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
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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. • 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

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.
•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.
•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.
•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 (± 0.913)	6.06 (± 0.852)		
Week 24 (n = 340, 339)	3.47 (± 1.298)	3.47 (± 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 sclerosus			
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