



Clinical trial results:

A Randomised, Blinded, Active-Controlled Study to Compare FKB327 Efficacy and Safety with the Comparator Humira® in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-000109-11 |
| Trial protocol | DE CZ BG ES |
| Global end of trial date | 12 July 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 July 2017 |
| First version publication date | 20 July 2017 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | FKB327-002 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|--------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02260791 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND Number: 116471 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | FUJIFILM KYOWA KIRIN BIOLOGICS Co., Ltd. |
| Sponsor organisation address | 1-6-1 Ohtemachi, Chiyoda-ku, Tokyo, Japan, 100-8185 |
| Public contact | Clinical-Trials@fk-b.com, Clinical Trial Information, Fujifilm Kyowa Kirin Biologics Co., Ltd., EU Branch, +44 1896 668 173, Clinical-Trials@fk-b.com |
| Scientific contact | Clinical-Trials@fk-b.com, Clinical Trial Information, Fujifilm Kyowa Kirin Biologics Co., Ltd., EU Branch, +44 1896 668 173, Clinical-Trials@fk-b.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 | 12 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary:

- To assess the efficacy of FKB327 compared with Humira®, when each was administered in combination with methotrexate (MTX).

Secondary:

- To compare the safety profiles of FKB327 and Humira, each in combination with MTX treatment.
- To assess the efficacy profiles of FKB327 and Humira over time, including initial onset of effect.
- To compare the proportions of patients on FKB327 and Humira, who develop anti-drug antibodies (ADAs) and to summarise the distribution of the level of ADA activity between patients on FKB327 and Humira.
- To compare the steady state pharmacokinetics (PK) of FKB327 and Humira administered by multiple dosing in patients with rheumatoid arthritis (RA) receiving concomitant treatment with MTX.

Protection of trial subjects:

The study was performed in compliance with European Union (EU) Directives 2001/20/EC and 2005/28/EC, the Declaration of Helsinki (South Africa Revision, 1996), Good Manufacturing Practice (GMP), and Good Clinical Practice (GCP).

The study was designed in accordance with the EU guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and other relevant guidelines for similar biological medicinal products.

Participants were given as long as they wished to read the patient information and informed consent form (ICF), and to ask as many questions as they wanted. Each participant had an opportunity to discuss the study in private with a fully registered physician who was familiar with the study. The physician observed the participant's signature, then countersigned the consent form. The participant gave consent freely and in writing.

During the study participants were monitored closely. In addition, the investigator and sponsor formally reviewed safety results at agreed intervals.

Participants could be withdrawn from the study if that was in their best interest and the study physician ensured that participants received any medical treatment that they needed.

Background therapy:

Methotrexate (MTX) represents the conventional disease modifying anti-rheumatic drug (DMARD) of choice for Rheumatoid Arthritis (RA) treatment and is thought to act by decreasing the activity of the immune system. Clinical studies with the originator product, Humira, in RA were conducted both in combination with MTX and as monotherapy. In this study concomitant folate therapy was used to counter the known adverse effects of MTX treatment.

In line with clinical practice, stable background doses of oral steroids and non-steroidal anti-inflammatory drugs (NSAIDs) were permitted during this study although they were not compulsory.

Evidence for comparator:

Adalimumab is a recombinant human monoclonal antibody against human Tumor Necrosis Factor (TNF)- α . It neutralises the biological activity of TNF- α by blocking its interaction with TNF- α cell surface receptors. TNF- α is a naturally occurring cytokine produced by many different cell types, including macrophages, mast cells and T cells. High concentrations of TNF- α lead to inflammation and injury, and TNF- α has been implicated as an important pro-inflammatory cytokine involved in the pathogenesis of numerous autoimmune diseases, such as RA, psoriasis (Ps), Crohn's disease (CD) and ulcerative colitis (UC).

Adalimumab was first approved for the treatment of RA in September 2003 in the European Union (EU),

and was subsequently launched globally under the brand name Humira. Humira is currently indicated in the EU in the adult population for RA, Ps, Psoriatic Arthritis (PsA), Ankylosing spondylitis (AS), axial spondyloarthritis (without radiographic evidence of AS), CD, UC, hidradenitis suppurativa (HS) and non-infectious uveitis. Approved indications in the paediatric population are polyarticular juvenile idiopathic arthritis in children from 2 years of age, active enthesitis-related arthritis from 6 years of age, severe chronic plaque psoriasis from 4 years of age, moderately to severe active CD from 6 years of age and moderate to severe HS in adolescents from 12 years of age.

| | |
|---|-----------------|
| Actual start date of recruitment | 05 January 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 | Poland: 134 |
| Country: Number of subjects enrolled | Romania: 28 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Bulgaria: 14 |
| Country: Number of subjects enrolled | Czech Republic: 67 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | Chile: 41 |
| Country: Number of subjects enrolled | Peru: 100 |
| Country: Number of subjects enrolled | Russian Federation: 109 |
| Country: Number of subjects enrolled | Ukraine: 114 |
| Country: Number of subjects enrolled | United States: 78 |
| Worldwide total number of subjects | 728 |
| EEA total number of subjects | 279 |

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) | 601 |
| From 65 to 84 years | 125 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

1. Men or women aged ≥ 18 years
2. RA, diagnosed to revised ACR criteria (2010) at least 3 months
3. Active RA, as confirmed by ≥ 6 tender and ≥ 6 swollen joint counts out of 68/66, respectively
4. CRP level ≥ 10 mg/L
5. Taking MTX for at least 3 months
6. A stable dose ≥ 4 weeks if taking oral steroids or NSAIDs
7. Pregnancy test negative

Pre-assignment

Screening details:

Patients were to be randomised in a 1:1 ratio to receive either FKB327 40 mg eow or Humira 40 mg eow using the following stratification factors: prior biological treatment for RA (yes/no) and Screening disease activity (DAS28-CRP ≤ 5.1 / >5.1).

Period 1

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

Blinding implementation details:

Patients will be randomised to receive either FKB327 40 mg eow or Humira 40 mg eow in a 1:1 ratio. A blinded kit containing a single dose of either FKB327 or Humira was supplied by the Sponsor. The person preparing the injection (pharmacist or other suitably qualified member of staff not otherwise involved in the study) was unblinded once the treatment kit was opened.

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | FKB327 |

Arm description:

Patients were administered subcutaneous (sc) FKB327 40 mg every other week (eow).

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | FKB327 |
| Investigational medicinal product code | FKB327 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients were administered subcutaneous (sc) FKB327 40 mg every other week (eow)

| | |
|------------------|--------|
| Arm title | Humira |
|------------------|--------|

Arm description:

Patients were administered subcutaneous (sc) Humira 40 mg every other week (eow).

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Humira |
| Investigational medicinal product code | Humira |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients were administered subcutaneous (sc) Humira 40 mg every other week (eow).

| Number of subjects in period 1 | FKB327 | Humira |
|---------------------------------------|--------|--------|
| Started | 366 | 362 |
| Completed | 333 | 328 |
| Not completed | 33 | 34 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 10 | 16 |
| Adverse event, non-fatal | 13 | 9 |
| Other | 7 | 7 |
| Screen failure | - | 1 |
| Lack of efficacy | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------|
| Reporting group title | FKB327 |
| Reporting group description: | |
| Patients were administered subcutaneous (sc) FKB327 40 mg every other week (eow). | |
| Reporting group title | Humira |
| Reporting group description: | |
| Patients were administered subcutaneous (sc) Humira 40 mg every other week (eow). | |

| Reporting group values | FKB327 | Humira | Total |
|--|----------|----------|-------|
| Number of subjects | 366 | 362 | 728 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 302 | 299 | 601 |
| From 65-84 years | 63 | 62 | 125 |
| 85 years and over | 1 | 1 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53 | 53.6 | |
| full range (min-max) | 18 to 85 | 21 to 93 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 281 | 284 | 565 |
| Male | 85 | 78 | 163 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 1 | 1 | 2 |
| Black or African American | 2 | 4 | 6 |
| White | 311 | 308 | 619 |
| Other | 51 | 48 | 99 |

Subject analysis sets

| | |
|--|---------------------|
| Subject analysis set title | Safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety Analysis Set was defined as the set of patients who received at least 1 dose of randomised treatment. The Safety Analysis Set was used for all safety analyses. Patient safety data were analysed according to treatment actually received. | |
| Subject analysis set title | Full Analysis Set |

| | |
|---|------------------------------|
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set (FAS) was defined as the set of patients who received at least 1 dose of the randomised treatment and who had at least 1 evaluable primary efficacy measurement after their first dose of randomised treatment. The FAS was used for the primary efficacy analysis and other efficacy endpoints and analyses. Patients were analysed according to the randomised treatment in the primary analysis. | |
| Subject analysis set title | Per-Protocol Analysis set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The Per-protocol Analysis Set (PPAS) was defined as the set of patients in the FAS that had not deviated sufficiently from the protocol as to impact on the primary efficacy endpoint. | |
| Subject analysis set title | Pharmacokinetic analysis set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The Pharmacokinetic Analysis Set (PKAS) was defined as the set of patients who received at least 1 dose of the randomised treatment and had at least 1 serum adalimumab concentration result after receiving randomised treatment. | |

| Reporting group values | Safety analysis set | Full Analysis Set | Per-Protocol Analysis set |
|--|---------------------|-------------------|---------------------------|
| Number of subjects | 728 | 721 | 639 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 601 | 596 | 541 |
| From 65-84 years | 125 | 123 | 96 |
| 85 years and over | 2 | 2 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.3 | 53.3 | 52.8 |
| full range (min-max) | 18 to 93 | 18 to 93 | 18 to 93 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 565 | 560 | 501 |
| Male | 163 | 161 | 138 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | 2 | 2 |
| Asian | 2 | 2 | 2 |
| Black or African American | 6 | 6 | 6 |
| White | 619 | 614 | 550 |
| Other | 99 | 97 | 79 |

| Reporting group values | Pharmacokinetic analysis set | | |
|------------------------|------------------------------|--|--|
| Number of subjects | 722 | | |

| | | | |
|---|----------|--|--|
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 597 | | |
| From 65-84 years | 123 | | |
| 85 years and over | 2 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.3 | | |
| full range (min-max) | 18 to 93 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 560 | | |
| Male | 162 | | |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 2 | | |
| Asian | 2 | | |
| Black or African American | 6 | | |
| White | 615 | | |
| Other | 97 | | |

End points

End points reporting groups

| | |
|--|------------------------------|
| Reporting group title | FKB327 |
| Reporting group description: Patients were administered subcutaneous (sc) FKB327 40 mg every other week (eow). | |
| Reporting group title | Humira |
| Reporting group description: Patients were administered subcutaneous (sc) Humira 40 mg every other week (eow). | |
| Subject analysis set title | Safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The Safety Analysis Set was defined as the set of patients who received at least 1 dose of randomised treatment. The Safety Analysis Set was used for all safety analyses. Patient safety data were analysed according to treatment actually received. | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The Full Analysis Set (FAS) was defined as the set of patients who received at least 1 dose of the randomised treatment and who had at least 1 evaluable primary efficacy measurement after their first dose of randomised treatment. The FAS was used for the primary efficacy analysis and other efficacy endpoints and analyses. Patients were analysed according to the randomised treatment in the primary analysis. | |
| Subject analysis set title | Per-Protocol Analysis set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Per-protocol Analysis Set (PPAS) was defined as the set of patients in the FAS that had not deviated sufficiently from the protocol as to impact on the primary efficacy endpoint. | |
| Subject analysis set title | Pharmacokinetic analysis set |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The Pharmacokinetic Analysis Set (PKAS) was defined as the set of patients who received at least 1 dose of the randomised treatment and had at least 1 serum adalimumab concentration result after receiving randomised treatment. | |

Primary: Percentage of Participants with an American College of Rheumatology (ACR) 20 Response at Week 24

| | |
|--|--|
| End point title | Percentage of Participants with an American College of Rheumatology (ACR) 20 Response at Week 24 |
| End point description: The primary efficacy endpoint is the ACR20 response rate at Week 24. An ACR20 response meant that the patient achieved a 20% improvement in Tender Joint Count and Swollen Joint Count and in at least 3 of the other 5 Core Data Set elements listed below. <ul style="list-style-type: none">• Acute phase reactant (CRP)• Patient global assessment of disease activity• Physician global assessment of disease activity• Patient pain scale• Disability/functional questionnaire (patient completed Health Assessment Questionnaire Disability Index [HAQ-DI]) | |
| End point type | Primary |
| End point timeframe: Week 24. | |

| End point values | FKB327 | Humira | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Percentage of participants | | | | |
| arithmetic mean (confidence interval 95%) | 74.4 (69.6 to 78.8) | 75.7 (70.9 to 80.1) | | |

Statistical analyses

| Statistical analysis title | Analysis of ACR20 Response Rate at Week 24 |
|--|--|
| Statistical analysis description: | |
| The primary hypothesis to be tested was that FKB327 is biosimilar to Humira. The difference and its 95% CI for primary endpoint between FKB327 and Humira were estimated. If the 95% CI fell entirely between pre-specified equivalence margin (+-13%), then FKB327 was considered equivalent to Humira. | |
| Comparison groups | FKB327 v Humira |
| Number of subjects included in analysis | 721 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 5 |

Secondary: Disease Activity Score 28 (DAS28) based on C-reactive protein (DAS28-CRP) score

| End point title | Disease Activity Score 28 (DAS28) based on C-reactive protein (DAS28-CRP) score |
|--|---|
| End point description: | |
| The DAS28 assessment involved evaluating the number of tender (TJC) and swollen (SJC) joints (out of 28 specified joints), serum CRP, and patient global assessment of disease activity (VAS from 0 to 100, very well to extremely bad). | |
| The DAS28-CRP is a number on a scale from 0 to 10 indicating the current activity of the patient's RA. | |
| End point type | Secondary |
| End point timeframe: | |
| DAS28-CRP scores from Baseline, Weeks 2, 4, 8, 12, 16, 20, and 24. | |

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 362, 358) | 6.05 (± 0.913) | 6.06 (± 0.852) | | |
| Week 2 (n = 361, 351) | 4.92 (± 1.07) | 4.86 (± 1.203) | | |
| Week 4 (n = 357, 348) | 4.44 (± 1.317) | 4.43 (± 1.383) | | |
| Week 8 (n = 348, 345) | 4.11 (± 1.295) | 4.09 (± 1.397) | | |
| Week 12 (n = 351, 340) | 3.81 (± 1.32) | 3.85 (± 1.339) | | |
| Week 16 (n = 350, 341) | 3.68 (± 1.304) | 3.67 (± 1.419) | | |
| Week 20 (n = 344, 336) | 3.58 (± 1.329) | 3.57 (± 1.388) | | |
| Week 24 (n = 340, 339) | 3.47 (± 1.298) | 3.47 (± 1.336) | | |

Statistical analyses

| Statistical analysis title | Analysis of DAS28-CRP at Week 24 |
|--|----------------------------------|
| Statistical analysis description: | |
| The key secondary hypothesis involved equivalence of the difference between FKB327 and Humira in DAS28-CRP at Week 24. Based on the repeated measures analysis model, the difference and its 95% CI in the least-squares means (LSMs) for DAS28-CRP at Week 24 between FKB327 and Humira were estimated. If the 95% CI fell entirely between the pre-specified margin (+- 0.6), then FKB327 was considered equivalent to Humira. | |
| Comparison groups | FKB327 v Humira |
| Number of subjects included in analysis | 721 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Difference in least square mean |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.16 |
| upper limit | 0.18 |

Secondary: ACR20 response rates over time

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|--|--------------------------------|
| End point title | ACR20 response rates over time |
| End point description: | |
| An ACR20 response meant that the patient achieved a 20% improvement in Tender Joint Count and Swollen Joint Count and in at least 3 of the other 5 Core Data Set elements listed below. | |
| <ul style="list-style-type: none"> •Acute phase reactant (CRP). •Patient global assessment of disease activity. •Physician global assessment of disease activity. •Patient pain scale. •Disability/functional questionnaire (patient completed Health AssessmentQuestionnaire Disability Index [HAQ-DI]). | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 2, 4, 8, 12, 16, 20, and 24. | |

| End point values | FKB327 | Humira | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Responders % | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n = 362, 352) | 37.3 (32.3 to 42.5) | 31 (26.2 to 36.1) | | |
| Week 4 (n = 359, 349) | 51 (45.7 to 56.3) | 52.4 (47.1 to 57.8) | | |
| Week 8 (n = 353, 347) | 64.6 (59.4 to 69.6) | 67.7 (62.5 to 72.6) | | |
| Week 12 (n = 351, 342) | 69.2 (64.1 to 74) | 72.2 (67.2 to 76.9) | | |
| Week 16 (n = 350, 342) | 74.6 (69.7 to 79.1) | 74.9 (69.9 to 79.4) | | |
| Week 20 (n = 345, 338) | 78 (73.2 to 82.2) | 77.8 (73 to 82.1) | | |
| Week 24 (n = 341, 338) | 77.1 (72.3 to 81.5) | 79.3 (74.6 to 83.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ACR50 response rates over time

| | |
|--|--------------------------------|
| End point title | ACR50 response rates over time |
| End point description: | |
| An ACR50 response meant that the patient achieved a 50% improvement in Tender Joint Count and Swollen Joint Count and in at least 3 of the other 5 Core Data Set elements listed below. | |
| <ul style="list-style-type: none"> •Acute phase reactant (CRP). •Patient global assessment of disease activity. •Physician global assessment of disease activity. •Patient pain scale. •Disability/functional questionnaire (patient completed Health AssessmentQuestionnaire Disability Index [HAQ-DI]). | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 2, 4, 8, 12, 16, 20, and 24. | |

| End point values | FKB327 | Humira | | |
|----------------------------------|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Responders % | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n = 362, 352) | 5 (3 to 7.7) | 8.8 (6.1 to 12.3) | | |

| | | | | |
|------------------------|---------------------|---------------------|--|--|
| Week 4 (n = 359, 349) | 17.3 (13.5 to 21.6) | 17.8 (13.9 to 22.2) | | |
| Week 8 (n = 353, 346) | 28.9 (24.2 to 33.9) | 30.9 (26.1 to 36.1) | | |
| Week 12 (n = 351, 342) | 37.6 (32.5 to 42.9) | 35.1 (30 to 40.4) | | |
| Week 16 (n = 350, 342) | 39.4 (34.3 to 44.8) | 44.7 (39.4 to 50.2) | | |
| Week 20 (n = 345, 339) | 45.5 (40.2 to 50.9) | 46 (40.6 to 51.5) | | |
| Week 24 (n = 341, 338) | 49 (43.6 to 54.4) | 49.4 (44 to 54.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ACR70 response rates over time

| | |
|--|--------------------------------|
| End point title | ACR70 response rates over time |
| End point description: | |
| An ACR70 response meant that the patient achieved a 70% improvement in Tender Joint Count and Swollen Joint Count and in at least 3 of the other 5 Core Data Set elements listed below. | |
| <ul style="list-style-type: none"> •Acute phase reactant (CRP). •Patient global assessment of disease activity. •Physician global assessment of disease activity. •Patient pain scale. •Disability/functional questionnaire (patient completed Health AssessmentQuestionnaire Disability Index [HAQ-DI]). | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 2, 4, 8, 12, 16, 20, and 24. | |

| End point values | FKB327 | Humira | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Responders % | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n = 362, 352) | 0.3 (0 to 1.5) | 2.3 (1 to 4.4) | | |
| Week 4 (n = 359, 349) | 4.5 (2.6 to 7.1) | 6.9 (4.5 to 10.1) | | |
| Week 8 (n = 353, 347) | 11.3 (8.2 to 15.1) | 10.7 (7.6 to 14.4) | | |
| Week 12 (n = 351, 342) | 15.4 (11.8 to 19.6) | 13.2 (9.8 to 17.2) | | |
| Week 16 (n = 350, 342) | 17.4 (13.6 to 21.8) | 19 (15 to 23.6) | | |
| Week 20 (n = 345, 339) | 20.9 (16.7 to 25.5) | 23.6 (19.2 to 28.5) | | |
| Week 24 (n = 342, 338) | 21.3 (17.1 to 26.1) | 25.1 (20.6 to 30.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (swollen joint count)

| | |
|-----------------|---|
| End point title | Individual ACR core set variables (swollen joint count) |
|-----------------|---|

End point description:

Counts of swollen joints from amongst 68/66 selected joints were to be performed by a trained and qualified joint assessor using standardised techniques recommended by the European League Against Rheumatism (EULAR).

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

End point timeframe:

Base line to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Count | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 363, 358) | 16.3 (± 9.1) | 16 (± 8.96) | | |
| Week 24 (n = 342, 339) | 3.8 (± 6.04) | 3.5 (± 5.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (tender joint count)

| | |
|-----------------|--|
| End point title | Individual ACR core set variables (tender joint count) |
|-----------------|--|

End point description:

Counts of tender from amongst 68/66 selected joints were to be performed by a trained and qualified joint assessor as scheduled using standardised techniques recommended by the European League Against Rheumatism (EULAR).

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

End point timeframe:

Baseline to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Count | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 363, 358) | 26.2 (± 14.49) | 25.9 (± 14.52) | | |
| Week 24 (n = 342, 339) | 8.5 (± 10.56) | 8.1 (± 9.36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (C-Reactive Protein)

| | |
|--|--|
| End point title | Individual ACR core set variables (C-Reactive Protein) |
| End point description: | |
| Analysis of serum C-Reactive Protein (CRP) concentrations for inclusion in the ACR20/50/70 and DAS28-CRP scores was performed by a central laboratory. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 24 | |

| End point values | FKB327 | Humira | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Count | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 362, 358) | 25.12 (± 26.746) | 26.73 (± 28.534) | | |
| Week 24 (n = 340, 340) | 10.98 (± 16.819) | 11.78 (± 18.528) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (patient's assessment of disease activity)

| | |
|---|--|
| End point title | Individual ACR core set variables (patient's assessment of disease activity) |
| End point description: | |
| Patient global assessment of disease activity visual analogue scale (VAS; ranging from very well to extremely bad) was assessed on 100-point scales. This VAS was to be completed by the patient themselves and results were recorded on an ePRO tablet device. | |
| End point type | Secondary |

End point timeframe:

Base line to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 363, 358) | 68 (± 17.98) | 68.2 (± 18.18) | | |
| Week 24 (n = 342, 339) | 35.2 (± 24.04) | 33.2 (± 23.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (physician's assessment of disease activity)

| | |
|-----------------|--|
| End point title | Individual ACR core set variables (physician's assessment of disease activity) |
|-----------------|--|

End point description:

Physician global assessment of disease activity visual analogue scale (VAS; ranging from very low to very high) was assessed on 100-point scales. This VAS was to be completed by the physician themselves and results were recorded on an ePRO tablet device.

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

End point timeframe:

Baseline to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 362, 358) | 68.4 (± 14.58) | 66.2 (± 15.48) | | |
| Week 24 (n = 342, 338) | 21.5 (± 17.29) | 21.5 (± 16.97) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (patient's assessment of pain)

| | |
|-----------------|--|
| End point title | Individual ACR core set variables (patient's assessment of pain) |
|-----------------|--|

End point description:

Patient assessment of pain was assessed on 100-point scales. This VAS were to be completed by the patient themselves and results were recorded on an ePRO tablet device.

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

End point timeframe:

Baseline to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 363, 358) | 66.8 (± 18.71) | 67.7 (± 18.56) | | |
| Week 24 (n = 342, 338) | 34.7 (± 23.86) | 33.6 (± 23.86) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Individual ACR core set variables (Health Assessment Questionnaire Disability Index [HAQ-DI]) over time)

| | |
|-----------------|--|
| End point title | Individual ACR core set variables (Health Assessment Questionnaire Disability Index [HAQ-DI]) over time) |
|-----------------|--|

End point description:

The HAQ-DI is a 20-question, self-administered instrument that measures the patient's functional ability on a 4-level difficulty scale (0 to 3, with 0 representing normal or no difficulty, and 3 representing inability to perform). Eight categories of functioning are included: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The HAQ-DI questionnaire was to be completed on the ePRO device by the patient themselves.

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

End point timeframe:

Baseline to Week 24

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 363, 358) | 1.78 (± 0.544) | 1.8 (± 0.538) | | |
| Week 24 (n = 342, 338) | 1.21 (± 0.696) | 1.26 (± 0.719) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DAS28-CRP score over time

| | |
|--|-------------------------------------|
| End point title | Change in DAS28-CRP score over time |
| End point description: The DAS28 score is a combined index that has been developed to measure the disease activity in patients with RA and has been extensively validated for its use in clinical studies. The DAS28 assessment involved evaluating the number of tender (TJC) and swollen (SJC) joints (out of 28 specified joints), serum CRP, and patient global assessment of disease activity (VAS from 0 to 100, very well to extremely bad). | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 24 | |

| End point values | FKB327 | Humira | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 362, 358) | 6.05 (\pm 0.913) | 6.06 (\pm 0.852) | | |
| Week 24 (n = 340, 339) | 3.47 (\pm 1.298) | 3.47 (\pm 1.336) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DAS28 score based on erythrocyte sedimentation rate (DAS28-ESR)

| | |
|--|---|
| End point title | DAS28 score based on erythrocyte sedimentation rate (DAS28-ESR) |
| End point description: The DAS28 score is a combined index that has been developed to measure the disease activity in patients with RA and has been extensively validated for its use in clinical studies. The DAS28-ESR assessment involved evaluating the number of tender (TJC) and swollen (SJC) joints (out of 28 specified joints), serum ESR, and patient global assessment of disease activity (VAS from 0 to 100, very well to extremely bad). | |
| End point type | Secondary |
| End point timeframe: Baseline to Week 24 | |

| End point values | FKB327 | Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 363 | 358 | | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 361, 355) | 6.52 (± 0.941) | 6.56 (± 0.902) | | |
| Week 24 (n = 342, 338) | 3.82 (± 1.384) | 3.85 (± 1.371) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients developing Anti Drug Antibodies (ADAs)

| | |
|--|---|
| End point title | Proportion of patients developing Anti Drug Antibodies (ADAs) |
| End point description: | |
| Blood samples for the assessment of ADA activity were to be collected at Baseline (Week 0), prior to dosing at Weeks 2, 4, 12, and 24. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to last sampling day | |

| End point values | FKB327 | Humira | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 366 | 362 | | |
| Units: percentage % | | | | |
| number (not applicable) | | | | |
| Baseline (Positive) | 4.4 | 5.5 | | |
| Baseline (Negative) | 95.4 | 94.2 | | |
| Baseline (Missing) | 0.3 | 0.3 | | |
| Last sampling day (Positive) | 61.7 | 59.1 | | |
| Last sampling day (Negative) | 38.3 | 40.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough adalimumab concentration

| | |
|---|---------------------------------|
| End point title | Trough adalimumab concentration |
| End point description: | |
| Blood samples for the quantification of adalimumab concentration in serum were to be collected at Baseline (Week 0), prior to dosing at Weeks 2, 4, 12 and 20, and Week 24. Samples were to be taken prior to dosing (trough samples). Concentrations of MTX were not assessed. | |
| End point type | Secondary |

End point timeframe:

Baseline to Week 24

| End point values | FKB327 | Humira | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 364 | 358 | | |
| Units: ng/ml | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 | 2434.6 (2321.4 to 2553.2) | 2089.1 (1990.9 to 2192.2) | | |
| Week 4 | 3450.6 (3223.2 to 3694.1) | 2932.1 (2737 to 3141.1) | | |
| Week 12 | 4316.3 (3919.6 to 4753.2) | 3851.5 (3493.9 to 4245.7) | | |
| Week 20 | 4369.8 (3892.3 to 4905.9) | 3873 (3445.9 to 4353) | | |
| Week 24 | 4126 (3645.1 to 4670.4) | 3758.2 (3316.8 to 4258.3) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were carefully monitored for AEs from signing of informed consent until Week 24 (for patients who will enter the open-label extension), Week 26 (for patients who did not enter the open-label extension), or the Early Termination visit.

Adverse event reporting additional description:

SAEs were followed until resolution, the Investigator confirmed the event was unlikely to resolve or the patient was recorded as lost to follow-up.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | FKB327 |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|--------|
| Reporting group title | Humira |
|-----------------------|--------|

Reporting group description: -

| Serious adverse events | FKB327 | Humira | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 366 (4.10%) | 19 / 362 (5.25%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine leiomyoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 2 / 362 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Amyloidosis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Lichen sclerosis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 366 (0.82%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated tuberculosis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 2 / 362 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervicitis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Latent tuberculosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 366 (0.00%) | 1 / 362 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 366 (0.27%) | 0 / 362 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | FKB327 | Humira | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 366 (7.10%) | 29 / 362 (8.01%) | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 26 / 366 (7.10%) | 29 / 362 (8.01%) | |
| occurrences (all) | 26 | 29 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 02 September 2014 | Global Amendment 1 incorporated comments received from the European Union Voluntary Harmonisation Procedure (VHP) reviewer and the US Food and Drug Administration (FDA) which, taken together, could potentially affect patient safety and the integrity of the data. |
| 05 June 2015 | Global Amendment 2; following interactions with regulatory authorities, a change was made to the margins used to assess equivalence based on the primary endpoint. This change necessitated an increase in the study sample size. Additionally, during the course of preparing study related documentation a number of non-substantial changes were identified which were also incorporated into this global amendment. |
| 09 July 2015 | Global Amendment 3; a potential safety issue concerning the comparator treatment arm only, which may affect handling of the study drug for site staff and current and future patients enrolled on the study protocol, was identified. The product information for the comparator treatment contains information on a potential safety risk for people with allergies to rubber or latex as the needle cover on the product contains dry natural rubber. All participating research sites were informed of appropriate steps to take to minimize any potential risks. These steps were not taken with regard to any specific known adverse event for any patient enrolled on the study, but rather due to the potential of an allergic reaction. The study protocol was amended to include this information. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported