



Clinical trial results:

A Multicenter Double-blind, Randomized Controlled Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Psoriatic Arthritis

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2014-004869-24 |
| Trial protocol | LV GR GB PT HU CZ BG PL ES FR |
| Global end of trial date | 06 July 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 15 July 2019 |
| First version publication date | 15 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20130207 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02376790 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 July 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of etanercept plus methotrexate therapy and etanercept monotherapy compared to methotrexate monotherapy, in subjects with psoriatic arthritis (PsA) as measured by the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at week 24.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material were submitted to the institutional IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form were received by Amgen before subjects were recruited into the study and before shipment of Amgen investigational product.

The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 03 March 2015 |
| 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 | Bulgaria: 45 |
| Country: Number of subjects enrolled | Argentina: 10 |
| Country: Number of subjects enrolled | Canada: 25 |
| Country: Number of subjects enrolled | Chile: 53 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Greece: 18 |
| Country: Number of subjects enrolled | Hungary: 31 |
| Country: Number of subjects enrolled | Latvia: 12 |
| Country: Number of subjects enrolled | Mexico: 73 |
| Country: Number of subjects enrolled | Poland: 61 |
| Country: Number of subjects enrolled | Portugal: 16 |
| Country: Number of subjects enrolled | Russian Federation: 77 |
| Country: Number of subjects enrolled | South Africa: 32 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | United Kingdom: 9 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 347 |
| Worldwide total number of subjects | 851 |
| EEA total number of subjects | 234 |

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) | 754 |
| From 65 to 84 years | 96 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 124 centers in Europe, Latin America, North America, and South Africa. Participants were enrolled from 03 March 2015 to 07 July 2017.

Pre-assignment

Screening details:

The study consisted of a 30-day screening period, a 48-week randomized double blind treatment period, and a 30-day safety follow-up period.

Participants were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Methotrexate Monotherapy |

Arm description:

Participants received oral methotrexate 20 mg weekly plus placebo to etanercept subcutaneous injection once a week for 48 weeks.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo to Etanercept |
| 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 to etanercept was administered by subcutaneous injection once a week.

| | |
|--|--------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Methotrexate capsules taken orally once a week. Dosing was initiated at 10 mg weekly and titrated up to a final dose of 20 mg weekly over a 4-week period.

| | |
|------------------|------------------------|
| Arm title | Etanercept Monotherapy |
|------------------|------------------------|

Arm description:

Participants received etanercept 50 mg weekly by subcutaneous injection plus oral placebo to methotrexate for 48 weeks.

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

| | |
|--|--|
| Dosage and administration details: | |
| Etanercept was administered by subcutaneous injection once a week. | |
| Investigational medicinal product name | Placebo to Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Placebo to methotrexate capsules taken orally once a week. | |
| Arm title | Etanercept + Methotrexate |
| Arm description: | |
| Participants received etanercept 50 mg a week by subcutaneous injection and oral methotrexate 20 mg a week for 48 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Methotrexate capsules taken orally once a week. Dosing was initiated at 10 mg weekly and titrated up to a final dose of 20 mg weekly over a 4-week period. | |
| Investigational medicinal product name | Etanercept |
| Investigational medicinal product code | |
| Other name | Enbrel |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Etanercept was administered by subcutaneous injection once a week. | |

| Number of subjects in period 1 | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate |
|---------------------------------------|---------------------------------|-------------------------------|----------------------------------|
| Started | 284 | 284 | 283 |
| Received Treatment | 282 | 284 | 282 |
| Completed | 224 | 237 | 230 |
| Not completed | 60 | 47 | 53 |
| Consent withdrawn by subject | 43 | 36 | 37 |
| Decision by Sponsor | 2 | 1 | 4 |
| Lost to follow-up | 15 | 10 | 12 |

Baseline characteristics

Reporting groups

| | |
|--|---------------------------|
| Reporting group title | Methotrexate Monotherapy |
| Reporting group description: | |
| Participants received oral methotrexate 20 mg weekly plus placebo to etanercept subcutaneous injection once a week for 48 weeks. | |
| Reporting group title | Etanercept Monotherapy |
| Reporting group description: | |
| Participants received etanercept 50 mg weekly by subcutaneous injection plus oral placebo to methotrexate for 48 weeks. | |
| Reporting group title | Etanercept + Methotrexate |
| Reporting group description: | |
| Participants received etanercept 50 mg a week by subcutaneous injection and oral methotrexate 20 mg a week for 48 weeks. | |

| Reporting group values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate |
|---|--------------------------|------------------------|---------------------------|
| Number of subjects | 284 | 284 | 283 |
| Age, Customized | | | |
| Units: Subjects | | | |
| ≤ 65 years | 257 | 251 | 259 |
| > 65 years | 27 | 33 | 24 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 48.7 | 48.5 | 48.1 |
| standard deviation | ± 13.1 | ± 13.5 | ± 12.7 |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 160 | 133 | 139 |
| Male | 124 | 151 | 144 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 11 | 11 | 8 |
| Asian | 3 | 1 | 1 |
| Black (or African American) | 4 | 0 | 3 |
| Mixed Race | 0 | 1 | 0 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 |
| Other | 10 | 18 | 6 |
| White | 255 | 252 | 265 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 58 | 70 | 69 |
| Not Hispanic or Latino | 226 | 214 | 214 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Body Mass Index (BMI) | | | |
| Units: Subjects | | | |
| ≤ 30 kg/m ² | 146 | 153 | 160 |
| > 30 kg/m ² | 138 | 130 | 123 |
| Missing | 0 | 1 | 0 |

| | | | |
|--|--------|--------|--------|
| Prior Use of Non-biologic Disease Modifying Antirheumatic Drugs (DMARDs) Units: Subjects | | | |
| Yes | 38 | 26 | 43 |
| No | 246 | 258 | 240 |
| Duration of Psoriatic Arthritis Disease | | | |
| Data are provided for participants with available data (N = 231, 222, 231) | | | |
| Units: years | | | |
| arithmetic mean | 3.64 | 3.10 | 2.96 |
| standard deviation | ± 6.85 | ± 5.96 | ± 5.99 |
| Swollen Joint Count | | | |
| A total of 66 joints were scored for presence or absence of swelling. Data are provided for all participants with available data (N = 284, 283, 282). | | | |
| Units: joints | | | |
| arithmetic mean | 12.9 | 11.5 | 11.2 |
| standard deviation | ± 9.9 | ± 9.6 | ± 9.1 |
| Tender Joint Count | | | |
| A total of 68 joints were scored for presence or absence of tenderness. Data are provided for all participants with available data (N = 284, 283, 282). | | | |
| Units: joints | | | |
| arithmetic mean | 20.9 | 18.8 | 20.0 |
| standard deviation | ± 15.0 | ± 14.5 | ± 15.3 |
| Physician Global Assessment of Disease Activity | | | |
| Assessed by the physician on a 100 mm visual analog scale (VAS), where 0 mm = No activity at all and 100 mm = Worst activity imaginable. Data are provided for all participants with available data (N = 284, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | 58.6 | 58.3 | 58.0 |
| standard deviation | ± 19.4 | ± 18.2 | ± 17.8 |
| Patient Global Assessment of Disease Activity | | | |
| Assessed by the participant on a 100 mm VAS, where 0 mm = No arthritis activity at all and 100 mm = Worst arthritis activity imaginable. Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | 60.7 | 62.9 | 61.0 |
| standard deviation | ± 22.5 | ± 22.1 | ± 20.8 |
| Patient Global Assessment of Joint Pain | | | |
| Participants assessed their joint pain on a 100 mm VAS, where 0 mm = No pain at all and 100 mm = Worst pain imaginable. Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | 56.1 | 56.5 | 55.7 |
| standard deviation | ± 21.7 | ± 22.3 | ± 21.6 |
| Disability Index of the Health Assessment Questionnaire (HAQ-DI) | | | |
| The HAQ-DI is a patient-reported questionnaire consisting of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task in the past week using the following responses: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores were summed and averaged to provide an overall score ranging from 0 (no disability) to 3 (very severe, high-dependency disability). Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 1.3 | 1.1 | 1.2 |

| | | | |
|---|------------|-------------|------------|
| standard deviation | ± 0.6 | ± 0.6 | ± 0.6 |
| C-reactive Protein (CRP) Concentration | | | |
| C-reactive protein (CRP) is a protein found in blood. CRP levels rise in response to inflammation. Data are provided for all participants with available data (N = 284, 282, 283). | | | |
| Units: mg/L | | | |
| arithmetic mean | 10.52 | 10.72 | 8.70 |
| standard deviation | ± 16.29 | ± 15.59 | ± 11.65 |
| Psoriatic Arthritis Disease Activity Score (PASDAS) | | | |
| <p>PASDAS is a measure of disease activity derived from:</p> <ul style="list-style-type: none"> • Physician and patient global assessment of disease activity (0-100 VAS) • 68 tender joint count • 66 swollen joint count • Short Form-36 Questionnaire (SF-36) physical component summary (score 0-100) • Tender dactylitis count (each digit assessed for tender dactylitis; total score 0-20) • Leeds enthesitis index (enthesitis assessed at 6 sites; total score 0-6) • CRP <p>The composite score is a weighted index with higher scores indicating more severe disease. Data are provided for subjects with available data (N = 282, 279, 280).</p> | | | |
| Units: units on a scale | | | |
| median | 6.10 | 6.02 | 5.95 |
| full range (min-max) | 2.2 to 9.1 | 2.5 to 10.2 | 3.0 to 9.4 |
| Clinical Disease Activity Index (CDAI) | | | |
| <p>The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the following items:</p> <ul style="list-style-type: none"> - 28 tender joint count, - 28 swollen joint count, - Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 = highest; - Physician's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 cm highest. <p>The CDAI score ranges from 0-76 where lower scores indicate less disease activity. Data are provided for subjects with available data (N = 283, 283, 281).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | 30.51 | 28.45 | 28.55 |
| standard deviation | ± 13.26 | ± 12.89 | ± 12.71 |
| Simplified Disease Activity Index (SDAI) | | | |
| <p>The Simplified Disease Activity Index (SDAI) is a composite index that is calculated as the sum of the following items:</p> <ul style="list-style-type: none"> - 28 tender joint count, - 28 swollen joint count, - Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 = highest; - Physician's Global Assessment of Disease Activity -measured on a 10 VAS, where 0 = lowest disease activity and 10 cm = highest. - CRP <p>The SDAI score ranges from 0 to 86 with higher scores representing worse disease. Data are provided for subjects with available data (N = 283, 281, 281).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | 31.56 | 29.52 | 29.43 |
| standard deviation | ± 13.52 | ± 13.19 | ± 12.90 |
| Disease Activity Score 28 (DAS28) | | | |
| <p>The DAS28 measures the severity of disease at a specific time and is derived from the following variables:</p> <ul style="list-style-type: none"> - 28 tender joint count - 28 swollen joint count - C-reactive protein (CRP) concentration - Patient's global assessment of disease activity, measured on a 100 mm VAS, where 0 = lowest disease activity and 100 = highest. <p>DAS28(CRP) scores range from 0 to approximately 10, with the upper bound dependent on the highest possible level of CRP. Higher scores indicate higher disease activity. Data are provided for subjects with available data (N = 283, 281, 281).</p> | | | |

| | | | |
|---|--------------------|--------------------|--------------------|
| Units: units on a scale arithmetic mean standard deviation | 4.93 ± 1.11 | 4.80 ± 1.13 | 4.75 ± 1.12 |
| Medical Outcomes Health Survey Short Form 36 Item (SF-36) Version 2 Physical Component Summary Score | | | |
| <p>The SF-36 is a health-related survey that assesses participant's quality of life and consists of 36 questions covering 8 health domains. Two summary component scores are calculated: mental component summary score (MCS) and physical component summary score (PCS). Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning.</p> <p>Data are provided for participants with available data (N = 282, 284, 282).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | 35.587 ± 8.411 | 37.835 ± 8.381 | 37.353 ± 9.243 |
| Medical Outcomes Health Survey Short Form 36 Item(SF-36) Version 2 Mental Component Summary Score | | | |
| <p>The SF-36 is a health-related survey that assesses participant's quality of life and consists of 36 questions covering 8 health domains. Two summary component scores are calculated: mental component summary score (MCS) and physical component summary score (PCS). Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning.</p> <p>Data are provided for participants with available data (N = 282, 284, 282)</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | 45.174 ± 12.073 | 45.107 ± 12.496 | 46.256 ± 11.236 |
| Leeds Dactylitis Index (LDI) | | | |
| <p>The Leeds dactylitis index quantitatively measures dactylitis using the circumference of involved digits and control digits and tenderness of involved digits (on a scale from 0-3). The ratio of circumference between an affected digit and the control digit is multiplied by the tenderness score for the affected digit. The results from each involved digit are summed to provide the LDI; higher LDI indicates worse dactylitis.</p> <p>Data are provided for subjects with available data (N = 284, 283, 282).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | 56.89 ± 174.56 | 50.07 ± 137.20 | 44.11 ± 143.17 |
| Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index | | | |
| <p>The SPARCC enthesitis index assesses enthesitis at 18 sites for palpitation with a resultant total score of 0 to 16 (for scoring purposes, the inferior patella and tibial tuberosity are considered 1 site because of their anatomical proximity). Tenderness at each site is quantified on a dichotomous basis (0 = non-tender, 1 = tender). A higher count represents greater enthesitis burden.</p> <p>Data are provided for subjects with available data (N = 284, 283, 282).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | 3.9 ± 4.3 | 3.7 ± 4.3 | 4.1 ± 4.5 |
| Percentage of Body Surface Area (BSA) Involved in Psoriasis | | | |
| The physician's assessment of the percentage of the participant's total body surface area involved with psoriasis. | | | |
| Units: percent body surface area arithmetic mean standard deviation | 12.68 ± 18.78 | 10.76 ± 14.66 | 10.74 ± 15.58 |
| Static Physician Global Assessment (sPGA) | | | |
| <p>The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:</p> <p>0 = clear (no evidence of plaque elevation, erythema or scaling)</p> <p>1 = almost clear</p> | | | |

| | | | |
|---|-------|-------|-------|
| 2 = mild 3 = moderate 4 = marked 5 = severe Data are provided for subjects with available data (N = 281, 284, 283). | | | |
| Units: units on a scale | | | |
| arithmetic mean | 2.6 | 2.6 | 2.5 |
| standard deviation | ± 1.1 | ± 1.0 | ± 1.0 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 851 | | |
| Age, Customized | | | |
| Units: Subjects | | | |
| ≤ 65 years | 767 | | |
| > 65 years | 84 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 432 | | |
| Male | 419 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 30 | | |
| Asian | 5 | | |
| Black (or African American) | 7 | | |
| Mixed Race | 1 | | |
| Native Hawaiian or Other Pacific Islander | 2 | | |
| Other | 34 | | |
| White | 772 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 197 | | |
| Not Hispanic or Latino | 654 | | |
| Unknown or Not Reported | 0 | | |
| Body Mass Index (BMI) | | | |
| Units: Subjects | | | |
| ≤ 30 kg/m ² | 459 | | |
| > 30 kg/m ² | 391 | | |
| Missing | 1 | | |
| Prior Use of Non-biologic Disease Modifying Antirheumatic Drugs (DMARDs) | | | |
| Units: Subjects | | | |
| Yes | 107 | | |
| No | 744 | | |
| Duration of Psoriatic Arthritis Disease | | | |
| Data are provided for participants with available data (N = 231, 222, 231) | | | |
| Units: years | | | |
| arithmetic mean | | | |

| | | | |
|--|---|--|--|
| standard deviation | - | | |
| Swollen Joint Count | | | |
| A total of 66 joints were scored for presence or absence of swelling. Data are provided for all participants with available data (N = 284, 283, 282). | | | |
| Units: joints | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Tender Joint Count | | | |
| A total of 68 joints were scored for presence or absence of tenderness. Data are provided for all participants with available data (N = 284, 283, 282). | | | |
| Units: joints | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Physician Global Assessment of Disease Activity | | | |
| Assessed by the physician on a 100 mm visual analog scale (VAS), where 0 mm = No activity at all and 100 mm = Worst activity imaginable. Data are provided for all participants with available data (N = 284, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Patient Global Assessment of Disease Activity | | | |
| Assessed by the participant on a 100 mm VAS, where 0 mm = No arthritis activity at all and 100 mm = Worst arthritis activity imaginable. Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Patient Global Assessment of Joint Pain | | | |
| Participants assessed their joint pain on a 100 mm VAS, where 0 mm = No pain at all and 100 mm = Worst pain imaginable. Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: mm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Disability Index of the Health Assessment Questionnaire (HAQ-DI) | | | |
| The HAQ-DI is a patient-reported questionnaire consisting of 20 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task in the past week using the following responses: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores were summed and averaged to provide an overall score ranging from 0 (no disability) to 3 (very severe, high-dependency disability). Data are provided for all participants with available data (N = 283, 284, 282). | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| C-reactive Protein (CRP) Concentration | | | |
| C-reactive protein (CRP) is a protein found in blood. CRP levels rise in response to inflammation. Data are provided for all participants with available data (N = 284, 282, 283). | | | |
| Units: mg/L | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Psoriatic Arthritis Disease Activity Score (PASDAS) | | | |
| PASDAS is a measure of disease activity derived from: • Physician and patient global assessment of disease activity (0-100 VAS) | | | |

| | | | |
|---|---|--|--|
| <ul style="list-style-type: none"> • 68 tender joint count • 66 swollen joint count • Short Form-36 Questionnaire (SF-36) physical component summary (score 0-100) • Tender dactylitis count (each digit assessed for tender dactylitis; total score 0-20) • Leeds enthesitis index (enthesitis assessed at 6 sites; total score 0-6) • CRP <p>The composite score is a weighted index with higher scores indicating more severe disease. Data are provided for subjects with available data (N = 282, 279, 280).</p> | | | |
| Units: units on a scale | | | |
| median | | | |
| full range (min-max) | - | | |
| Clinical Disease Activity Index (CDAI) | | | |
| <p>The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the following items:</p> <ul style="list-style-type: none"> - 28 tender joint count, - 28 swollen joint count, - Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 = highest; - Physician's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 cm highest. <p>The CDAI score ranges from 0-76 where lower scores indicate less disease activity. Data are provided for subjects with available data (N = 283, 283, 281).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Simplified Disease Activity Index (SDAI) | | | |
| <p>The Simplified Disease Activity Index (SDAI) is a composite index that is calculated as the sum of the following items:</p> <ul style="list-style-type: none"> - 28 tender joint count, - 28 swollen joint count, - Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 = lowest disease activity and 10 = highest; - Physician's Global Assessment of Disease Activity -measured on a 10 VAS, where 0 = lowest disease activity and 10 cm = highest. - CRP <p>The SDAI score ranges from 0 to 86 with higher scores representing worse disease. Data are provided for subjects with available data (N = 283, 281, 281).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Disease Activity Score 28 (DAS28) | | | |
| <p>The DAS28 measures the severity of disease at a specific time and is derived from the following variables:</p> <ul style="list-style-type: none"> - 28 tender joint count - 28 swollen joint count - C-reactive protein (CRP) concentration - Patient's global assessment of disease activity, measured on a 100 mm VAS, where 0 = lowest disease activity and 100 = highest. <p>DAS28(CRP) scores range from 0 to approximately 10, with the upper bound dependent on the highest possible level of CRP. Higher scores indicate higher disease activity. Data are provided for subjects with available data (N = 283, 281, 281).</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Medical Outcomes Health Survey Short Form 36 Item (SF-36) Version 2 Physical Component Summary Score | | | |
| <p>The SF-36 is a health-related survey that assesses participant's quality of life and consists of 36 questions covering 8 health domains. Two summary component scores are calculated: mental component summary score (MCS) and physical component summary score (PCS). Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning. Data are provided for participants with available data (N = 282, 284, 282).</p> | | | |

| | | | |
|--|---|--|--|
| Units: units on a scale arithmetic mean standard deviation | - | | |
| Medical Outcomes Health Survey Short Form 36 Item(SF-36) Version 2 Mental Component Summary Score | | | |
| <p>The SF-36 is a health-related survey that assesses participant's quality of life and consists of 36 questions covering 8 health domains. Two summary component scores are calculated: mental component summary score (MCS) and physical component summary score (PCS). Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning.</p> <p>Data are provided for participants with available data (N = 282, 284, 282)</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | - | | |
| Leeds Dactylitis Index (LDI) | | | |
| <p>The Leeds dactylitis index quantitatively measures dactylitis using the circumference of involved digits and control digits and tenderness of involved digits (on a scale from 0-3). The ratio of circumference between an affected digit and the control digit is multiplied by the tenderness score for the affected digit. The results from each involved digit are summed to provide the LDI; higher LDI indicates worse dactylitis.</p> <p>Data are provided for subjects with available data (N = 284, 283, 282).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | - | | |
| Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index | | | |
| <p>The SPARCC enthesitis index assesses enthesitis at 18 sites for palpitation with a resultant total score of 0 to 16 (for scoring purposes, the inferior patella and tibial tuberosity are considered 1 site because of their anatomical proximity). Tenderness at each site is quantified on a dichotomous basis (0 = non-tender, 1 = tender). A higher count represents greater enthesitis burden.</p> <p>Data are provided for subjects with available data (N = 284, 283, 282).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | - | | |
| Percentage of Body Surface Area (BSA) Involved in Psoriasis | | | |
| <p>The physician's assessment of the percentage of the participant's total body surface area involved with psoriasis.</p> | | | |
| Units: percent body surface area arithmetic mean standard deviation | - | | |
| Static Physician Global Assessment (sPGA) | | | |
| <p>The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:</p> <p>0 = clear (no evidence of plaque elevation, erythema or scaling) 1 = almost clear 2 = mild 3 = moderate 4 = marked 5 = severe</p> <p>Data are provided for subjects with available data (N = 281, 284, 283).</p> | | | |
| Units: units on a scale arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|---------------------------|
| Reporting group title | Methotrexate Monotherapy |
| Reporting group description: Participants received oral methotrexate 20 mg weekly plus placebo to etanercept subcutaneous injection once a week for 48 weeks. | |
| Reporting group title | Etanercept Monotherapy |
| Reporting group description: Participants received etanercept 50 mg weekly by subcutaneous injection plus oral placebo to methotrexate for 48 weeks. | |
| Reporting group title | Etanercept + Methotrexate |
| Reporting group description: Participants received etanercept 50 mg a week by subcutaneous injection and oral methotrexate 20 mg a week for 48 weeks. | |

Primary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 24

| | |
|---|---|
| End point title | Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 24 |
| End point description: A positive ACR20 response is defined if the following 3 criteria for improvement from baseline were met: <ul style="list-style-type: none">• $\geq 20\%$ improvement in 68 tender joint count;• $\geq 20\%$ improvement in 66 swollen joint count; and• $\geq 20\%$ improvement in at least 3 of the 5 following parameters:<ul style="list-style-type: none">◦ Patient's assessment of joint pain (measured on a 100 mm visual analog scale [VAS]);◦ Patient's global assessment of disease activity (measured on a 100 mm VAS);◦ Physician's global assessment of disease activity (measured on a 100 mm VAS);◦ Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]);◦ C-reactive protein concentration. Participants with missing postbaseline data were counted as non-responders. | |
| End point type | Primary |
| End point timeframe: Baseline and week 24 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 50.7 | 60.9 | 65.0 | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Analysis of ACR 20 at Week 24 |
| Statistical analysis description: The primary hypothesis of this study is that etanercept plus methotrexate therapy and etanercept | |

monotherapy are more efficacious than methotrexate monotherapy as measured by the percentage of participants with psoriatic arthritis achieving ACR 20 response at week 24.

| | |
|---|--|
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.005 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 13.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.8 |
| upper limit | 22 |

Notes:

[1] - Adjusted p-value was obtained by applying a Bonferroni-based testing procedure for multiplicity adjustment to control the family-wise, two-sided type one error rate at 0.05.

[2] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Analysis of ACR 20 at Week 24 |
|-----------------------------------|-------------------------------|

Statistical analysis description:

The primary hypothesis of this study is that etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate monotherapy as measured by the percentage of participants with psoriatic arthritis achieving ACR 20 response at week 24.

| | |
|---|---|
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.029 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 9.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1 |
| upper limit | 17.3 |

Notes:

[3] - Adjusted p-value was obtained by applying a Bonferroni-based testing procedure for multiplicity adjustment to control the family-wise, two-sided type one error rate at 0.05.

[4] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.

Secondary: Percentage of Participants With a Minimal Disease Activity (MDA) Response at Week 24

| | |
|-----------------|--|
| End point title | Percentage of Participants With a Minimal Disease Activity (MDA) Response at Week 24 |
|-----------------|--|

End point description:

Minimal Disease Activity (MDA) is a measure of low disease activity specific for psoriatic arthritis (PsA) that incorporates measures of joint and enthesal inflammation, skin disease, patient reported outcomes and functional disability to assess disease activity. Participants were classified as achieving MDA if they fulfilled 5 of the following 7 outcome measures:

- Tender joint count (0-68) ≤ 1
- Swollen joint count (0-66) ≤ 1
- Body surface area (BSA) involvement with psoriasis (0% to 100%) $\leq 3\%$

- Patient global assessment of joint pain VAS (0-100) ≤ 15
 - Patient global assessment of disease activity VAS (0-100) ≤ 20
 - HAQ-DI (0-3) ≤ 0.5
 - Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index (18 sites assessed for enthesitis with an overall score of 0 - 16) ≤ 1
- Participants with missing data were counted as non-responders.

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

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 22.9 | 35.9 | 35.7 | |

Statistical analyses

| Statistical analysis title | Analysis of MDA at Week 24 |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

The secondary hypothesis of this study was that etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate monotherapy as measured by the percentage of participants with PsA achieving MDA response at week 24.

| | |
|---|--|
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.005 ^[6] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 12.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.9 |
| upper limit | 19.6 |

Notes:

[5] - Adjusted p-value was obtained by applying a Bonferroni-based testing procedure for multiplicity adjustment to control the family-wise, two-sided type one error rate at 0.05.

[6] - Cochran-Mantel-Haenszel test with baseline body mass index (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.

| Statistical analysis title | Analysis of MDA at Week 24 |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

The secondary hypothesis of this study was that etanercept plus methotrexate therapy and etanercept monotherapy are more efficacious than methotrexate monotherapy as measured by the percentage of participants with PsA achieving MDA response at week 24.

| | |
|-------------------|---|
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
|-------------------|---|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.005 ^[8] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 11.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.2 |
| upper limit | 18.9 |

Notes:

[7] - Adjusted p-value was obtained by applying a Bonferroni-based testing procedure for multiplicity adjustment to control the family-wise, two-sided type one error rate at 0.05.

[8] - Cochran-Mantel-Haenszel test with baseline body mass index (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.

Secondary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response Over Time

| | |
|-----------------|--|
| End point title | Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response Over Time |
|-----------------|--|

End point description:

A positive ACR20 response is defined if the following 3 criteria for improvement from baseline were met:

- $\geq 20\%$ improvement in 68 tender joint count;
- $\geq 20\%$ improvement in 66 swollen joint count; and
- $\geq 20\%$ improvement in at least 3 of the 5 following parameters:
 - Patient's assessment of joint pain (measured on a 100 mm visual analog scale [VAS]);
 - Patient's global assessment of disease activity (measured on a 100 mm VAS);
 - Physician's global assessment of disease activity (measured on a 100 mm VAS);
 - Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]);
 - C-reactive protein.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 4 (N = 280, 280, 276) | 25.0 | 44.3 | 46.4 | |
| Week 8 (N = 271, 274, 268) | 46.5 | 60.2 | 60.8 | |
| Week 12 (N = 267, 267, 263) | 46.8 | 65.5 | 70.3 | |
| Week 16 (N = 253, 256, 248) | 58.5 | 69.5 | 71.8 | |
| Week 24 (N = 253, 256, 256) | 56.9 | 67.6 | 71.9 | |
| Week 36 (N = 243, 248, 240) | 66.3 | 77.0 | 74.2 | |
| Week 48 (N = 229, 237, 230) | 70.7 | 83.1 | 80.4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response Over Time

| | |
|-----------------|--|
| End point title | Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response Over Time |
|-----------------|--|

End point description:

A positive ACR50 response is defined if the following 3 criteria for improvement from baseline were met:

- $\geq 50\%$ improvement in 68 tender joint count;
- $\geq 50\%$ improvement in 66 swollen joint count; and
- $\geq 50\%$ improvement in at least 3 of the 5 following parameters:
 - Patient's assessment of joint pain (measured on a 100 mm visual analog scale [VAS]);
 - Patient's global assessment of disease activity (measured on a 100 mm VAS);
 - Physician's global assessment of disease activity (measured on a 100 mm VAS);
 - Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]);
 - C-reactive protein.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 4 (N = 281, 279, 276) | 6.0 | 16.5 | 18.8 | |
| Week 8 (N = 272, 275, 269) | 15.1 | 31.3 | 30.1 | |
| Week 12 (N = 267, 267, 263) | 16.9 | 40.4 | 39.2 | |
| Week 16 (N = 253, 256, 251) | 29.2 | 43.8 | 43.4 | |
| Week 24 (N = 252, 257, 256) | 30.6 | 44.4 | 45.7 | |
| Week 36 (N = 244, 246, 241) | 41.8 | 57.3 | 56.0 | |
| Week 48 (N = 229, 238, 231) | 49.3 | 63.0 | 60.2 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of ACR50 Response at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[9] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 14.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.4 |
| upper limit | 23 |

Notes:

[9] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of ACR50 Response at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 ^[10] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.4 |
| upper limit | 20.2 |

Notes:

[10] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response Over Time

| | |
|-----------------|--|
| End point title | Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response Over Time |
|-----------------|--|

End point description:

A positive ACR70 response is defined if the following 3 criteria for improvement from baseline were met:

- $\geq 70\%$ improvement in 68 tender joint count;
- $\geq 70\%$ improvement in 66 swollen joint count; and
- $\geq 70\%$ improvement in at least 3 of the 5 following parameters:
 - Patient's assessment of joint pain (measured on a 100 mm visual analog scale [VAS]);
 - Patient's global assessment of disease activity (measured on a 100 mm VAS);
 - Physician's global assessment of disease activity (measured on a 100 mm VAS);
 - Patient's self-assessment of physical function (Health Assessment Questionnaire - Disability Index [HAQ-DI]);
 - C-reactive protein.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 4 (N = 281, 280, 276) | 2.8 | 3.6 | 5.1 | |
| Week 8 (N = 272, 277, 269) | 4.4 | 15.2 | 14.5 | |
| Week 12 (N = 267, 268, 264) | 5.2 | 24.3 | 22.3 | |
| Week 16 (N = 252, 256, 251) | 10.7 | 24.2 | 25.5 | |
| Week 24 (N = 253, 257, 256) | 13.8 | 29.2 | 27.7 | |
| Week 36 (N = 245, 247, 242) | 19.6 | 38.5 | 33.5 | |
| Week 48 (N = 230, 237, 232) | 25.2 | 39.7 | 39.7 | |

Statistical analyses

| Statistical analysis title | Analysis of ACR70 Response at Week 24 |
|---|--|
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[11] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 13.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.5 |
| upper limit | 20.4 |

Notes:

[11] - Cochran-Mantel-Haenszel test with baseline body mass index (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

| Statistical analysis title | Analysis of ACR70 Response at Week 24 |
|---|---|
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[12] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 13.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.7 |
| upper limit | 20.7 |

Notes:

[12] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in Tender Joint Count Over Time

| | |
|--|--|
| End point title | Change From Baseline in Tender Joint Count Over Time |
| End point description: The tender joint count is an assessment of the pain and/or tenderness of 68 joints using a 0 to 1 point scale (0 = none, 1 = present). The total tender joint count is calculated by summing the number of joints with present tenderness. | |
| End point type | Secondary |
| End point timeframe: Baseline and weeks 4, 8, 12, 16, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: tender joints | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 280, 279, 277) | -5.7 (± 0.6) | -6.4 (± 0.6) | -7.4 (± 0.6) | |
| Week 8 (N = 271, 276, 269) | -7.8 (± 0.7) | -8.9 (± 0.6) | -9.4 (± 0.7) | |
| Week 12 (N = 266, 267, 264) | -9.7 (± 0.7) | -9.8 (± 0.7) | -10.8 (± 0.7) | |
| Week 16 (N = 253, 257, 251) | -10.0 (± 0.7) | -10.9 (± 0.7) | -11.9 (± 0.8) | |
| Week 24 (N = 253, 257, 257) | -10.8 (± 0.8) | -10.9 (± 0.8) | -11.0 (± 0.9) | |
| Week 36 (N = 245, 248, 243) | -13.5 (± 0.8) | -12.7 (± 0.8) | -12.9 (± 0.9) | |
| Week 48 (N = 230, 239, 232) | -14.5 (± 0.8) | -13.9 (± 0.8) | -12.9 (± 0.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swollen Joint Count Over Time

| | |
|--|---|
| End point title | Change From Baseline in Swollen Joint Count Over Time |
| End point description: The swollen joint count is an assessment of the swelling of 66 joints using a 0 to 1 point scale (0 = none, 1 = present). The total swollen joint count is calculated by summing the number of joints with present swelling. | |
| End point type | Secondary |
| End point timeframe: Baseline and weeks 4, 8, 12, 16, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: swollen joints | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 280, 279, 277) | -4.1 (± 0.4) | -4.8 (± 0.3) | -4.7 (± 0.4) | |
| Week 8 (N = 271, 276, 269) | -5.4 (± 0.5) | -6.2 (± 0.4) | -6.5 (± 0.4) | |
| Week 12 (N = 266, 267, 264) | -6.6 (± 0.5) | -6.8 (± 0.4) | -7.2 (± 0.4) | |
| Week 16 (N = 253, 257, 251) | -7.0 (± 0.5) | -7.3 (± 0.4) | -7.8 (± 0.4) | |
| Week 24 (N = 253, 257, 257) | -7.0 (± 0.5) | -7.6 (± 0.5) | -7.7 (± 0.5) | |
| Week 36 (N = 245, 248, 243) | -9.2 (± 0.5) | -9.0 (± 0.5) | -8.4 (± 0.5) | |
| Week 48 (N = 230, 239, 232) | -9.6 (± 0.5) | -9.2 (± 0.5) | -8.7 (± 0.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician Global Assessment of Disease Activity Over Time

| | |
|--|---|
| End point title | Change From Baseline in Physician Global Assessment of Disease Activity Over Time |
| End point description: A global assessment of the participant's arthritis assessed by the physician on a 100 mm visual analog scale (VAS) where 0 mm = No activity at all and 100 mm = Worst activity imaginable. | |
| End point type | Secondary |
| End point timeframe: Baseline and weeks 4, 8, 12, 16, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: mm | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 278, 278, 277) | -16.8 (± 1.2) | -23.1 (± 1.2) | -22.8 (± 1.3) | |
| Week 8 (N = 271, 277, 269) | -25.0 (± 1.4) | -29.7 (± 1.4) | -30.4 (± 1.4) | |
| Week 12 (N = 266, 267, 264) | -26.8 (± 1.6) | -32.7 (± 1.6) | -33.9 (± 1.3) | |
| Week 16 (N = 251, 257, 252) | -30.3 (± 1.7) | -34.9 (± 1.5) | -36.2 (± 1.4) | |
| Week 24 (N = 250, 257, 257) | -29.6 (± 1.8) | -35.7 (± 1.7) | -35.8 (± 1.6) | |
| Week 36 (N = 241, 246, 241) | -37.1 (± 1.7) | -42.8 (± 1.5) | -39.9 (± 1.5) | |
| Week 48 (N = 229, 239, 232) | -41.4 (± 1.5) | -43.8 (± 1.4) | -41.5 (± 1.6) | |

Statistical analyses

Secondary: Change From Baseline in Patient Global Assessment of Disease Activity Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in Patient Global Assessment of Disease Activity Over Time |
|-----------------|---|

End point description:

A global assessment of the participant's arthritis, assessed by the participant on a 100 mm VAS where 0 mm = No arthritis activity at all and 100 mm = Worst arthritis activity imaginable.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: mm | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 280, 281, 277) | -11.0 (± 1.5) | -21.9 (± 1.6) | -21.0 (± 1.5) | |
| Week 8 (N = 271, 277, 269) | -15.6 (± 1.6) | -27.3 (± 1.6) | -26.4 (± 1.6) | |
| Week 12 (N = 266, 268, 264) | -18.6 (± 1.6) | -29.9 (± 1.7) | -28.0 (± 1.7) | |
| Week 16 (N = 252, 257, 250) | -22.7 (± 1.7) | -30.9 (± 1.7) | -29.3 (± 1.7) | |
| Week 24 (N = 252, 258, 257) | -23.0 (± 1.8) | -32.3 (± 1.7) | -29.6 (± 1.8) | |
| Week 36 (N = 243, 248, 241) | -26.0 (± 1.8) | -36.4 (± 1.8) | -32.4 (± 1.8) | |
| Week 48 (N = 228, 238, 232) | -28.9 (± 1.9) | -38.8 (± 1.7) | -33.3 (± 1.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Global Assessment of Joint Pain Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in Patient Global Assessment of Joint Pain Over Time |
|-----------------|---|

End point description:

A global assessment of the severity of the participant's joint pain, assessed by the participant on a 100 mm VAS where 0 mm = No pain at all and 100 mm = Worst pain imaginable.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: mm | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 280, 281, 277) | -8.9 (± 1.4) | -18.4 (± 1.5) | -18.5 (± 1.6) | |
| Week 8 (N = 271, 277, 269) | -14.5 (± 1.5) | -23.5 (± 1.5) | -24.0 (± 1.5) | |
| Week 12 (N = 266, 268, 264) | -16.0 (± 1.6) | -24.1 (± 1.7) | -24.9 (± 1.6) | |
| Week 16 (N = 252, 257, 250) | -20.9 (± 1.7) | -25.9 (± 1.7) | -25.6 (± 1.7) | |
| Week 24 (N = 252, 258, 257) | -20.6 (± 1.7) | -26.4 (± 1.7) | -26.9 (± 1.7) | |
| Week 36 (N = 243, 248, 241) | -23.9 (± 1.7) | -31.5 (± 1.7) | -28.8 (± 1.8) | |
| Week 48 (N = 228, 238, 232) | -27.2 (± 1.8) | -32.5 (± 1.7) | -31.1 (± 1.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire- Disability Index (HAQ-DI) Over Time

| | |
|--|--|
| End point title | Change From Baseline in Health Assessment Questionnaire- Disability Index (HAQ-DI) Over Time |
| End point description: | |
| <p>The Health Assessment Questionnaire - Disability Index is a patient-reported questionnaire consisting of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task are summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. Negative mean changes from Baseline in the overall score indicate improvement in functional ability.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 8, 12, 16, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 280, 281, 277) | -0.188 (± 0.024) | -0.266 (± 0.024) | -0.306 (± 0.029) | |
| Week 8 (N = 271, 276, 269) | -0.277 (± 0.029) | -0.365 (± 0.031) | -0.403 (± 0.032) | |
| Week 12 (N = 266, 268, 264) | -0.310 (± 0.030) | -0.404 (± 0.029) | -0.450 (± 0.033) | |
| Week 16 (N = 252, 257, 250) | -0.378 (± 0.036) | -0.454 (± 0.033) | -0.483 (± 0.036) | |
| Week 24 (N = 252, 258, 257) | -0.412 (± 0.036) | -0.444 (± 0.035) | -0.468 (± 0.038) | |

| | | | | |
|-----------------------------|-----------------------|-----------------------|-----------------------|--|
| Week 36 (N = 243, 248, 241) | -0.452 (\pm 0.038) | -0.496 (\pm 0.039) | -0.548 (\pm 0.040) | |
| Week 48 (N = 228, 238, 232) | -0.526 (\pm 0.041) | -0.557 (\pm 0.038) | -0.554 (\pm 0.041) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in C-reactive Protein Concentration Over Time

| | |
|-----------------|--|
| End point title | Change From Baseline in C-reactive Protein Concentration Over Time |
|-----------------|--|

End point description:

C-reactive protein (CRP) is a specific measure of inflammatory activity.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: mg/L | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 275, 265, 256) | -0.93 (\pm 0.93) | -5.91 (\pm 1.01) | -5.49 (\pm 0.74) | |
| Week 8 (N = 270, 265, 257) | -2.31 (\pm 0.90) | -7.51 (\pm 0.94) | -5.19 (\pm 0.88) | |
| Week 12 (N = 262, 255, 247) | -3.36 (\pm 0.84) | -7.38 (\pm 0.99) | -5.71 (\pm 0.82) | |
| Week 16 (N = 248, 246, 241) | -2.81 (\pm 0.82) | -7.40 (\pm 1.03) | -5.59 (\pm 0.85) | |
| Week 24 (N = 246, 249, 247) | -2.60 (\pm 0.91) | -6.91 (\pm 1.15) | -5.82 (\pm 0.70) | |
| Week 36 (N = 236, 234, 230) | -4.16 (\pm 0.96) | -7.36 (\pm 1.13) | -5.82 (\pm 0.80) | |
| Week 48 (N = 223, 226, 219) | -4.88 (\pm 1.03) | -7.45 (\pm 1.10) | -5.81 (\pm 0.95) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a American Minimal Disease Activity (MDA) Response Over Time

| | |
|-----------------|--|
| End point title | Percentage of Participants With a American Minimal Disease Activity (MDA) Response Over Time |
|-----------------|--|

End point description:

Minimal Disease Activity (MDA) is a measure of low disease activity specific for psoriatic arthritis (PsA) that incorporates measures of joint and enthesal inflammation, skin disease, patient reported outcomes and functional disability to assess disease activity. Participants were classified as achieving MDA if they fulfilled 5 of the following 7 outcome measures:

- Tender joint count (0-68) \leq 1
- Swollen joint count (0-66) \leq 1

- Body surface area (BSA) involvement with psoriasis (0% to 100%) $\leq 3\%$
- Patient global assessment of joint pain VAS (0-100) ≤ 15
- Patient global assessment of disease activity VAS (0-100) ≤ 20
- HAQ-DI (0-3) ≤ 0.5
- Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index (18 sites assessed for enthesitis with an overall score of 0 - 16) ≤ 1

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 4, 8, 12, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 4 (N = 281, 280, 278) | 5.7 | 11.1 | 12.6 | |
| Week 8 (N = 271, 276, 270) | 3.0 | 9.4 | 7.4 | |
| Week 12 (N = 267, 268, 265) | 11.6 | 29.9 | 29.1 | |
| Week 24 (N = 253, 258, 258) | 25.7 | 39.5 | 39.1 | |
| Week 36 (N = 244, 248, 242) | 30.3 | 43.5 | 46.7 | |
| Week 48 (N = 229, 238, 233) | 35.8 | 51.3 | 53.2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Psoriatic Arthritis Disease Activity Score (PASDAS) Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in Psoriatic Arthritis Disease Activity Score (PASDAS) Over Time |
|-----------------|---|

End point description:

PASDAS is a measure of disease activity derived from the following variables:

- Physician and patient global assessment of disease activity (assessed on a 0-100 VAS)
- 68 tender joint count
- 66 swollen joint count
- Short Form-36 Questionnaire (SF-36) physical component summary (general health status on a scale from 0-100)
- Tender dactylitis count (each digit assessed for tender dactylitis; total score 0-20)
- Leeds enthesitis index (enthesitis assessed at 6 sites; total score of 0-6)
- CRP level (mg/L)

The composite score is a weighted index where higher scores indicate more severe disease.

| | |
|---------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 12, 24, 36, and 48 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 12 (N = 261, 263, 261) | -1.63 (± 0.08) | -2.32 (± 0.09) | -2.37 (± 0.09) | |
| Week 24 (N = 246, 250, 255) | -1.98 (± 0.10) | -2.64 (± 0.10) | -2.63 (± 0.11) | |
| Week 36 (N = 234, 238, 232) | -2.46 (± 0.10) | -3.10 (± 0.10) | -2.95 (± 0.11) | |
| Week 48 (N = 226, 232, 229) | -2.70 (± 0.10) | -3.23 (± 0.09) | -3.10 (± 0.11) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in PASDAS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[13] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.91 |
| upper limit | -0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

Notes:

[13] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in PASDAS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[14] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | -0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.15 |

Notes:

[14] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use. P-value is unadjusted and considered descriptive

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) Over Time

| | |
|-----------------|--|
| End point title | Change From Baseline in Clinical Disease Activity Index (CDAI) Over Time |
|-----------------|--|

End point description:

The Clinical Disease Activity Index (CDAI) is a composite index that is calculated as the sum of the following items:

- 28 tender joint count,
- 28 swollen joint count,
- Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest;
- Physician's Global Assessment of Disease Activity -measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest.

The CDAI score ranges from 0-76 where lower scores indicate less disease activity.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 276, 277, 276) | -8.38 (± 0.62) | -10.59 (± 0.61) | -10.68 (± 0.60) | |
| Week 8 (N = 270, 276, 268) | -11.56 (± 0.73) | -14.13 (± 0.66) | -14.56 (± 0.65) | |
| Week 12 (N = 265, 266, 263) | -13.93 (± 0.74) | -15.61 (± 0.75) | -16.12 (± 0.71) | |
| Week 16 (N = 250, 256, 248) | -15.20 (± 0.80) | -16.49 (± 0.70) | -17.37 (± 0.76) | |
| Week 24 (N = 249, 257, 256) | -15.74 (± 0.85) | -17.12 (± 0.78) | -16.43 (± 0.85) | |
| Week 36 (N = 240, 246, 239) | -18.90 (± 0.76) | -19.79 (± 0.76) | -18.86 (± 0.79) | |
| Week 48 (N = 228, 238, 231) | -20.16 (± 0.80) | -20.78 (± 0.75) | -19.35 (± 0.83) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Analysis of Change in CDAI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.59 ^[15] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.93 |
| upper limit | 1.68 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.18 |

Notes:

[15] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in CDAI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.26 ^[16] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -1.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.63 |
| upper limit | 0.99 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.18 |

Notes:

[16] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use. P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in Simplified Disease Activity Index (SDAI) Over Time

| | |
|-----------------|--|
| End point title | Change From Baseline in Simplified Disease Activity Index (SDAI) Over Time |
|-----------------|--|

End point description:

The Simplified Disease Activity Index (SDAI) is a composite index that is calculated as the sum of the following items:

- 28 tender joint count,
- 28 swollen joint count,
- Patient's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest;
- Physician's Global Assessment of Disease Activity measured on a 10 cm VAS, where 0 cm = lowest disease activity and 10 cm = highest.
- CRP

The SDAI score ranges from 0 to 86 with higher scores representing worse disease.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 275, 273, 273) | -8.38 (± 0.62) | -11.12 (± 0.62) | -11.18 (± 0.61) | |
| Week 8 (N = 270, 272, 267) | -11.77 (± 0.72) | -14.92 (± 0.69) | -15.14 (± 0.66) | |
| Week 12 (N = 264, 264, 263) | -14.32 (± 0.75) | -16.44 (± 0.77) | -16.67 (± 0.73) | |
| Week 16 (N = 248, 253, 246) | -15.55 (± 0.81) | -17.25 (± 0.72) | -17.79 (± 0.78) | |
| Week 24 (N = 248, 253, 256) | -15.96 (± 0.86) | -17.75 (± 0.81) | -17.01 (± 0.87) | |
| Week 36 (N = 239, 242, 235) | -19.27 (± 0.77) | -20.50 (± 0.78) | -19.46 (± 0.82) | |
| Week 48 (N = 228, 234, 229) | -20.65 (± 0.81) | -21.61 (± 0.77) | -19.94 (± 0.87) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in SDAI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.41 ^[17] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.35 |
| upper limit | 1.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.2 |

Notes:

[17] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive

| | |
|----------------------------|---|
| Statistical analysis title | Analysis of Change in SDAI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.15 ^[18] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -1.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.09 |
| upper limit | 0.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.21 |

Notes:

[18] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in the Disease Activity Score 28 (DAS28) Over Time

| | |
|-----------------|---|
| End point title | Change From Baseline in the Disease Activity Score 28 (DAS28) Over Time |
|-----------------|---|

End point description:

The DAS28 measures the severity of disease at a specific time and is derived from the following variables:

- 28 tender joint count
- 28 swollen joint count
- C-reactive protein (CRP)
- Patient's global assessment of disease activity, measured on a 100 mm VAS, where 0 mm = lowest disease activity and 100 mm = highest.

DAS28(CRP) scores range from 0 to approximately 10, with the upper bound dependent on the highest possible level of CRP. A DAS28 score higher than 5.1 indicates high disease activity, a DAS28 score less than 3.2 indicates low disease activity, and a DAS28 score less than 2.6 indicates clinical remission.

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

End point timeframe:

Baseline and weeks 4, 8, 12, 16, 24, 36, and 48

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 284 | 284 | 283 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 4 (N = 278, 275, 273) | -0.73 (± 0.05) | -1.18 (± 0.06) | -1.21 (± 0.06) | |
| Week 8 (N = 270, 272, 267) | -1.05 (± 0.06) | -1.64 (± 0.07) | -1.61 (± 0.07) | |
| Week 12 (N = 264, 265, 263) | -1.34 (± 0.06) | -1.78 (± 0.08) | -1.80 (± 0.08) | |
| Week 16 (N = 250, 253, 246) | -1.47 (± 0.07) | -1.90 (± 0.08) | -1.92 (± 0.08) | |
| Week 24 (N = 251, 253, 256) | -1.55 (± 0.08) | -1.97 (± 0.08) | -1.86 (± 0.08) | |
| Week 36 (N = 242, 244, 236) | -1.88 (± 0.07) | -2.25 (± 0.08) | -2.20 (± 0.09) | |
| Week 48 (N = 228, 234, 229) | -2.04 (± 0.07) | -2.38 (± 0.08) | -2.23 (± 0.09) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in DAS28 at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 567 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 ^[19] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.29 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.52 |
| upper limit | -0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.11 |

Notes:

[19] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in DAS28 at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 568 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[20] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.62 |
| upper limit | -0.17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.12 |

Notes:

[20] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in Health Assessment Questionnaire- Disability Index (HAQ-DI) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Health Assessment Questionnaire- |
|-----------------|--|

End point description:

The Health Assessment Questionnaire - Disability Index is a patient-reported questionnaire consisting of 20 questions referring in 8 functional areas: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task are summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. Negative mean changes from Baseline in the overall score indicate improvement in functional ability.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 252 | 258 | 257 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | -0.412 (\pm 0.036) | -0.444 (\pm 0.035) | -0.468 (\pm 0.038) | |

Statistical analyses

| Statistical analysis title | Analysis of Change in HAQ-DI at Week 24 |
|---|--|
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.34 ^[21] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.05 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.05 |

Notes:

[21] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| Statistical analysis title | Analysis of Change in HAQ-DI at Week 24 |
|----------------------------|---|
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 510 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.67 ^[22] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.12 |
| upper limit | 0.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.05 |

Notes:

[22] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in Medical Outcomes Health Survey Short Form 36 Items Version 2 (SF-36 v2) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Medical Outcomes Health Survey Short Form 36 Items Version 2 (SF-36 v2) at Week 24 |
|-----------------|--|

End point description:

The SF-36 is a health-related survey that assesses participant's quality of life and consists of 36 questions covering 8 health domains. Two summary component scores are calculated: mental component summary score (MCS) and physical component summary score (PCS). The MCS consists of social functioning, vitality, mental health, and role-emotional scales and the PCS consists of physical functioning, bodily pain, role-physical, and general health scales. Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 253 | 256 | 257 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Physical Component Summary | 5.952 (\pm 0.550) | 7.808 (\pm 0.546) | 8.011 (\pm 0.598) | |
| Mental Component Summary | 3.259 (\pm 0.589) | 2.835 (\pm 0.624) | 3.321 (\pm 0.572) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Analysis of Change in PCS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 510 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015 ^[23] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 1.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 3.51 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

Notes:

[23] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in PCS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.033 ^[24] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 1.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.13 |
| upper limit | 3.28 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

Notes:

[24] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|--|
| Statistical analysis title | Analysis of Change in MCS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 510 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.97 ^[25] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.03 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.69 |
| upper limit | 1.63 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.84 |

Notes:

[25] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in MCS at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 509 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.56 ^[26] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.16 |
| upper limit | 1.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.85 |

Notes:

[26] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Change From Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) at Week 24

| | |
|-----------------|--|
| End point title | Change From Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) at Week 24 |
|-----------------|--|

End point description:

The modified NAPSI scale is a grading system for nail psoriasis that incorporates the following 7 clinical features:

- pitting (scores 0-3, depending on the number of pits)
- nail plate crumbling (scores 0-3, depending on the % of nail involvement)
- onycholysis and oil drop dyschromia (scores 0-3, depending on the % of nail involvement)
- leukonychia (0 = absent, 1 = present)
- red spots in lunula (0 = absent, 1 = present)
- nail bed hyperkeratosis (0 = absent, 1 = present)
- splinter hemorrhages (0 = absent, 1 = present)

In participants with fingernails involved with psoriasis, each fingernail was scored at baseline to determine the worst fingernail (ie, the fingernail with the highest mNAPSI score). This fingernail was followed for the remainder of the study. mNAPSI scores range from 0-13 where higher scores represent worse nail disease.

The analysis includes participants with non-zero mNAPSI score at baseline and available data at week 24.

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

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 121 | 115 | 123 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | -1.1 (± 0.2) | -1.5 (± 0.2) | -1.7 (± 0.2) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in mNAPSI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[27] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.03 |
| upper limit | -0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[27] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in mNAPSI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 236 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 ^[28] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.88 |
| upper limit | 0.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[28] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With Clear mNAPSI at Week 24

| | |
|-----------------|---|
| End point title | Percentage of Participants With Clear mNAPSI at Week 24 |
|-----------------|---|

End point description:

The modified NAPSI scale is a grading system for nail psoriasis that incorporates the following 7 clinical features:

- pitting (scores 0-3, depending on the number of pits)
- nail plate crumbling (scores 0-3, depending on the % of nail involvement)
- onycholysis and oil drop dyschromia (scores 0-3, depending on the % of nail involvement)
- leukonychia (0 = absent, 1 = present)
- red spots in lunula (0 = absent, 1 = present)
- nail bed hyperkeratosis (0 = absent, 1 = present)
- splinter hemorrhages (0 = absent, 1 = present)

In participants with fingernails involved with psoriasis, each fingernail was scored at baseline to determine the worst fingernail (ie, with the highest mNAPSI score). This fingernail was followed for the remainder of the study. mNAPSI scores range from 0-13 where higher scores represent worse nail disease. Clear mNAPSI is defined as a score = 0.

The analysis includes participants with non-zero mNAPSI score at baseline and available data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 121 | 115 | 123 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.0 | 0.0 | 0.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Leeds Dactylitis Index (LDI) at Week 24

| | |
|-----------------|---|
| End point title | Change from Baseline in Leeds Dactylitis Index (LDI) at Week 24 |
|-----------------|---|

End point description:

The Leeds dactylitis index quantitatively measures dactylitis using the circumference of involved digits and control digits and tenderness of involved digits. Digits affected by dactylitis are defined as those with a 10% difference in the ratio of circumference of the affected digit to the contralateral digit. The control digit is either the contralateral digit (digit on opposite hand or foot), or if the contralateral digit is also affected, values from a standard reference table. Tenderness of affected digits is assessed on a scale from 0 [none] to 3 [worst]. The ratio of circumference between an affected digit and the control digit is multiplied by the tenderness score for the affected digit. The results from each involved digit are summed to provide the final LDI. A higher LDI indicates worse dactylitis.

The analysis includes participants with non-zero LDI score at baseline and available data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 89 | 87 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | -128.80 (\pm 26.76) | -119.09 (\pm 20.66) | -110.15 (\pm 22.70) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in LDI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.68 ^[29] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 13.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.52 |
| upper limit | 79.36 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 33.23 |

Notes:

[29] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Change in LDI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 ^[30] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 6.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -58.75 |
| upper limit | 71.42 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 33.05 |

Notes:

[30] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With Clear LDI at Week 24

| | |
|-----------------|--|
| End point title | Percentage of Participants With Clear LDI at Week 24 |
|-----------------|--|

End point description:

The Leeds dactylitis index quantitatively measures dactylitis using the circumference of involved digits and control digits and tenderness of involved digits. Digits affected by dactylitis are defined as those with a 10% difference in the ratio of circumference of the affected digit to the contralateral digit. The control digit is either the contralateral digit (digit on opposite hand or foot), or if the contralateral digit is also affected, values from a standard reference table. Tenderness of affected digits is assessed on a scale from 0 [none] to 3 [worst]. The ratio of circumference between an affected digit and the control digit is multiplied by the tenderness score for the affected digit. The results from each involved digit are summed to provide the final LDI. A higher LDI indicates worse dactylitis. Clear LDI is defined as a score = 0.

The analysis includes participants with non-zero LDI score at baseline and available data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 89 | 89 | 87 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 65.2 | 76.4 | 79.3 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Clear LDI at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.057 ^[31] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 12.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 26.2 |

Notes:

[31] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.

P-value is unadjusted and considered descriptive.

| | |
|----------------------------|----------------------------------|
| Statistical analysis title | Analysis of Clear LDI at Week 24 |
|----------------------------|----------------------------------|

| | |
|---|---|
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.12 ^[32] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 24.4 |

Notes:

[32] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.

P-value is unadjusted and considered descriptive.

Secondary: Change from Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at Week 24

| | |
|-----------------|--|
| End point title | Change from Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at Week 24 |
|-----------------|--|

End point description:

The SPARCC enthesitis index assesses enthesitis at 18 sites for palpitation with a resultant total score of 0 to 16 (for scoring purposes, the inferior patella and tibial tuberosity are considered 1 site because of their anatomical proximity). Tenderness at each site is quantified on a dichotomous basis (0 = non-tender, 1 = tender). Entheses assessed are medial epicondyle (left and right), lateral epicondyle (left and right), supraspinatus insertion into greater tuberosity of humerus (left and right), greater trochanter (left and right), quadriceps insertion into superior border of patella (left and right), patellar ligament insertion into inferior pole of patella or tibial tubercle (left and right), Achilles tendon insertion into calcaneum (left and right), plantar fascia insertion into calcaneum (left and right). A higher count represents greater enthesitis burden.

The analysis includes participants with non-zero SPARCC enthesitis index at baseline and available data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 173 | 179 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | -3.1 (± 0.3) | -3.0 (± 0.3) | -2.9 (± 0.3) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Analysis of Change in SPARCC Enthesitis at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7 ^[33] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.66 |
| upper limit | 0.98 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

Notes:

[33] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|---|--|
| Statistical analysis title | Analysis of Change in SPARCC Enthesitis at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 340 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.93 ^[34] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.79 |
| upper limit | 0.86 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

Notes:

[34] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or >30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With Clear SPARCC Enthesitis Index Score at Week 24

| | |
|-----------------|--|
| End point title | Percentage of Participants With Clear SPARCC Enthesitis Index Score at Week 24 |
|-----------------|--|

End point description:

The SPARCC enthesitis index assesses enthesitis at 18 sites with a resultant total score of 0 to 16 (for scoring purposes, the inferior patella and tibial tuberosity are considered 1 site due to their anatomical proximity). Tenderness at each site is scored as either 0 (non-tender) or 1 (tender). Entheses assessed are medial epicondyle, lateral epicondyle, supraspinatus insertion into greater tuberosity of humerus, greater trochanter, quadriceps insertion into superior border of patella, patellar ligament insertion into inferior pole of patella or tibial tubercle, Achilles tendon insertion into calcaneum, plantar fascia insertion into calcaneum.

A higher count represents greater enthesitis burden. Clear SPARCC enthesitis is defined as a score = 0. The analysis includes participants with non-zero SPARCC enthesitis index at baseline and available data at week 24.

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

End point timeframe:
Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 173 | 179 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 43.1 | 52.6 | 47.8 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Clear SPARCC Enthesitis at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 346 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 ^[35] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 13.7 |

Notes:

[35] - Cochran-Mantel-Haenszel test with baseline body mass index (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of Clear SPARCC Enthesitis at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 340 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.11 ^[36] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 19.4 |

Notes:

[36] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

Secondary: Percent Improvement from Baseline in the Percentage of Body Surface Area (BSA) Involved in Psoriasis at Week 24

| | |
|-----------------|---|
| End point title | Percent Improvement from Baseline in the Percentage of Body Surface Area (BSA) Involved in Psoriasis at Week 24 |
|-----------------|---|

End point description:

The physician's assessment of the percentage of the participant's total body surface area involved with psoriasis. Percent improvement from baseline = (Baseline Value - Post-baseline Value) / Baseline * 100
The analysis includes participants with $\geq 3\%$ body surface area (BSA) psoriasis involvement at baseline and available data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 179 | 166 | 163 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | 66.12 (± 2.76) | 69.80 (± 2.73) | 75.53 (± 3.71) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change in BSA Involvement at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 342 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.031 [37] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 9.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 17.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.33 |

Notes:

[37] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$) and prior non-biologic DMARD use.
P-value is unadjusted and considered descriptive.

| | |
|----------------------------|---|
| Statistical analysis title | Analysis of Change in BSA Involvement at Week 24 |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 345 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.49 ^[38] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 3.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.49 |
| upper limit | 11.54 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.33 |

Notes:

[38] - ANCOVA model adjusted for baseline BMI status ($\leq 30 \text{ kg/m}^2$ or $>30 \text{ kg/m}^2$) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Percent Improvement from Baseline in the Percentage of Body Surface Area (BSA) Involved in Psoriasis by Baseline BSA Involvement Subgroups

| | |
|-----------------|--|
| End point title | Percent Improvement from Baseline in the Percentage of Body Surface Area (BSA) Involved in Psoriasis by Baseline BSA Involvement Subgroups |
|-----------------|--|

End point description:

The physician's assessment of the percentage of the participant's total body surface area involved with psoriasis. Percent improvement from baseline = (Baseline Value – Post-baseline Value) / Baseline * 100

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|---|--------------------------|-------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 254 | 259 | 259 | |
| Units: percent change | | | | |
| arithmetic mean (standard error) | | | | |
| < 3% BSA involvement (N = 75, 93, 96) | -24.49 (± 46.71) | -92.18 (± 108.54) | 17.66 (± 51.97) | |
| $\geq 3\%$ to $< 10\%$ BSA involvement (N = 87, 75, 77) | 66.61 (± 4.18) | 64.42 (± 4.43) | 68.76 (± 7.26) | |
| $\geq 10\%$ BSA involvement (N = 92, 91, 86) | 65.66 (± 3.66) | 74.23 (± 3.32) | 81.61 (± 2.55) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Analysis of BSA Improvement in BSA $\geq 10\%$ Subgroup |
|----------------------------|---|

Statistical analysis description:

Analysis of percent improvement from baseline in the percentage of BSA involved in psoriasis in the subgroup of participants with $\geq 10\%$ BSA involvement at baseline.

| | |
|---|--|
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 513 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[39] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 15.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.99 |
| upper limit | 24.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.55 |

Notes:

[39] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

| | |
|--|---|
| Statistical analysis title | Analysis of BSA Improvement in BSA $\geq 10\%$ Subgroup |
| Statistical analysis description: | |
| Analysis of percent improvement from baseline in the percentage of BSA involved in psoriasis in the subgroup of participants with $\geq 10\%$ BSA involvement at baseline. | |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 513 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.12 ^[40] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Treatment Difference |
| Point estimate | 6.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.89 |
| upper limit | 15.83 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.5 |

Notes:

[40] - ANCOVA model adjusted for baseline BMI status (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD use.

P-value is unadjusted and considered descriptive.

Secondary: Static Physician Global Assessment (sPGA) at Week 24

| | |
|-----------------|--|
| End point title | Static Physician Global Assessment (sPGA) at Week 24 |
|-----------------|--|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

The analysis includes participants with $\geq 3\%$ body surface area (BSA) psoriasis involvement at baseline and available sPGA data at week 24.

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

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 178 | 166 | 161 | |
| Units: participants | | | | |
| 0 (clear) | 38 | 36 | 63 | |
| 1 (almost clear) | 80 | 84 | 62 | |
| 2 (mild) | 34 | 28 | 25 | |
| 3 (moderate) | 22 | 12 | 10 | |
| 4 (marked) | 3 | 6 | 1 | |
| 5 (severe) | 1 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Static Physician Global Assessment (sPGA) at Week 24 by Baseline BSA Involvement Subgroups

| | |
|-----------------|--|
| End point title | Static Physician Global Assessment (sPGA) at Week 24 by Baseline BSA Involvement Subgroups |
|-----------------|--|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

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

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|--|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 253 | 258 | 257 | |
| Units: participants | | | | |
| < 3% BSA involvement at baseline: Total | 75 | 92 | 96 | |

| | | | | |
|--|----|----|----|--|
| < 3% BSA involvement: 0 (clear) | 26 | 29 | 52 | |
| < 3% BSA involvement: 1 (almost clear) | 28 | 37 | 32 | |
| < 3% BSA involvement: 2 (mild) | 15 | 19 | 9 | |
| < 3% BSA involvement: 3 (moderate) | 4 | 6 | 3 | |
| < 3% BSA involvement: 4 (marked) | 2 | 1 | 0 | |
| < 3% BSA involvement: 5 (severe) | 0 | 0 | 0 | |
| ≥ 3% to < 10% BSA involvement at baseline: Total | 87 | 75 | 76 | |
| ≥ 3% to < 10% BSA involvement: 0 (clear) | 23 | 16 | 35 | |
| ≥ 3% to < 10% BSA involvement: 1 (almost clear) | 41 | 32 | 23 | |
| ≥ 3% to < 10% BSA involvement: 2 (mild) | 13 | 18 | 12 | |
| ≥ 3% to < 10% BSA involvement: 3 (moderate) | 10 | 7 | 5 | |
| ≥ 3% to < 10% BSA involvement: 4 (marked) | 0 | 2 | 1 | |
| ≥ 3% to < 10% BSA involvement: 5 (severe) | 0 | 0 | 0 | |
| ≥ 10% BSA involvement at baseline: Total | 91 | 91 | 85 | |
| ≥ 10% BSA involvement at baseline: 0 (clear) | 15 | 20 | 28 | |
| ≥ 10% BSA involvement: 1 (almost clear) | 39 | 52 | 39 | |
| ≥ 10% BSA involvement at baseline: 2 (mild) | 21 | 10 | 13 | |
| ≥ 10% BSA involvement at baseline: 3 (moderate) | 12 | 5 | 5 | |
| ≥ 10% BSA involvement at baseline: 4 (marked) | 3 | 4 | 0 | |
| ≥ 10% BSA involvement at baseline: 5 (severe) | 1 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Static Physician Global Assessment (sPGA) Score at Week 24

| | |
|-----------------|---|
| End point title | Mean Static Physician Global Assessment (sPGA) Score at Week 24 |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

The analysis includes participants with ≥ 3% body surface area (BSA) psoriasis involvement at baseline and available sPGA data at week 24.

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

End point timeframe:

Week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 178 | 166 | 161 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | 1.3 (\pm 0.1) | 1.2 (\pm 0.1) | 0.9 (\pm 0.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Static Physician Global Assessment (sPGA) Score at Week 24 by Baseline BSA Involvement Subgroups

| | |
|-----------------|---|
| End point title | Mean Static Physician Global Assessment (sPGA) Score at Week 24 by Baseline BSA Involvement Subgroups |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

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

End point timeframe:

Week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|---|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 253 | 258 | 257 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| < 3% BSA involvement (N = 75, 92, 96) | 1.0 (\pm 0.1) | 1.1 (\pm 0.1) | 0.6 (\pm 0.1) | |
| \geq 3% to < 10% BSA involvement (N = 87, 75, 76) | 1.1 (\pm 0.1) | 1.3 (\pm 0.1) | 0.9 (\pm 0.1) | |
| \geq 10% BSA involvement (N = 91, 91, 85) | 1.5 (\pm 0.1) | 1.1 (\pm 0.1) | 0.9 (\pm 0.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an sPGA Score of 0 (Clear) or 1 (Almost Clear) at Week 24

| | |
|-----------------|---|
| End point title | Percentage of Participants With an sPGA Score of 0 (Clear) or 1 (Almost Clear) at Week 24 |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

The analysis included participants with $\geq 3\%$ body surface area (BSA) psoriasis involvement at baseline and available sPGA data at week 24.

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

End point timeframe:

Week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 178 | 166 | 161 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 66.3 | 72.3 | 77.6 | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of sPGA Clear or Almost Clear |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 339 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 ^[41] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 11.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2 |
| upper limit | 20.8 |

Notes:

[41] - Cochran-Mantel-Haenszel test with baseline body mass index (≤ 30 kg/m² or > 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.

P-value is unadjusted and considered descriptive.

| | |
|---|---|
| Statistical analysis title | Analysis of sPGA Clear or Almost Clear |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 344 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4 ^[42] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 4.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.6 |
| upper limit | 14 |

Notes:

[42] - Cochran-Mantel-Haenszel test with baseline body mass index ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) and prior non-biologic DMARD treatment as stratification factors.

P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With an sPGA Score of 0 (Clear) or 1 (Almost Clear) at Week 24 by Baseline BSA Involvement Subgroups

| | |
|-----------------|---|
| End point title | Percentage of Participants With an sPGA Score of 0 (Clear) or 1 (Almost Clear) at Week 24 by Baseline BSA Involvement Subgroups |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

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

End point timeframe:

Week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|--|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 253 | 258 | 257 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| < 3% BSA involvement (N = 75, 92, 96) | 72.0 | 71.7 | 87.5 | |
| $\geq 3\%$ to < 10% BSA involvement (N = 87, 75, 76) | 73.6 | 64.0 | 76.3 | |
| $\geq 10\%$ BSA involvement (N = 91, 91, 85) | 59.3 | 79.1 | 78.8 | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Analysis of sPGA 0 or 1 in BSA \geq 10% Subgroup |
| Statistical analysis description: Analysis of percentage of participants with an sPGA of 0 or 1 at Week 24 in participants with baseline BSA involvement with psoriasis \geq 10%. | |
| Comparison groups | Methotrexate Monotherapy v Etanercept + Methotrexate |
| Number of subjects included in analysis | 510 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 ^[43] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 20.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.8 |
| upper limit | 33.3 |

Notes:

[43] - Cochran-Mantel-Haenszel test with baseline body mass index (\leq 30 kg/m² or $>$ 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

| | |
|--|--|
| Statistical analysis title | Analysis of sPGA 0 or 1 in BSA \geq 10% Subgroup |
| Statistical analysis description: Analysis of percentage of participants with an sPGA of 0 or 1 at Week 24 in participants with baseline BSA involvement with psoriasis \geq 10%. | |
| Comparison groups | Methotrexate Monotherapy v Etanercept Monotherapy |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.012 ^[44] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Treatment Difference |
| Point estimate | 17.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4 |
| upper limit | 30.2 |

Notes:

[44] - Cochran-Mantel-Haenszel test with baseline body mass index (\leq 30 kg/m² or $>$ 30 kg/m²) and prior non-biologic DMARD treatment as stratification factors.
P-value is unadjusted and considered descriptive.

Secondary: Percentage of Participants With at Least a 1 Grade Improvement in sPGA From Baseline at Week 24

| | |
|---|---|
| End point title | Percentage of Participants With at Least a 1 Grade Improvement in sPGA From Baseline at Week 24 |
| End point description: The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5: 0 = clear (no evidence of plaque elevation, erythema or scaling) 1 = almost clear (minimal plaque elevation, erythema or scaling) 2 = mild (mild plaque elevation or scaling, light red coloration) 3 = moderate (moderate plaque elevation, scaling, light red coloration) 4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration) 5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration). The analysis includes participants with $\geq 3\%$ body surface area (BSA) psoriasis involvement at baseline and available sPGA data at week 24. | |
| End point type | Secondary |
| End point timeframe: Baseline and week 24 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 177 | 166 | 161 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 29.9 | 28.9 | 18.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 1 Grade Improvement in sPGA From Baseline at Week 24 by Baseline BSA Involvement Subgroups

| | |
|---|---|
| End point title | Percentage of Participants With at Least a 1 Grade Improvement in sPGA From Baseline at Week 24 by Baseline BSA Involvement Subgroups |
| End point description: The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5: 0 = clear (no evidence of plaque elevation, erythema or scaling) 1 = almost clear (minimal plaque elevation, erythema or scaling) 2 = mild (mild plaque elevation or scaling, light red coloration) 3 = moderate (moderate plaque elevation, scaling, light red coloration) 4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration) 5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration). | |
| End point type | Secondary |
| End point timeframe: Baseline and week 24 | |

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|--|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 250 | 258 | 257 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| < 3% BSA involvement (N = 73, 92, 96) | 37.0 | 44.6 | 43.8 | |
| ≥ 3% to < 10% BSA involvement (N = 86, 75, 76) | 27.9 | 38.7 | 21.1 | |
| ≥ 10% BSA involvement (N = 91, 91, 85) | 31.9 | 20.9 | 15.3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 2 Grade Improvement in sPGA From Baseline at Week 24

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least a 2 Grade Improvement in sPGA From Baseline at Week 24 |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

The analysis includes participants with ≥ 3% body surface area (BSA) psoriasis involvement at baseline and available sPGA data at week 24.

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|-----------------------------------|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 177 | 166 | 161 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.5 | 28.9 | 35.4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 2 Grade Improvement in

sPGA From Baseline at Week 24 by Baseline BSA Involvement Subgroups

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least a 2 Grade Improvement in sPGA From Baseline at Week 24 by Baseline BSA Involvement Subgroups |
|-----------------|---|

End point description:

The static Physician Global Assessment of psoriasis (sPGA) evaluates the physician's global assessment of the participant's psoriasis based on severity of induration, scaling, and erythema. The sPGA is assessed on a scale from 0 to 5:

0 = clear (no evidence of plaque elevation, erythema or scaling)

1 = almost clear (minimal plaque elevation, erythema or scaling)

2 = mild (mild plaque elevation or scaling, light red coloration)

3 = moderate (moderate plaque elevation, scaling, light red coloration)

4 = marked (marked plaque elevation, thick, non-tenacious scale predominates, bright red coloration)

5 = severe (severe plaque elevation, very thick tenacious scaling, dusky to deep red coloration).

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

End point timeframe:

Baseline and week 24

| End point values | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate | |
|--|--------------------------|------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 250 | 258 | 257 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| < 3% BSA involvement (N = 73, 92, 96) | 15.1 | 20.7 | 30.2 | |
| ≥ 3% to < 10% BSA involvement (N = 86, 75, 76) | 34.9 | 25.3 | 32.9 | |
| ≥ 10% BSA involvement (N = 91, 91, 85) | 26.4 | 31.9 | 37.6 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48-week treatment period plus 30-day safety follow-up

Adverse event reporting additional description:

Two participants randomized to the Etanercept Monotherapy arm also received methotrexate in error, so are counted in the Etanercept + Methotrexate group for safety.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Methotrexate Monotherapy |
|-----------------------|--------------------------|

Reporting group description:

Participants received oral methotrexate 20 mg weekly plus placebo to etanercept subcutaneous injection once a week for 48 weeks.

| | |
|-----------------------|------------------------|
| Reporting group title | Etanercept Monotherapy |
|-----------------------|------------------------|

Reporting group description:

Participants received etanercept 50 mg weekly by subcutaneous injection plus oral placebo to methotrexate for 48 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Etanercept + Methotrexate |
|-----------------------|---------------------------|

Reporting group description:

Participants received etanercept 50 mg a week by subcutaneous injection and oral methotrexate 20 mg a week for 48 weeks.

| Serious adverse events | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate |
|---|--------------------------|------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 282 (5.67%) | 19 / 282 (6.74%) | 17 / 284 (5.99%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer stage II | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-Hodgkin's lymphoma | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid neoplasm | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Surgical and medical procedures | | | |
| Spinal fusion surgery | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 2 / 284 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 282 (1.06%) | 0 / 282 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| 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 | | | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 282 (0.71%) | 0 / 282 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Cardiac failure congestive subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Cardiomyopathy subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Coronary artery disease subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Supraventricular tachyarrhythmia subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders Cerebrovascular accident subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Neuropathy peripheral subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Radiculopathy subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 282 (0.00%) | 2 / 282 (0.71%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Liver injury | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Psoriasis | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Vertebral foraminal stenosis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Acute pulmonary histoplasmosis | | | |
| subjects affected / exposed | 1 / 282 (0.35%) | 0 / 282 (0.00%) | 0 / 284 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 2 / 284 (0.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 282 (0.00%) | 2 / 282 (0.71%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 2 / 282 (0.71%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis streptococcal | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia necrotising | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 0 / 282 (0.00%) | 1 / 284 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 282 (0.00%) | 1 / 282 (0.35%) | 0 / 284 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 282 (0.71%) | 0 / 282 (0.00%) | 0 / 284 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 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 | Methotrexate Monotherapy | Etanercept Monotherapy | Etanercept + Methotrexate |
|---|-------------------------------------|-----------------------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 89 / 282 (31.56%) | 75 / 282 (26.60%) | 109 / 284 (38.38%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 15 / 282 (5.32%) | 12 / 282 (4.26%) | 17 / 284 (5.99%) |
| occurrences (all) | 16 | 17 | 22 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 17 / 282 (6.03%) | 13 / 282 (4.61%) | 14 / 284 (4.93%) |
| occurrences (all) | 23 | 17 | 15 |
| Nausea | | | |
| subjects affected / exposed | 37 / 282 (13.12%) | 18 / 282 (6.38%) | 41 / 284 (14.44%) |
| occurrences (all) | 48 | 26 | 57 |
| Vomiting | | | |
| subjects affected / exposed | 15 / 282 (5.32%) | 7 / 282 (2.48%) | 10 / 284 (3.52%) |
| occurrences (all) | 28 | 10 | 14 |

| | | | |
|---|------------------------|------------------------|------------------------|
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 9 / 282 (3.19%) 10 | 12 / 282 (4.26%) 13 | 18 / 284 (6.34%) 20 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 22 / 282 (7.80%) 25 | 21 / 282 (7.45%) 23 | 27 / 284 (9.51%) 34 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 21 / 282 (7.45%) 28 | 18 / 282 (6.38%) 23 | 23 / 284 (8.10%) 30 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 20 May 2015 | <ul style="list-style-type: none">- reporting of hepatotoxicity as a serious adverse event was clarified- etanercept indications in US and Canada were updated/clarified- updated inclusion/exclusion criteria regarding tender and swollen joint counts, minimum number of stable dosing for NSAIDS, excluded medications, and minimum number of months since use of excluded medications- clarified joint assessments and allowed for assessment by principal investigators; added folinic acid dosing information and additional information regarding laboratory assessments to determine subject eligibility- Clarified process for inadvertent blinding- Administrative corrections and clarifications were made throughout |
| 09 July 2015 | <ul style="list-style-type: none">- several secondary endpoints to assess disease activity (DAS-28, SDAI, and CDAI) were added- clarifications to psoriatic arthritis disease assessments were made |
| 30 October 2015 | <ul style="list-style-type: none">- updated to be consistent with international regulations and requirements, including those regarding tuberculosis screening in the setting of anti-TNF therapy |
| 31 August 2016 | <ul style="list-style-type: none">- to reflect the most recent version, CTCAE grading was updated to version 4.0- added language for confirmatory reflex testing by HBV DNA PCR for subjects with Hepatitis-B positive core antibody |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported