# Clinical trial results:
# A randomized, double-blind, placebo-controlled Phase III multicenter study of subcutaneous secukinumab in prefilled syringes to demonstrate the efficacy at 16 weeks and to assess the long-term efficacy, safety and tolerability up to 5 years in patients with active Ankylosing Spondylitis

## Summary

| | |
|---|---|
| EudraCT number | 2012-000046-35 |
| Trial protocol | GB CZ IT NL AT FI DE ES |
| Global end of trial date | 18 September 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 August 2019 |
| First version publication date | 31 August 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CAIN457F2310 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01649375 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 18 September 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that the efficacy of secukinumab 75 mg sc or 150 mg sc at Week 16 was superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS20 (Assessment of SpondyloArthritis International Society criteria) response.

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 | 18 October 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Czech Republic: 51 |
| Country: Number of subjects enrolled | Finland: 17 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Netherlands: 6 |
| Country: Number of subjects enrolled | Russian Federation: 37 |
| Country: Number of subjects enrolled | Singapore: 7 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Switzerland: 6 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 219 |
| EEA total number of subjects | 136 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 212 |
| From 65 to 84 years | 5 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Two hundred fifty-three subjects were screened and 219 were randomized

### Period 1

| | |
|---|---|
| Period 1 title | Up to Week 16 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Secukinumab 75 mg |

Arm description:

Secukinumab 75 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 75 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Secukinumab 75 mg once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4

| | |
|---|---|
| **Arm title** | Secukinumab 150 mg |

Arm description:

Secukinumab 150 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 150 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for infusion in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Secukinumab 150 mg once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks up to week 16

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks up to week 16

| **Number of subjects in period 1** | Secukinumab 75 mg | Secukinumab 150 mg | Placebo |
|---|---|---|---|
| Started | 73 | 72 | 74 |
| Completed | 68 | 66 | 66 |
| Not completed | 5 | 6 | 8 |
| Adverse event, serious fatal | 1 | - | - |
| Consent withdrawn by subject | 2 | 1 | 2 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | 2 | 5 | 4 |
| Lack of efficacy | - | - | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Week 16 up to Week 260 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Trial continued to be blinded up to week 52 and then was unblinded for the remainder of the trial

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Secukinumab 75 mg |

Arm description:

Secukinumab 75 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 75 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Secukinumab 75 mg once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4

| **Arm title** | Secukinumab 150 mg |
|---|---|

Arm description:

Secukinumab 150 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 150 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Secukinumab 150 mg once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4

| **Arm title** | Placebo - secukinumab 75 mg |
|---|---|

Arm description:

Placebo patients re-randomized to secukinumab 75 mg subcutaneous injection every 4 weeks starting from week 16.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 75 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients re-randomized to secukinumab 75 mg subcutaneous injection every 4 weeks starting from week 16

| **Arm title** | Placebo - secukinumab 150 mg |
|---|---|

Arm description:

Placebo patients re-randomized to secukinumab 150 mg subcutaneous injection every 4 weeks starting from week 16.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Secukinumab 75 mg |
| Investigational medicinal product code | AIN457 |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients re-randomized to secukinumab 75 mg subcutaneous injection every 4 weeks starting from week 16

| **Number of subjects in period 2** | Secukinumab 75 mg | Secukinumab 150 mg | Placebo - secukinumab 75 mg |
|---|---|---|---|
| Started | 68 | 66 | 32 |
| Completed | 48 | 53 | 20 |
| Not completed | 20 | 13 | 12 |
| Adverse event, serious fatal | 1 | 1 | - |
| Consent withdrawn by subject | 7 | 2 | 3 |
| Physician decision | - | 2 | - |
| Adverse event, non-fatal | 5 | 2 | 3 |

| | | | |
|---|---|---|---|
| Non-compliance | - | 1 | 1 |
| Technical issues | - | 1 | 1 |
| Lack of efficacy | 7 | 4 | 4 |

| **Number of subjects in period 2** | Placebo - secukinumab 150 mg |
|---|---|
| Started | 34 |
| Completed | 29 |
| Not completed | 5 |
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | 1 |
| Physician decision | - |
| Adverse event, non-fatal | 2 |
| Non-compliance | - |
| Technical issues | - |
| Lack of efficacy | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Secukinumab 75 mg |
| Reporting group description: | |
| Secukinumab 75 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks. | |
| Reporting group title | Secukinumab 150 mg |
| Reporting group description: | |
| Secukinumab 150 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks up to week 16 | |

| Reporting group values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo |
|---|---|---|---|
| Number of subjects | 73 | 72 | 74 |
| Age, Customized<br>Units: Subjects | | | |
| < 65 | 70 | 70 | 72 |
| >= 65 to 74 | 2 | 2 | 1 |
| >= 75 | 1 | 0 | 1 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 22 | 26 | 18 |
| Male | 51 | 46 | 56 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 70 | 69 | 70 |
| Asian | 3 | 2 | 4 |
| American Indian or Alaska Native | 0 | 1 | 0 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 219 | | |
| Age, Customized<br>Units: Subjects | | | |
| < 65 | 212 | | |
| >= 65 to 74 | 5 | | |
| >= 75 | 2 | | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 66 | | |
| Male | 153 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 209 | | |
| Asian | 9 | | |
| American Indian or Alaska Native | 1 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Secukinumab 75 mg |
| Reporting group description: | |
| Secukinumab 75 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks. | |
| Reporting group title | Secukinumab 150 mg |
| Reporting group description: | |
| Secukinumab 150 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks up to week 16 | |
| Reporting group title | Secukinumab 75 mg |
| Reporting group description: | |
| Secukinumab 75 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks. | |
| Reporting group title | Secukinumab 150 mg |
| Reporting group description: | |
| Secukinumab 150 mg subcutaneous injection once weekly at baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks | |
| Reporting group title | Placebo - secukinumab 75 mg |
| Reporting group description: | |
| Placebo patients re-randomized to secukinumab 75 mg subcutaneous injection every 4 weeks starting from week 16. | |
| Reporting group title | Placebo - secukinumab 150 mg |
| Reporting group description: | |
| Placebo patients re-randomized to secukinumab 150 mg subcutaneous injection every 4 weeks starting from week 16. | |

### Primary: Percentage of participants achieving ASAS 20 (SpondyloArthritis International Society criteria) response at week 16

| | |
|---|---|
| End point title | Percentage of participants achieving ASAS 20 (SpondyloArthritis International Society criteria) response at week 16 |
| End point description: | |
| ASAS 20 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe an improvement of 20% and ≥1 unit on a scale of 10 in at least three of the four ASAS main domains and no worsening of ≥20% and ≥1 unit in the remaining domain. ASAS 20 is used to assess the efficacy of at least one dose of secukinumab against placebo. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to 16 weeks | |

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 41.1 | 61.1 | 28.4 | |

**Statistical analyses**

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0967 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 3.67 |

| Statistical analysis title | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.14 |
| upper limit | 8.96 |

**Secondary: Percentage of participants achieving ASAS 40 (SpondyloArthritis International Society criteria) response at week 16**

| End point title | Percentage of participants achieving ASAS 40 (SpondyloArthritis International Society criteria) response at week 16 |
|---|---|

End point description:

ASAS 40 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe an improvement of ≥40% and ≥2 units on a scale of 10 in at least three of the four ASAS main domains and no worsening at all in the remaining domain. ASAS 40 is used to assess the efficacy of at least one dose of secukinumab against placebo.

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

End point timeframe:

Baseline up to 16 weeks

| **End point values** | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 26.0 | 36.1 | 10.8 | |

**Statistical analyses**

| **Statistical analysis title** | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0194 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.19 |
| upper limit | 7.48 |

| **Statistical analysis title** | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0004 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 5.07 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.06 |
| upper limit | 12.44 |

## Secondary: Change from baseline at week 16 in serum hsCRP

| | |
|---|---|
| End point title | Change from baseline at week 16 in serum hsCRP |

End point description:

The change from baseline in hsCRP is expressed as a ratio of post-baseline to baseline values. With the ratio normalized to 1.0 at baseline, ratios less than 1.0 represent decreased post-baseline values, whereas ratios greater than 1.0 represent increased post-baseline values. Blood levels of C-reactive protein (CRP), an acute phase reactant, are indicative of inflammation and of its severity, and can be used to monitor treatment response. A high sensitvity CRP (hsCRP) test is implemented in this study to assess the efficacy of at least one dose of secukinumab versus placebo in reducing AS elicited systemic inflammation over time.

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

End point timeframe:

16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: mg/L | | | | |
| least squares mean (standard error) | 0.61 (± 1.103) | 0.55 (± 1.104) | 1.13 (± 1.105) | |

### Statistical analyses

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 0.71 |

| Statistical analysis title | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.64 |

**Secondary: Percentage of participants achieving ASAS 5/6 (SpondyloArthritis International Society criteria) response at week 16**

| End point title | Percentage of participants achieving ASAS 5/6 (SpondyloArthritis International Society criteria) response at week 16 |
|---|---|

End point description:

ASAS 5/6 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe at least 20% improvement in score in at least 5 of a conventional set of 6 clinical domains relevant to AS. In this study, ASAS 5/6 is used to assess the efficacy of at least one dose of secukinumab against placebo.

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

End point timeframe:

Baseline up to 16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 34.2 | 43.1 | 8.1 | |

**Statistical analyses**

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0003 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 6.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.31 |
| upper limit | 16.26 |

| **Statistical analysis title** | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 9.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.47 |
| upper limit | 24.12 |

## Secondary: Change from baseline at week 16 for total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

| | |
|---|---|
| End point title | Change from baseline at week 16 for total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) |

End point description:

BASDAI is a validated assessment tool using 0 through 10 scales (0 indicating "no problem" and 10 indicating " worst problem"), to characterize six clinical domains pertaining to five major symptoms of AS perceived by the patients. Computed composite scores of 4 or greater indicate suboptimal disease control. In this study, the BASDAI is used to assess the efficacy of at least one dose of secukinumab verus placebo.

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

End point timeframe:

Baseline up to 16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | -1.92 (± 0.249) | -2.19 (± 0.248) | -0.85 (± 0.252) | |

**Statistical analyses**

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.77 |
| upper limit | -0.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.353 |

| Statistical analysis title | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.04 |
| upper limit | -0.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.353 |

## Secondary: Change from baseline at week 16 in Physical Function Component

| Summary (PCS) of the Medical Outcomes Study Questionnaire Short-form Health Survey (SF-36) | |
|---|---|
| End point title | Change from baseline at week 16 in Physical Function Component Summary (PCS) of the Medical Outcomes Study Questionnaire Short-form Health Survey (SF-36) |

End point description:

SF-36 is a 36 item questionnaire which measures Quality of Life across eight domains, which are both phyically and emotionally based. Two overall summary scores, the Phyical Component Summary (PCS) and Mental Component Summary (MCS) can be computed. In this study, SF-36 PCS is used to assess improvement from baseline of at least one dose of secukinumab versus placebo.

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

End point timeframe:

Baseline up to 16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | 4.77 (± 0.798) | 6.06 (± 0.784) | 1.92 (± 0.786) | |

### Statistical analyses

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 5.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.108 |

| Statistical analysis title | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.96 |
| upper limit | 6.32 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.105 |

## Secondary: Change from baseline at week 16 in ASQoL

| | |
|---|---|
| End point title | Change from baseline at week 16 in ASQoL |

End point description:

ASQoL is an 18 item questionnaire that assesses disease-specific quality of life (QoL), consisting of statements that are relevant to the physical and mental conditions for a participant with AS: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each statement is answered by the participant as a 'Yes' (scored as 1) or 'No' (scored as 0). All item scores are summed to give a total score. Total score can range from 0 (good QoL) to 18 (poor QoL). In this study, ASQoL is used to assess improvement from baseline of at least one dose of secukinumab versus placebo.

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

End point timeframe:

Baseline up to 16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | -3.33 (± 0.537) | -4.00 (± 0.528) | -1.37 (± 0.530) | |

## Statistical analyses

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0096 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.43 |
| upper limit | -0.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.748 |

| | |
|---|---|
| **Statistical analysis title** | 150 mg vs placebo |
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0005 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.09 |
| upper limit | -1.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.743 |

## Secondary: Percentage of participants achieving ASAS partial remission at week 16

| | |
|---|---|
| End point title | Percentage of participants achieving ASAS partial remission at week 16 |

End point description:

ASAS partial remission is a composite assessment, reflecting the proportion of treated patients who achieve within a defined time frame a value not above 2 units in each of the 4 ASAS domains on a scale of 10. In this study ASAS partial remission is used to assess the efficacy of at least one dose of secukinumab versus placebo.

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

End point timeframe:

Baseline up to 16 weeks

| End point values | Secukinumab 75 mg | Secukinumab 150 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 73 | 72 | 74 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 15.1 | 13.9 | 4.1 | |

**Statistical analyses**

| Statistical analysis title | 75 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 75 mg v Placebo |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0325 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.13 |
| upper limit | 16.21 |

| Statistical analysis title | 150 mg vs placebo |
|---|---|
| Comparison groups | Secukinumab 150 mg v Placebo |
| Number of subjects included in analysis | 146 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0471 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 15.01 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Timeframe for AE | |
| Adverse event reporting additional description: | |
| AE additional description | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Any AIN457 75 mg |
| Reporting group description: | |
| Any AIN457 75 mg | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |
| Reporting group title | Any AIN457 150 mg |
| Reporting group description: | |
| Any AIN457 150 mg | |

| Serious adverse events | Any AIN457 75 mg | Placebo | Any AIN457 150 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 105 (23.81%) | 4 / 74 (5.41%) | 31 / 155 (20.00%) |
| number of deaths (all causes) | 2 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Glioblastoma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraganglion neoplasm | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage unspecified | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 74 (1.35%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Drug ineffective | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Sarcoidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 74 (1.35%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 74 (1.35%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury cervical | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic rupture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 2 / 155 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 2 / 155 (1.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadriparesis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadriplegia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iritis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis microscopic | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 74 (0.00%) | 2 / 155 (1.29%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated hiatus hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stress urinary incontinence | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 74 (1.35%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Costochondritis | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 74 (1.35%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 74 (0.00%) | 1 / 155 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin abscess | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 74 (0.00%) | 2 / 155 (1.29%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 74 (0.00%) | 0 / 155 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Any AIN457 75 mg | Placebo | Any AIN457 150 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 76 / 105 (72.38%) | 26 / 74 (35.14%) | 99 / 155 (63.87%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 105 (8.57%) | 0 / 74 (0.00%) | 15 / 155 (9.68%) |
| occurrences (all) | 10 | 0 | 15 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 4 / 74 (5.41%) | 3 / 155 (1.94%) |
| occurrences (all) | 2 | 6 | 3 |
| Headache | | | |
| subjects affected / exposed | 9 / 105 (8.57%) | 6 / 74 (8.11%) | 15 / 155 (9.68%) |
| occurrences (all) | 10 | 6 | 26 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 5 / 74 (6.76%) | 5 / 155 (3.23%) |
| occurrences (all) | 4 | 5 | 9 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 9 / 105 (8.57%) | 1 / 74 (1.35%) | 17 / 155 (10.97%) |
| occurrences (all) | 13 | 1 | 18 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 1 / 74 (1.35%) | 11 / 155 (7.10%) |
| occurrences (all) | 6 | 1 | 12 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 105 (3.81%) | 2 / 74 (2.70%) | 8 / 155 (5.16%) |
| occurrences (all) | 5 | 2 | 9 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 1 / 74 (1.35%) | 4 / 155 (2.58%) |
| occurrences (all) | 6 | 1 | 4 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Ankylosing spondylitis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 1 / 74 (1.35%) | 6 / 155 (3.87%) |
| occurrences (all) | 6 | 1 | 9 |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 2 / 74 (2.70%) | 10 / 155 (6.45%) |
| occurrences (all) | 14 | 2 | 12 |
| Back pain | | | |
| subjects affected / exposed | 7 / 105 (6.67%) | 2 / 74 (2.70%) | 13 / 155 (8.39%) |
| occurrences (all) | 8 | 2 | 13 |
| Bursitis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 0 / 74 (0.00%) | 4 / 155 (2.58%) |
| occurrences (all) | 6 | 0 | 7 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 7 / 105 (6.67%) | 0 / 74 (0.00%) | 8 / 155 (5.16%) |
| occurrences (all) | 7 | 0 | 11 |
| Osteoarthritis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 1 / 74 (1.35%) | 4 / 155 (2.58%) |
| occurrences (all) | 6 | 1 | 5 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 1 / 74 (1.35%) | 11 / 155 (7.10%) |
| occurrences (all) | 2 | 1 | 13 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 1 / 74 (1.35%) | 14 / 155 (9.03%) |
| occurrences (all) | 23 | 1 | 15 |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 1 / 74 (1.35%) | 13 / 155 (8.39%) |
| occurrences (all) | 8 | 1 | 17 |
| Influenza | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | 0 / 74 (0.00%) | 14 / 155 (9.03%) |
| occurrences (all) | 15 | 0 | 16 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 30 / 105 (28.57%) | 3 / 74 (4.05%) | 35 / 155 (22.58%) |
| occurrences (all) | 71 | 3 | 73 |
| Oral herpes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 105 (5.71%) | 0 / 74 (0.00%) | 8 / 155 (5.16%) |
| occurrences (all) | 16 | 0 | 32 |
| Pharyngitis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 0 / 74 (0.00%) | 3 / 155 (1.94%) |
| occurrences (all) | 7 | 0 | 3 |
| Rhinitis | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 1 / 74 (1.35%) | 5 / 155 (3.23%) |
| occurrences (all) | 7 | 1 | 5 |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 1 / 74 (1.35%) | 8 / 155 (5.16%) |
| occurrences (all) | 6 | 1 | 11 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | 2 / 74 (2.70%) | 16 / 155 (10.32%) |
| occurrences (all) | 38 | 2 | 32 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 2 / 74 (2.70%) | 9 / 155 (5.81%) |
| occurrences (all) | 6 | 2 | 13 |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 1 / 74 (1.35%) | 8 / 155 (5.16%) |
| occurrences (all) | 5 | 1 | 8 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 November 2013 | -To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which were relevant to determining the overall therapeutic value of a<br>therapy for Ankylosing Spondylitis. These endpoints included but were not limited to ASQoL, BASDAI and SF-36.<br>-Analysis was changed to include all patients in the FAS, rather than focusing only on the subset of patients who were TNFα-inhibitor naïve, as the FAS would be more representative of the general population of AS patients.<br>- Align the primary and secondary assessments with the ASAS Handbook (Sieper et al 2009)<br>-Limit blinded study duration to reduce patient burden in administering a second syringe containing placebo to maintain blind . As the primary endpoint analysis (PEA) was conducted after all patients completed Week 16, there was no longer a need for the sponsor to be blinded past this analysis.<br>-The conduct of the interim analysis was revised. However, sites and patients remained blinded until all patients reached Week 52 to reduce bias when assessing the effect of the<br>secukinumab doses over 52 weeks. |
| 18 September 2015 | -The study medication for patients on the 75 mg sc treatment arm could have been be escalated from 75 mg sc to 150 mg sc every 4 weeks for patients whose overall therapeutic<br>response is not fully achieved with the current dose of 75 mg sc and may improve with a higher dose, as judged by the investigator. The escalation of the study medication may be determined at any site visit. - DMC discontinued after week 52. - To align with these specifications in local prescribing information, protocol exclusion criterion #12 was changed to: Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the entire study or longer if required by locally approved prescribing information. - Protocol exclusion criterion #16 was updated for greater clarity to "If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the<br>direct and indirect reacting bilirubin." |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported