |
| Wk36,n=107,98,na,na,32,31,21,20,85,18,15    | -12.19 (± 24.535)    | -4.38 (± 14.479)                       | -0.47 (± 27.932)                        |  |
| Wk40,n=101,96,na,na,29,29,22,20,86,15,17    | -12.63 (± 23.788)    | -2.75 (± 17.297)                       | -7.95 (± 18.343)                        |  |
| Wk44,n=97,92,na,na,,28,28,20,19,85,15,16    | -12.32 (± 25.47)     | -1.33 (± 4.846)                        | -3.69 (± 24.389)                        |  |
| Wk48,n=97,91,na,na,28,29,20,19,79,13,14     | -13.9 (± 25.636)     | -3.5 (± 21.343)                        | -4.48 (± 16.918)                        |  |
| Wk52,n=95,92,na,na,29,28,20,18,83,16,16     | -11.19 (± 27.768)    | -6.73 (± 14.972)                       | -5.78 (± 18.534)                        |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Erythrocyte Sedimentation Rate (ESR) - observed data

|   |  |
|---|--|
| End point title   | Change from baseline in Erythrocyte Sedimentation Rate (ESR) - observed data |
| End point description:  |  |
| Blood samples were obtained to monitor disease activity and response to treatment. A negative change from baseline indicates improvement. The ESR results from baseline up to week 52 were based on observed data, i.e. without imputation. |  |
| End point type  | Secondary  |

End point timeframe:

baseline, weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

| End point values                                | AIN457<br>10mg/kg - 75<br>mg | AIN457<br>10mg/kg - 150<br>mg | Placebo         | Abatacept       |
|---|------------------------------|-------------------------------|-----------------|-----------------|
| Subject group type                              | Reporting group              | Reporting group               | Reporting group | Reporting group |
| Number of subjects analysed                     | 138                          | 137                           | 138             | 138             |
| Units: mm/hr                                    |                              |                               |                 |                 |
| arithmetic mean (standard deviation)            |                              |                               |                 |                 |
| Wk1,n=133,130,131,131,39,36,21,22,9<br>7,17,17, | -7.5 (± 18.74)               | -8.4 (± 19.2)                 | -5.7 (± 15.68)  | -9.5 (± 16.55)  |
| Wk2,n=133,130,135,134,39,36,23,22,9<br>9,17,18  | -12.2 (± 19.06)              | -10.5 (± 19.05)               | -5.7 (± 18.22)  | -11 (± 19.5)    |
| Wk4,n=133,135,131,133,39,39,23,21,9<br>7,17,19  | -12.7 (± 22.23)              | -12.1 (± 21.88)               | -6 (± 18.9)     | -12.6 (± 18.14) |
| Wk8,n=133,129,131,132,39,39,23,22,9<br>6,17,19  | -15.4 (± 20.38)              | -15.7 (± 21.62)               | -6.4 (± 22.72)  | -17.6 (± 20.89) |
| Wk12,n=133,118,127,131,39,39,23,21,<br>96,17,18 | -14.7 (± 20.08)              | -18.4 (± 21.18)               | -5.8 (± 21.02)  | -19.4 (± 20.97) |
| Wk16,n=129,121,122,130,36,38,21,22,<br>95,16,19 | -16.2 (± 21.22)              | -15.6 (± 19.09)               | -6.5 (± 23.48)  | -18.5 (± 24.32) |
| Wk20,n=123,116,120,127,38,37,23,21,<br>91,17,19 | -16.3 (± 20.9)               | -17.7 (± 19.9)                | -9.1 (± 26.29)  | -21.1 (± 23.66) |
| Wk24,n=122,113,117,123,38,36,21,22,<br>88,17,18 | -13.9 (± 23.65)              | -16 (± 20.2)                  | -12 (± 24.31)   | -19.6 (± 24.52) |
| Wk28,n=119,110,na,na,34,35,21,21,89,<br>17,19   | -15.4 (± 22.95)              | -16.8 (± 23.05)               | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk32,n=108,101,na,na,34,32,21,21,88,<br>17,16   | -18.3 (± 23.51)              | -17.4 (± 21.57)               | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk36,n=107,98,na,na,32,31,21,20,87,1<br>8,16    | -16.6 (± 25.2)               | -18.4 (± 21.51)               | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk40,n=101,96,na,na,29,29,22,20,85,1<br>5,17    | -18.1 (± 21.06)              | -17.3 (± 21.05)               | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk44,n=98,93,na,na,28,28,20,19,85,15<br>,16     | -18 (± 21.08)                | -16.7 (± 23.87)               | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk48,n=97,92,na,na,28,30,20,19,79,13<br>,14     | -17.8 (± 23.11)              | -19.8 (± 20.3)                | 9999 (± 9999)   | 9999 (± 9999)   |
| Wk52,n=94,91,na,na,29,28,20,18,83,16<br>,16     | -17.7 (± 21.08)              | -20.6 (± 23.48)               | 9999 (± 9999)   | 9999 (± 9999)   |

| End point values                                | Placebo non-<br>responder -<br>AIN457 75mg | Placebo non-<br>responder -<br>AIN457 150mg | Placebo<br>responder -<br>AIN457 75mg | Placebo<br>responder -<br>AIN457 150mg |
|---|--|---|---------------------------------------|--|
| Subject group type                              | Subject analysis set                       | Subject analysis set                        | Subject analysis set                  | Subject analysis set                   |
| Number of subjects analysed                     | 39   | 39  | 23                                    | 22                                     |
| Units: mm/hr                                    |  |   |                                       |  |
| arithmetic mean (standard deviation)            |  |   |                                       |  |
| Wk1,n=133,130,131,131,39,36,21,22,9<br>7,17,17, | -8.4 (± 12.65)                             | -1.1 (± 18.88)                              | -5.7 (± 14.97)                        | -7.1 (± 13.22)                         |
| Wk2,n=133,130,135,134,39,36,23,22,9<br>9,17,18  | -4 (± 12.69)                               | -5.6 (± 26.44)                              | -9.7 (± 17.86)                        | -6.6 (± 14.44)                         |

|   |                    |                    |                    |                    |
|---|--------------------|--------------------|--------------------|--------------------|
| Wk4,n=133,135,131,133,39,39,23,21,9<br>7,17,19  | -3.7 (± 14.35)     | -3.8 (± 20.5)      | -9.3 (± 13.81)     | -8.2 (± 23.89)     |
| Wk8,n=133,129,131,132,39,39,23,22,9<br>6,17,19  | -9.4 (± 19.24)     | -0.9 (± 27.25)     | -8.2 (± 24.09)     | -8.3 (± 14.29)     |
| Wk12,n=133,118,127,131,39,39,23,21,<br>96,17,18 | -5.9 (± 17.96)     | -1.5 (± 25.62)     | -11.2 (±<br>18.06) | -5.5 (± 20.06)     |
| Wk16,n=129,121,122,130,36,38,21,22,<br>95,16,19 | -3.1 (± 19.21)     | -1.1 (± 25.47)     | -17.6 (±<br>23.03) | -4.9 (± 20.54)     |
| Wk20,n=123,116,120,127,38,37,23,21,<br>91,17,19 | -21.1 (±<br>23.66) | -10.5 (±<br>20.08) | -7.4 (± 29.4)      | -11.6 (±<br>34.23) |
| Wk24,n=122,113,117,123,38,36,21,22,<br>88,17,18 | -10.8 (±<br>20.33) | -14.7 (±<br>27.77) | -16.1 (±<br>21.57) | -5.5 (± 27.07)     |
| Wk28,n=119,110,na,na,34,35,21,21,89,<br>17,19   | -17.9 (±<br>24.87) | -12.5 (±<br>30.87) | -12.3 (± 24.1)     | -14.6 (±<br>17.31) |
| Wk32,n=108,101,na,na,34,32,21,21,88,<br>17,16   | -17.2 (± 16.7)     | -12.8 (±<br>26.21) | -16.8 (±<br>24.37) | -14.1 (±<br>20.72) |
| Wk36,n=107,98,na,na,32,31,21,20,87,1<br>8,16    | -17.8 (±<br>21.72) | -13.4 (±<br>29.49) | -17.3 (±<br>22.02) | -16.5 (±<br>17.95) |
| Wk40,n=101,96,na,na,29,29,22,20,85,1<br>5,17    | -20.6 (±<br>19.66) | -12.3 (±<br>26.37) | -13.3 (±<br>18.78) | -16.4 (±<br>21.79) |
| Wk44,n=98,93,na,na,28,28,20,19,85,15<br>,16     | -20.1 (±<br>17.61) | -16 (± 25.3)       | -12 (± 29.2)       | -19.2 (±<br>22.57) |
| Wk48,n=97,92,na,na,28,30,20,19,79,13<br>,14     | -20.8 (±<br>18.26) | -7.2 (± 22.58)     | -12.2 (±<br>29.55) | -19.4 (±<br>20.58) |
| Wk52,n=94,91,na,na,29,28,20,18,83,16<br>,16     | -14.9 (±<br>20.53) | -15.1 (± 21.5)     | -14.4 (±<br>24.54) | -13.6 (±<br>27.16) |

| End point values                                | Abatacept<br>responders | Abatacept non-<br>responders -<br>AIN457 75mg | Abatacept non-<br>responders -<br>AIN457 150mg |  |
|---|-------------------------|---|--|--|
| Subject group type                              | Subject analysis set    | Subject analysis set                          | Subject analysis set                           |  |
| Number of subjects analysed                     | 101                     | 18  | 19   |  |
| Units: mm/hr                                    |                         |   |  |  |
| arithmetic mean (standard deviation)            |                         |   |  |  |
| Wk1,n=133,130,131,131,39,36,21,22,9<br>7,17,17, | -10.2 (±<br>17.11)      | -7.7 (± 13.9)                                 | -7.2 (± 16.3)                                  |  |
| Wk2,n=133,130,135,134,39,36,23,22,9<br>9,17,18  | -10.2 (±<br>20.33)      | -12.5 (±<br>16.71)                            | -13.6 (±<br>17.78)                             |  |
| Wk4,n=133,135,131,133,39,39,23,21,9<br>7,17,19  | -12.3 (±<br>18.66)      | -15.8 (±<br>17.49)                            | -11.3 (±<br>16.46)                             |  |
| Wk8,n=133,129,131,132,39,39,23,22,9<br>6,17,19  | -18.3 (±<br>21.56)      | -13.9 (±<br>23.29)                            | -17.6 (±<br>15.03)                             |  |
| Wk12,n=133,118,127,131,39,39,23,21,<br>96,17,18 | -19.9 (±<br>21.08)      | -18.4 (±<br>23.07)                            | -17.9 (±<br>19.31)                             |  |
| Wk16,n=129,121,122,130,36,38,21,22,<br>95,16,19 | -21.1 (±<br>24.73)      | -14.9 (±<br>17.78)                            | -8.8 (± 25.22)                                 |  |
| Wk20,n=123,116,120,127,38,37,23,21,<br>91,17,19 | -7 (± 22.32)            | -22 (± 23.6)                                  | -20.5 (±<br>22.81)                             |  |
| Wk24,n=122,113,117,123,38,36,21,22,<br>88,17,18 | -21.1 (±<br>24.62)      | -20.7 (±<br>20.65)                            | -11.4 (±<br>26.96)                             |  |
| Wk28,n=119,110,na,na,34,35,21,21,89,<br>17,19   | -22.4 (± 22.9)          | -26.1 (±<br>19.83)                            | -17.4 (±<br>24.77)                             |  |
| Wk32,n=108,101,na,na,34,32,21,21,88,<br>17,16   | -25.5 (±<br>24.89)      | -25.7 (±<br>21.14)                            | -23.1 (±<br>21.46)                             |  |
| Wk36,n=107,98,na,na,32,31,21,20,87,1<br>8,16    | -21.7 (± 25.4)          | -26 (± 21.21)                                 | -16.6 (±<br>23.31)                             |  |
| Wk40,n=101,96,na,na,29,29,22,20,85,1<br>5,17    | -22.2 (±<br>26.24)      | -23.8 (±<br>22.96)                            | -22.9 (±<br>15.57)                             |  |

|   |                 |                 |                 |  |
|---|-----------------|-----------------|-----------------|--|
| Wk44,n=98,93,na,na,28,28,20,19,85,15,16 | -24.9 (± 25.66) | -22.3 (± 23.36) | -18.5 (± 21)    |  |
| Wk48,n=97,92,na,na,28,30,20,19,79,13,14 | -23.9 (± 25.56) | -18.9 (± 26.41) | -20.2 (± 18.16) |  |
| Wk52,n=94,91,na,na,29,28,20,18,83,16,16 | -25.2 (± 27.88) | -27.4 (± 22.71) | -15.4 (± 22.53) |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Any AIN457 75 mg |
|-----------------------|------------------|

Reporting group description:

Any AIN457 75mg included patients who originally were randomized to this treatment and placebo/abatacept-switchers to this dose.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Any AIN457 150 mg |
|-----------------------|-------------------|

Reporting group description:

Any AIN457 150mg included patients who originally were randomized to this treatment and placebo/abatacept-switchers to this dose.

|                       |            |
|-----------------------|------------|
| Reporting group title | Any AIN457 |
|-----------------------|------------|

Reporting group description:

Any AIN457 included patients who originally were randomized to AIN457 75 mg or AIN457 150mg and placebo/abatacept-switchers to this dose.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Abatacept |
|-----------------------|-----------|

Reporting group description:

Abatacept

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events  | Any AIN457 75 mg  | Any AIN457 150 mg | Any AIN457        |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed   | 30 / 218 (13.76%) | 28 / 215 (13.02%) | 58 / 433 (13.39%) |
| number of deaths (all causes)                                       | 3                 | 1                 | 4                 |
| number of deaths resulting from adverse events                      | 0                 | 0                 | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Breast cancer   |                   |                   |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                 | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Fibroadenoma of breast</b>                               |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Lipoma</b>   |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Papillary thyroid cancer</b>                             |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 1           | 1 / 2           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Squamous cell carcinoma</b>                              |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Vascular disorders</b>                                   |                 |                 |                 |
| <b>Venous thrombosis limb</b>                               |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>General disorders and administration site conditions</b> |                 |                 |                 |
| <b>Cyst</b>   |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Death</b>  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                  | 0 / 1           | 0 / 0           | 0 / 1           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Device dislocation                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| General physical health deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Cystocele                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metrorrhagia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectocele                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute pulmonary oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Pulmonary hypertension                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Psychiatric disorders                           |                 |                 |                 |
| Delirium  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Contusion                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Laceration                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar vertebral fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Procedural headache                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 218 (0.92%) | 0 / 215 (0.00%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 2           |
| Mitral valve incompetence                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinus tachycardia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Cerebral ischaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrospinal fluid leakage                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Formication                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar radiculopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningorrhagia                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Perineurial cyst                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 218 (0.92%) | 1 / 215 (0.47%) | 3 / 433 (0.69%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vertebrobasilar insufficiency                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Sudden hearing loss                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Cataract  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Umbilical hernia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal polyp                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Bile duct stone                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic steatosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Liver disorder                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Angioedema                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rash  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Acquired claw toe                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Back pain                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 218 (0.92%) | 1 / 215 (0.47%) | 3 / 433 (0.69%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bursitis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot deformity                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 2 / 215 (0.93%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc disorder                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 2 / 215 (0.93%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 218 (1.83%) | 2 / 215 (0.93%) | 6 / 433 (1.39%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 2           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoporotic fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rheumatoid arthritis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 2 / 215 (0.93%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Cellulitis                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye abscess                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Escherichia urinary tract infection             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 1 / 215 (0.47%) | 2 / 433 (0.46%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis salmonella                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| H1N1 influenza                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster oticus                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint abscess                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningitis bacterial                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia influenzal                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 218 (0.00%) | 0 / 215 (0.00%) | 0 / 433 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 218 (0.46%) | 0 / 215 (0.00%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tooth abscess                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 218 (0.00%) | 1 / 215 (0.47%) | 1 / 433 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                       | Abatacept       | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events                   |                 |                 |  |
| subjects affected / exposed   | 9 / 137 (6.57%) | 7 / 139 (5.04%) |  |
| number of deaths (all causes)                                       | 0               | 0               |  |
| number of deaths resulting from adverse events                      | 0               | 0               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Breast cancer   |                 |                 |  |
| subjects affected / exposed   | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Fibroadenoma of breast  |                 |                 |  |
| subjects affected / exposed   | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Lipoma  |                 |                 |  |
| subjects affected / exposed   | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Papillary thyroid cancer  |                 |                 |  |
| subjects affected / exposed   | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma   |                 |                 |  |
| subjects affected / exposed   | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           |  |
| Vascular disorders  |                 |                 |  |
| Venous thrombosis limb  |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Cyst   |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Device dislocation                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| Cystocele  |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Metrorrhagia   |                 |                 |  |
| subjects affected / exposed                          | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Rectocele  |                 |                 |  |
| subjects affected / exposed                          | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Delirium  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laceration                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar vertebral fracture                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural headache                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Palpitations                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrospinal fluid leakage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Formication                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar radiculopathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningorrhagia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perineurial cyst                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vertebrobasilar insufficiency                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Sudden hearing loss                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colitis ischaemic                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal polyp                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stone                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic steatosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Angioedema                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| disorders                                       |                 |                 |  |
| Acquired claw toe                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot deformity                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoporotic fracture                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rheumatoid arthritis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye abscess                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis salmonella                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 1 / 139 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| H1N1 influenza                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster oticus                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis bacterial                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia influenzal                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 137 (0.73%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 137 (0.00%) | 0 / 139 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Any AIN457 75 mg   | Any AIN457 150 mg  | Any AIN457         |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 110 / 218 (50.46%) | 114 / 215 (53.02%) | 224 / 433 (51.73%) |
| Vascular disorders                                    |                    |                    |                    |
| Hypertension  |                    |                    |                    |
| subjects affected / exposed                           | 20 / 218 (9.17%)   | 10 / 215 (4.65%)   | 30 / 433 (6.93%)   |
| occurrences (all)                                     | 25                 | 10                 | 35                 |
| Nervous system disorders                              |                    |                    |                    |
| Headache  |                    |                    |                    |
| subjects affected / exposed                           | 18 / 218 (8.26%)   | 11 / 215 (5.12%)   | 29 / 433 (6.70%)   |
| occurrences (all)                                     | 23                 | 12                 | 35                 |
| Blood and lymphatic system disorders                  |                    |                    |                    |
| Anaemia   |                    |                    |                    |
| subjects affected / exposed                           | 10 / 218 (4.59%)   | 10 / 215 (4.65%)   | 20 / 433 (4.62%)   |
| occurrences (all)                                     | 12                 | 10                 | 22                 |
| Gastrointestinal disorders                            |                    |                    |                    |
| Diarrhoea   |                    |                    |                    |
| subjects affected / exposed                           | 16 / 218 (7.34%)   | 12 / 215 (5.58%)   | 28 / 433 (6.47%)   |
| occurrences (all)                                     | 22                 | 16                 | 38                 |
| Musculoskeletal and connective tissue disorders       |                    |                    |                    |

|   |                         |                         |                        |
|---|-------------------------|-------------------------|------------------------|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                        | 17 / 218 (7.80%)<br>26  | 15 / 215 (6.98%)<br>20  | 32 / 433 (7.39%)<br>46 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 12 / 218 (5.50%)<br>16  | 10 / 215 (4.65%)<br>11  | 22 / 433 (5.08%)<br>27 |
| Rheumatoid arthritis<br>subjects affected / exposed<br>occurrences (all)              | 19 / 218 (8.72%)<br>24  | 22 / 215 (10.23%)<br>27 | 41 / 433 (9.47%)<br>51 |
| Infections and infestations   |                         |                         |                        |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 10 / 218 (4.59%)<br>11  | 12 / 215 (5.58%)<br>17  | 22 / 433 (5.08%)<br>28 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 218 (3.21%)<br>7    | 13 / 215 (6.05%)<br>17  | 20 / 433 (4.62%)<br>24 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 24 / 218 (11.01%)<br>42 | 17 / 215 (7.91%)<br>33  | 41 / 433 (9.47%)<br>75 |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 8 / 218 (3.67%)<br>10   | 12 / 215 (5.58%)<br>15  | 20 / 433 (4.62%)<br>25 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 18 / 218 (8.26%)<br>28  | 21 / 215 (9.77%)<br>34  | 39 / 433 (9.01%)<br>62 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 16 / 218 (7.34%)<br>19  | 10 / 215 (4.65%)<br>10  | 26 / 433 (6.00%)<br>29 |
| Metabolism and nutrition disorders  |                         |                         |                        |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 7 / 218 (3.21%)<br>7    | 7 / 215 (3.26%)<br>7    | 14 / 433 (3.23%)<br>14 |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)                   | 6 / 218 (2.75%)<br>6    | 11 / 215 (5.12%)<br>11  | 17 / 433 (3.93%)<br>17 |

|                                   |           |         |  |
|-----------------------------------|-----------|---------|--|
| <b>Non-serious adverse events</b> | Abatacept | Placebo |  |
|-----------------------------------|-----------|---------|--|

|  |  |  |  |
|--|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 58 / 137 (42.34%)  | 36 / 139 (25.90%)  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 5 / 137 (3.65%)<br>5   | 4 / 139 (2.88%)<br>4   |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 9 / 137 (6.57%)<br>10  | 4 / 139 (2.88%)<br>4   |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 137 (4.38%)<br>6   | 8 / 139 (5.76%)<br>9   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 9 / 137 (6.57%)<br>9   | 0 / 139 (0.00%)<br>0   |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Rheumatoid arthritis<br>subjects affected / exposed<br>occurrences (all) | 5 / 137 (3.65%)<br>7<br><br>6 / 137 (4.38%)<br>6<br><br>6 / 137 (4.38%)<br>6 | 1 / 139 (0.72%)<br>1<br><br>2 / 139 (1.44%)<br>2<br><br>6 / 139 (4.32%)<br>8 |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis  | 5 / 137 (3.65%)<br>7<br><br>1 / 137 (0.73%)<br>1                             | 0 / 139 (0.00%)<br>0<br><br>1 / 139 (0.72%)<br>1                             |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 8 / 137 (5.84%)<br>11  | 4 / 139 (2.88%)<br>7 |  |
| Rhinitis   |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 137 (2.19%)<br>3   | 1 / 139 (0.72%)<br>1 |  |
| Upper respiratory tract infection                |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 6 / 137 (4.38%)<br>7   | 9 / 139 (6.47%)<br>9 |  |
| Urinary tract infection                          |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 137 (5.84%)<br>8   | 2 / 139 (1.44%)<br>3 |  |
| Metabolism and nutrition disorders               |                        |                      |  |
| Hypercholesterolaemia                            |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 10 / 137 (7.30%)<br>10 | 6 / 139 (4.32%)<br>6 |  |
| Hyperlipidaemia                                  |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 137 (0.73%)<br>1   | 2 / 139 (1.44%)<br>2 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 04 August 2011  | Amendment 1 introduced the following changes: Wording on the patient number for re-screened patient was removed. Each patient was tracked using a unique patient identifier, that was applied within the database but not visible for the investigator and therefore the sentence was misleading. A serum biomarker sample log was added. Typographic errors were corrected and some sentences clarified. The changes described in this amended protocol were non- substantial and did not require IRB/IEC approval prior to implementation.   |
| 08 January 2014 | Amendment 2 introduced the following change(s): Amending the handling of missing values in the analysis plan in line with guidance received in discussions with FDA. The sequence of the hierarchical testing strategy was aligned with Draft FDA guidance released May 2013 for clinical trials in patients with rheumatoid arthritis. This placed more emphasis on DAS28 and parameters related to physical function, in particular HAQ-DI, and accounted for other data obtained from Phase IIb studies in the RA development program with secukinumab and newly available data from other RA programs. Implementing a full primary analysis after all patients completed 24 weeks replacing a potential futility analysis after 25-50% of patients had completed Week 16. Simplifying the protocol section on study drug preparations and administration, including removing details covered in pharmacist manual. This resulted in improved patient convenience for the remainder of the trial, as patient did not have to stay at site for a mandatory length of time after administration of study drug was completed. Providing investigator with more flexibility to be able to apply own best clinical judgment when study treatment interruptions for safety reasons were indicated, and clarification of the requirements to be observed with regards to live vaccines. Clarification on the restrictions with regards to concomitant medications, mostly to clarify what had to be followed (otherwise considered protocol deviation) as compared to what is only a general guidance (indicated by words like 'should'). Clarification that any laboratory abnormalities that in the judgment of the investigator were clinically significant and were deemed to place the patient at a safety risk for continuation in the study should result in study treatment discontinuation, and updated general guidance for investigators with regards to notable laboratory abnormalities for the most relevant lab parameters. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> for complete trial results.

Notes: