FUJIFILM KYOWA KIRIN BIOLOGICS CO., LTD

CLINICAL PROTOCOL

INCORPORATES GLOBAL AMENDMENT 4 AND LOCAL AMENDMENT 1 FOR CZECH REPUBLIC, GERMANY, POLAND, ROMANIA, AND SPAIN

An Open-label Extension Study to Compare the Long-term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE)

Protocol Number:	FKB327-003
Protocol Acronym:	ARABESC-OLE
Compound:	FKB327 (adalimumab)
EudraCT Number:	2014-000110-61
Phase:	Phase 3
Version and Date:	Version 4.3 (Based on Global Amendment 4 and Local Amendment 1), 15 April 2016.
Name and Address of the Sponsor:	Fujifilm Kyowa Kirin Biologics Co., Ltd 1-6-1 Ohtemachi Chiyoda-ku Tokyo 100-8185 Japan
Name and Address of the Medical Monitors:	Redacted

PROTOCOL SUMMARY

Sponsor: Fujifilm Kyowa Kirin Biologics Co., Ltd.

Study Title: An Open-label Extension Study to Compare the Long-term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE)

Study Number: FKB327-003.

Protocol Acronym: ARABESC-OLE.

EudraCT Number: 2014-000110-61.

Name of Investigational Product: FKB327.

Name of Active Ingredient: adalimumab.

Study Phase: 3.

Number of Patients Planned: up to 680 patients (estimated 544 patients; approximately 272 patients in each of the FKB327 and Humira® arms, allowing 20% dropout from study FKB327-002).

Number of Sites Planned: approximately 130 - the sites will be the same as for study FKB327-002.

Study Population: Only patients who completed the double-blind study FKB327-002 will be permitted to continue into this extension study. These will be patients with rheumatoid arthritis (RA) who are taking concomitant methotrexate (MTX) and folate.

Primary Objective: The primary objective of this study is to compare the safety of long-term treatment with FKB327 and Humira in patients with RA.

Secondary Objectives: The secondary objectives of this study are as follows:

- To compare the efficacy of long-term treatment with FKB327 and Humira in patients with RA.
- To compare the proportion of patients developing anti-drug antibodies (ADAs) on long-term treatment with FKB327 and Humira in patients with RA.
- To compare the pharmacokinetics (PK) of long-term treatment with FKB327 and Humira in patients with RA.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who are switched from Humira in the preceding FKB327-002 double-blind study to FKB327 in the FKB327-003 open-label extension (OLE) study, and of patients who are switched from FKB327 to Humira, respectively.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who are switched from FKB327 in the preceding FKB327-002 double-blind study to Humira in the FKB327-003 OLE study, and then switch back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch).

Inclusion Criteria: Patients will be eligible for enrolment into the study if they meet all of the following inclusion criteria:

1. Have completed all 24 weeks of study procedures (including dosing) according to protocol FKB327-002, with a minimum of 9 doses of study drug received, and are continuing with stable concomitant MTX and folate.
2. In the investigator's opinion, the patient showed a clinical response to treatment during Study FKB327-002.
3. Are willing to participate in the study and have provided written informed consent.
4. Females of childbearing potential must have a negative pregnancy test prior to study dosing. Both sexes must be willing to take adequate contraceptive precautions throughout the study period and continuing for at least 5 months post study. Acceptable methods of contraception in this study are: surgical sterilisation, intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptives, partner's vasectomy, or a double-protection method (condom or diaphragm with spermicide).

Exclusion Criteria: Patients will be excluded from the study if any of the following exclusion criteria are met:

1. Evidence of a serious adverse event (SAE) ongoing from Study FKB327-002 at entry to this study, including a serious infection, malignancy, or any other condition that may put patients at increased risk when receiving treatment with adalimumab.
2. Presence of active and/or untreated latent tuberculosis (TB) as detected by QuantiFERON test at Week 22 combined with chest X-ray at Week 24 in Study FKB327-002. Latent TB, treated with prophylactic anti-mycobacterial therapy for at least 3 weeks before study dosing is resumed, is acceptable. Patients may have up to a maximum of 4 weeks interruption of dosing between the last dose in Study FKB327-002 and Week 0 dosing in study FKB327-003 for this purpose.
3. Were non-compliant with FKB327-002 study procedures, or with any condition or circumstances, which, in the opinion of the Investigator, makes them unlikely or unable to comply with study procedures and requirements.
4. American College of Rheumatology (ACR) Functional Class IV.
5. Acute infection requiring antibiotic treatment within 2 weeks of Week 0 dosing. Patients may have up to a maximum of 4 weeks interruption of dosing between the last dose in Study FKB327-002 and Week 0 dosing in Study FKB327-003 in order to recover from infection requiring antibiotic treatment.
6. Presence of serious, uncontrolled disease of another body system including cardiovascular, neurological, pulmonary, renal and hepatic disease.
7. Presence of New York Heart Association (NYHA) Class III/IV heart failure.
8. Presence of any uncontrolled disease for which steroid treatment is regularly required for flares, eg, asthma.
9. Patients with demyelinating diseases (eg, multiple sclerosis).
10. Pregnant or breastfeeding women.

Study Drug: Patients will receive subcutaneous (sc) FKB327 40 mg every other week (eow) or sc Humira 40 mg eow from Week 0 to Week 28; after this, all patients will receive FKB327 40 mg eow from Week 30 to Week 76. Patients will continue to take the same stable dose of MTX (10-25 mg/week) throughout this study as taken in Study FKB327-002, with folic/folinic acid at a dose of at least 5 mg/week.

Presentations: FKB327 will be supplied in a plastic pre-filled syringe (PFS) with a safety device. FKB327 in an Auto-Injector device presentation will be introduced during the open-label

follow-up treatment period depending on availability of the Auto-Injector relative to the patient's progress within the study. In both presentations, the dose will be 40 mg in 0.8 mL.

From Week 0 to Week 28 only, patients randomised to Humira will be supplied US-licensed Humira in a glass PFS. The dose will be 40 mg in 0.8 mL. Note: The needle cover of the Humira PFS contains dry rubber (latex) which should not be handled by persons sensitive to this substance without using latex-free gloves.

Blinding and Randomisation: This extension study is open-label throughout. Patients from Study FKB327-002 will be randomised to receive either FKB327 40 mg eow or Humira 40 mg eow from Week 0 to Week 28. Patients who received FKB327 in Study FKB327-002 will be randomised to receive FKB327 or Humira in a 2:1 ratio. Patients who received Humira in Study FKB327-002 will be randomised to receive Humira or FKB327 in a 2:1 ratio. From Week 30 to Week 76, all patients will receive FKB327 40 mg eow.

Duration of Participation: Patients may remain on study treatment for up to 76 weeks with a further post-treatment follow-up period of 4 weeks, making a total maximum duration of 80 weeks.

Study Design and Methodology: The first part of this study is an open-label, randomised, comparative, multi-centre, 2-arm extension Phase 3 study in patients with RA who are taking a stable dose of MTX who will continue from the preceding Study FKB327-002. Patients who complete Study FKB327-002 and consent to this open-label extension study will be randomised to receive treatment with either FKB327 40 mg eow or Humira 40 mg eow from Week 0 to Week 28. The second part of the study is an open-label, multi-centre, single arm extension in which all patients receive prolonged FKB327 treatment from Week 30 to Week 76, followed by a 4-week follow-up period. Scheduled clinic visits will be conducted at Weeks 0, 2, 4, 8, 12, 24, 30, 32, 34, 42, 54, 66, 76, and 80. The patient or carer will administer interim doses of study drug at home (eow) between clinic visits. FKB327 in an Auto-Injector device presentation will be introduced during the open label follow up treatment period depending on availability of the Auto-injector relative to the patient's progress within the study.

At the Week 22 visit in Study FKB327-002, the investigator will discuss participation in this open-label extension study with the patient, if appropriate. If the patient is eligible for this study and gives informed consent to participate, the patient will be randomised into the study and Week 0 study drug dose for this study will be administered after the Week 24 study procedures for Study FKB327-002 have been performed. The first 3 doses of study drug (Weeks 0, 2, and 4 for all patients and Weeks 30, 32, and 34 for patients switching from Humira to FKB327 at that point) will be self-administered (or administered by a carer) at the study site after training has been given. Subsequent doses may be administered by the patient or carer at home, except when clinic visits for blood tests and efficacy assessments are scheduled when the dose must be given only after the blood samples have been drawn.

Primary Efficacy Endpoint: As the primary endpoint is safety, there is no primary efficacy endpoint in this study.

Secondary Efficacy Endpoint: The secondary efficacy endpoints are as follows:

- ACR20, ACR50 and ACR70 response rates from baseline (Week 0 from Study FKB327-002).
- Changes in Disease Activity Score 28 based on C-reactive protein (CRP) (DAS28-CRP) score compared to baseline (Week 0 from Study FKB327-002).

Other Endpoints: The other endpoints are as follows:

- Immunogenicity.
- PK

Safety Endpoints: The primary endpoint of the study is safety. Safety will be evaluated using the following assessments:

- Adverse events (AEs).
- SAEs, including serious infections and malignancies.
- Vital signs.
- Clinical laboratory tests.

Statistical Methods:

Safety endpoints: AEs will be summarised by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated by treatment sequence and relationship to treatment. SAEs, in particular infections and malignancies, will be summarised by treatment sequence. Safety data including vital signs, haematology, serum chemistry and urinalysis will be summarised by treatment sequence for each visit. Withdrawals from the study will be summarised by treatment sequence.

The incidence and size of injection site reactions and injection site pain VAS scores will be summarised by FKB327-003 treatment using descriptive statistics.

Efficacy endpoints: ACR20, ACR50 and ACR70 response rates from Baseline (Week 0) in Study FKB327-002 will be summarised by treatment sequence and visit. DAS28 score and the change from Baseline (Week 0 in the FKB327-002 study) in DAS28 score, and individual ACR core set variables (swollen joint count, tender joint count, CRP, patient's assessment of disease activity, physician's assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index [HAQ-DI]) will be summarised by treatment sequence and visit.

Other endpoints: The proportion of patients positive for ADAs in the confirmatory and neutralising assays at each sampling time point will be summarised by treatment sequence.

A mixed model for repeated measures will be fitted to the log transformed PK trough concentrations at Weeks 12, 24 and 30 (ie, during the randomised treatment period) with patient included as a random effect and fixed effect terms for week, treatment sequence, and Week x treatment sequence interaction. Provided the interaction term for Week x treatment sequence is not significant at the 10% level, only differences (ratios of geometric means) averaged over all time points will be estimated with 90% confidence intervals (CIs). The following comparisons will be of interest:

- FKB327 to Humira (based on treatment in FKB327-003).
- Sequence group FKB327-Humira relative to Humira-Humira.
- Sequence group Humira-FKB327 relative to Humira-Humira.

Due to the potential formation of ADAs, a secondary PK analysis will also be performed with ADA titre results.

PK samples collected during the follow-up treatment period (ie, Weeks 54 and 76) will be listed and summarised only.

Interim analysis: An interim analysis of planned endpoints for all patients will be performed once 100 patients randomised to FKB327 in study FKB327-002 and also to FKB327 in the randomised

phase of study FKB327-003 plus 100 patients randomised to Humira in study FKB327-002 and also to Humira in the randomised phase of study FKB327-003 have reached Week 30 in this study. This will provide more than 100 patient-years of exposure to FKB327 and to Humira across studies FKB327-002 and FKB327-003 for comparison.

SCHEDULE OF EVENTS

Table 1: Study Schedule - Randomised Treatment Period

Study Visit	**Treatment Period**									
Visit	**1[a]**	**2**	**3**	**NA**	**4**	**NA**	**5**	**NA**	**6**	**NA**
Week	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14-22**	**24**	**26 and 28[b]**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**
Informed consent	●									
Medical history including contact with active TB	●*									
Check of concomitant medication	(●)*		●		●		●		●	
Physical examination	(●)									
Weight	(●)								●	
Vital signs	(●)		●		●		●		●	
12-lead ECG	(●)									
Chest X-ray	(●)[c]									
Randomisation	●									
Provide patient with study medication and dosing diary, and instruct on their use			●		●		●		●	
Provide Patient Instruction Sheet			●		●		●		●	
Dosing Diary				●		●		●		●
Study medication administration (mg)	40[d]	40[d]	40[d]	40	40	40	40	40 (eow)	40	40 (eow)
Concomitant MTX and folate	→	→	→	→	→	→	→	→	→	→
Haematology	(●)*		●		●		●		●	
Serum chemistry	(●)*		●		●		●		●	
Dipstick urinalysis[e]	(●)*		●		●		●		●	
Pregnancy testing[f]	(●)*		●		●		●		●	
QuantiFERON test[g]									●	
CRP[h,i]	(●)*		●		●		●		●	
ESR[j]	(●)*									

Study Visit	**Treatment Period**									
Visit	**1[a]**	**2**	**3**	**NA**	**4**	**NA**	**5**	**NA**	**6**	**NA**
Week	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14-22**	**24**	**26 and 28[b]**
Visit Type	**Clinic**	**Clinic**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**
MMP-3	(●)									
Serum drug concentration ADA test	(●)* (●)*						● ●		● ●	
Injection site assessment (including injection site pain VAS)	●									
Adverse events[k]	→	→	→	→	→	→	→	→	→	→
Assessment of tender/swollen joints (68/66 joints)[h,i]	(●)*		●		●		●		●	
Patient global assessment of disease activity VAS[h,i]	(●)*		●		●		●		●	
Patient assessment of pain VAS[i]	(●)*		●		●		●		●	
Patient questionnaire for physical function (HAQ-DI)[i]	(●)*		●		●		●		●	
Physician global assessment of disease activity VAS[i]	(●)*		●		●		●		●	

Study Visit	Treatment Period									
Visit	1[a]	2	3	NA	4	NA	5	NA	6	NA
Week	0	2	4	6	8	10	12	14-22	24	26 and 28[b]
Visit Type	Clinic	Clinic	Clinic	Home	Clinic	Home	Clinic	Home	Clinic	Home

TB = tuberculosis; ECG = electrocardiogram; eow = every other week; MTX = methotrexate; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ADA = anti-drug antibody; HAQ-DI = Health Assessment Questionnaire Disability Index; VAS = visual analogue scale.

Note: for Visit 2 and Visit 3 there will be a window of ±3 days. For example, the Week 2 visit (Visit 2) should take place on Day 15, but could be as early as Day 12 or as late as Day 18. From Visit 4 (Week 8) onwards, a window of ±7 days is permissible.

At each visit all procedures are to be performed prior to dosing except recording of injection site reaction and any post-injection AEs.

[a] Pre-dose Week 0 assessments (represented by '(●)' in the table) are performed as part of the Week 24 visit of Study FKB327-002, which is the same as the Week 0 visit in this study.

[b] The Week 28 dose is the last dose of randomised study drug (FKB327 or Humira). All patients will then switch to dosing with FKB327 for the remainder of the study.

[c] X-ray to be performed unless patient has negative QuantiFERON test at Week 22 of study FKB327-002 with no signs/symptoms suggestive of lower respiratory infection.

[d] The first 3 doses of study drug (Weeks 0, 2, and 4) will be self-administered at the study site after training has been given. Subsequent doses may be administered by the patient or carer at home, except when clinic visits for blood tests and efficacy assessments are scheduled when the dose must be given after blood samples are drawn.

[e] If the dipstick reveals any clinically significant abnormalities a second sample (provided on the same day if, possible), should be sent to the central laboratory.

[f] Females of childbearing potential only.

[g] May be omitted if patient is receiving anti-mycobacterial treatment for latent tuberculosis.

[h] Assessment contributes to DAS28 score.

[i] Assessment contributes to determination of achievement of ACR20, ACR50, and ACR70 response.

[j] Part of Study FKB327-002 only.

[k] Ongoing events from Study FKB327-002 will be recorded in that study. Any new or worsening events will be recorded for Study FKB327-003.

* Procedures marked with an asterisk need to be repeated if there is a delay of 2 weeks or more (up to the maximum allowed delay of 4 weeks) between Week 24 of study FKB327-002 and Week 0 of study FKB327-003, for example, due to the need to interrupt study drug while serious infection or latent tuberculosis is treated.

Table 2: Study Schedule - Follow-up Treatment Period

Study Visit	**Treatment Period**										
Visit	**7**	**8 & 9**	**NA**	**10**	**NA**	**11**	**NA**	**12**	**NA**	**13**	**14**
Week	**30**	**32 & 34**	**36-40**	**42**	**44-52**	**54**	**56-64**	**66**	**68-74**	**76**	**80 or EOS**
Visit Type	**Clinic**	**Clinic or Home[a]**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Clinic**
Check of concomitant medication	●			●		●		●		●	●
Physical examination											●
Vital signs											●
Chest X-ray[b]	●										●
Provide patient with study medication and dosing diary, and instruct on their use	●			●		●		●		●	
Provide Patient Instruction Sheet	●			●		●		●		●	
FKB327 administration (mg)	40[c]	40[c]	40 (eow)	40	40 (eow)	40	40 (eow)	40	40 (eow)	40	
Dosing Diary		●	●		●		●		●		
Concomitant MTX and folate	→										→
Haematology	●			●		●		●		●	●
Serum chemistry	●			●		●		●		●	●
Dipstick urinalysis[d]	●			●		●		●		●	●
Pregnancy testing[e]	●			●		●		●		●	
QuantiFERON test[f]										●	●[g]
CRP[h,i]	●			●		●		●		●	●
Serum drug concentration	●					●				●	●
ADA test	●					●				●	●
Injection site assessment (including injection site pain VAS)[j]	●										

Study Visit	**Treatment Period**										
Visit	**7**	**8 & 9**	**NA**	**10**	**NA**	**11**	**NA**	**12**	**NA**	**13**	**14**
Week	**30**	**32 & 34**	**36-40**	**42**	**44-52**	**54**	**56-64**	**66**	**68-74**	**76**	**80 or EOS**
Visit Type	**Clinic**	**Clinic or Home[a]**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Home**	**Clinic**	**Clinic**
Adverse events	→	→	→	→	→	→	→	→	→	→	→
Assessment of tender/swollen joints (68/66 joints)[h,i]	●			●		●		●		●	●
Patient global assessment of disease activity VAS[h,i]	●			●		●		●		●	●
Patient assessment of pain VAS[i]	●			●		●		●		●	●
Patient questionnaire for physical function (HAQ-DI)[i]	●			●		●		●		●	●
Physician global assessment of disease activity VAS[i]	●			●		●		●		●	●

Study Visit	Treatment Period										
Visit	7	8 & 9	NA	10	NA	11	NA	12	NA	13	14
Week	30	32 & 34	36-40	42	44-52	54	56-64	66	68-74	76	80 or EOS
Visit Type	Clinic	Clinic or Home[a]	Home	Clinic	Home	Clinic	Home	Clinic	Home	Clinic	Clinic

EOS = end-of-study; eow = every other week; MTX = methotrexate; CRP = C-reactive protein; ADA = anti-drug antibody; HAQ-DI = Health Assessment Questionnaire Disability Index; VAS = visual analogue scale; MMP-3 = matrix metalloproteinase-3.

Note: for all visits during the follow-up treatment period, a window of ±7 days is permissible.

At each visit all procedures are to be performed prior to dosing except recording of injection site reaction and any post-injection AEs.

[a] The Week 32 and 34 visits are to be performed in the clinic for patients who have switched from Humira to FKB327 only. Patients remaining on FKB327 can dose at home.

[b] X-ray to be performed at Week 30/80 or EOS unless patient has negative QuantiFERON test at Week 24/76 or EOS, respectively, with no signs/symptoms suggestive of lower respiratory infection.

[c] For patients switching from Humira to FKB327, the first 3 doses of FKB327 (Weeks 30, 32, and 34) will be self-administered at the study site after training has been given. Subsequent doses of FKB327 may be administered by the patient or carer at home, except when clinic visits for blood tests and efficacy assessments are scheduled when the dose must be given after blood samples are drawn.

[d] If the dipstick reveals any clinically significant abnormalities a second sample (provided on the same day if, possible), should be sent to the central laboratory.

[e] Females of childbearing potential only.

[f] May be omitted if patient is receiving anti-mycobacterial treatment for latent tuberculosis.

[g] EOS only.

[h] Assessment contributes to DAS28 score.

[i] Assessment contributes to determination of achievement of ACR20, ACR50, and ACR70 response.

[j] An additional injection site assessment will be performed at the time of switching to the Auto-Injector during the open-label follow up treatment period

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADAs	Anti-drug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
BCG	Bacillus Calmette–Guérin
CD	Crohn's disease
CDM	Clinical Data Manager
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
CRA	Clinical Research Associate
CRP	C-reactive protein
CS	Clinically significant
CSR	Clinical Study Report
DAS28	Disease Activity Score 28
DCR	Device Complaint Report
DMARD	Disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDCF	Electronic Data Clarification Forms
eow	Every other week
ePRO	Electronic patient-reported outcomes
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HAQ-DI	Health Assessment Questionnaire Disability Index
Hb	Haemoglobin
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
KHK	Kyowa Hakko Kirin Co Ltd
LSM	Least squares means
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP-3	Matrix metalloproteinase-3
mTNF-α	Transmembrane TNF-α
MTX	Methotrexate
NCS	Not clinically significant
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	Open-label extension
PDF	Portable Document Format
PFS	Pre-filled syringe

PK	Pharmacokinetics
PKAS	PK Analysis Set
PPD	Purified protein derivative
PT	Preferred Term
RA	Rheumatoid arthritis
RBC	Red blood cell
rhTNF-α	Human recombinant TNF-α
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SDV	Source Data Verification
SJC	Swollen joint count
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Elimination half-life
TB	Tuberculosis
TJC	Tender joint count
t_{max}	Time of maximum concentration
TNF-α	Tumour necrosis factor-alpha
TSE	Transmissible spongiform encephalopathy
US	United States of America
VAS	Visual analogue scale
WBC	White blood cell

1 BACKGROUND INFORMATION

1.1 Indication

Tumour necrosis factor (TNF)-α is a pro-inflammatory cytokine that is involved in normal inflammatory and immune response. Overexpressed TNF-α has been implicated in the pathogenesis of various immunological diseases. One such immunological disease is rheumatoid arthritis (RA), a common, chronic, inflammatory disorder. The disease is characterised by a progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction. This bony destruction is thought to be irreversible. RA is a systemic disease with non-articular manifestations including serositis and nodule formation. There is currently no known cure for RA.

RA produces substantial morbidity and increased mortality. Specifically, pain, swelling and stiffness in multiple joints are the hallmark of the disease. Analgesics are usually required on a chronic basis. Patients usually experience moderate disability within 2 years of diagnosis, and 30% of patients are severely disabled after 10 years. In addition to loss of employment, this disability often compromises the ability of patients to undertake their activities of daily living and can impact sexual and social functioning.

Cytokines play critical roles in normal biologic processes, such as cell growth, inflammation and immunity. TNF and the other inflammatory cytokines are critical in the progression of inflammatory synovitis and articular matrix degradation and, therefore, represent promising targets for therapeutic intervention in RA. Clinical experience with agents that block TNF activity demonstrate the central role for this cytokine in the pathogenesis of RA and other autoimmune diseases.[1]

1.2 Investigational Product

Adalimumab is a recombinant human monoclonal antibody against human 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. TNF production is induced by a wide variety of stimuli, including bacteria, viruses, trauma, immune complexes, and other cytokines. At low concentrations, TNF-α has beneficial effects, such as augmentation of host defence against infection. However, 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, Crohn's disease (CD) and ulcerative colitis.

Adalimumab was first approved for the treatment of RA in December 2002 in the United States of America (US) and in September 2003 in the European Union (EU), and was subsequently launched globally under the brand name Humira®. Humira is currently indicated in the US for the treatment of RA, psoriatic arthritis, ankylosing spondylitis, CD, ulcerative colitis and plaque psoriasis in adults, and for the treatment of CD and polyarticular juvenile idiopathic arthritis in children, and in the EU for axial spondyloarthritis in adults, children from 4 years of age with severe plaque psoriasis, and

for active enthesitis-related arthritis from 6 years of age. The approved adult dose of Humira for all indications is 40 mg administered by subcutaneous (sc) injection every other week (eow). Higher loading and maintenance doses are approved for indications other than RA. Humira is presented for adult use as a pre-filled syringe (PFS) or pre-filled pen containing 40 mg adalimumab in 0.8 mL solution for injection.[2]

FKB327 is being developed as a proposed biosimilar product that contains adalimumab, the same active ingredient as Humira. FKB327 contains different excipients to those in Humira, but the FKB327 excipients are all commonly used. FKB327 is manufactured under current Good Manufacturing Practice (cGMP) and is supplied as a highly purified biological product, with appropriate steps for virus inactivation and removal, and there are no transmissible spongiform encephalopathy (TSE) risks.

1.3 Background Therapy

Methotrexate (MTX) is an antimetabolite that has traditionally been used to treat certain types of cancer. MTX is also used in lower doses in the treatment of RA, where it is thought to act by decreasing the activity of the immune system, and represents the conventional disease modifying anti-rheumatic drug (DMARD) of choice for RA treatment.[3] In this study, MTX will be administered with concomitant folate therapy to counter the adverse effects on red blood cells.

1.4 Nonclinical Studies

In vitro studies have shown that FKB327 and Humira are similar in terms of binding to the target antigens (human recombinant TNF-α [rhTNF-α] and transmembrane TNF-α [mTNF-α]), binding to Fcγ receptors and neonatal Fc receptors, inhibition of cell killing, induction of apoptosis, and cellular cytotoxicity (antibody-dependent and complement-dependent). An *in vivo* study using the mouse polyarthritis model showed that the symptoms of arthritis were ameliorated to a similar extent by FKB327 and Humira, indicating similarity. In this *in vivo* study, the toxicokinetic profile and anti-drug antibody (ADA) formation were also similar.

The non-clinical data for Humira did not show any special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.[2] A comparative 4-week repeat dose toxicity of FKB327 and Humira in cynomolgus monkeys using a dose of 30 mg/kg sc once weekly has been performed in order to prepare for a global submission. The results did not show any difference between FKB327 and Humira in terms of toxicity.

Further information on the nonclinical studies of FKB327 can be found in the Investigator's Brochure.[2]

1.5 Clinical Studies

1.5.1 Clinical Studies with FKB327

A Phase 1 study comparing the pharmacokinetic (PK) characteristics, safety and immunogenicity of a single dose of FKB327 with those of EU- and US-Humira in healthy subjects has been completed (Study FKB327-001). In this parallel group study,

180 healthy male and female subjects were randomly assigned to receive a single 40 mg sc injection of FKB327, EU-licensed Humira, or US-licensed Humira in a 1:1:1 ratio. All subjects completed the study with the exception of 1 subject in the FKB327 treatment group who withdrew himself from the study. The primary endpoints were the PK parameters area under the concentration-time up to the last non-zero value (AUC_{0-t}), area under concentration-time curve extrapolated to infinite time ($AUC_{0-\infty}$), and maximum concentration (C_{max}).

The serum concentration time profiles of adalimumab following single sc administration of FKB327, EU-Humira, and US-Humira were similar, and were measurable, on average, up to 1536 hours post-dose across all treatments (ie, the last sampling time point post-dose). C_{max} of adalimumab was attained (t_{max}) at approximately 144 hours post-dose (median estimates) following single sc administration of FKB327 and US-Humira, with t_{max} attained slightly later for EU-Humira at 192 hours post-dose. Thereafter, serum concentrations declined with geometric mean elimination half-life ($t_{½}$) of 324, 345 and 366 hours for FKB327, EU-Humira, and US-Humira, respectively.

Using an analysis of covariance (ANCOVA), as the 90% confidence intervals (CIs) around the ratio of geometric least squares means (LSMs) were within the pre-defined limits of 0.80 to 1.25 for all treatment comparisons and primary PK endpoints ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}), similarity was indicated between all 3 treatments. Similarity was also indicated between all 3 treatments for the secondary PK endpoint AUC_{0-360h}, and for 2 of the 3 treatment comparisons for the secondary PK endpoint $t_{½}$ (similarity could not be concluded between FKB327/US-Humira based on $t_{½}$); however, with ADA titre values included as an additional covariate in the equivalence analysis, similarity was indicated between all 3 treatments for all median treatment comparisons and PK endpoints (including $t_{½}$).

Preliminary results of an analysis of variance (ANOVA) of these data, assuming equal variance, were similar to those of the ANCOVA analyses, although the 90% CI were wider. The ANOVA results for the FKB327/US-Humira and EU-Humira/US-Humira comparisons still met the pre-specified limits (0.80 to 1.25) for all 3 primary endpoints. However, for the FKB327/EU-Humira comparison; C_{max} (a primary endpoint) and AUC_{0-360h} (a secondary endpoint) both had upper 90% CI which fell slightly outside the equivalence criteria of 0.80 to 1.25 using the ANOVA approaches. The increased variability for FKB327/EU-Humira may be explained by differences in selected covariates (age, body weight, and sex) between the treatment groups. Indeed, by accounting for these pre-specified covariates in the primary ANCOVA analysis, the 90% CI for C_{max} met the equivalence limits (0.80, 1.25). Overall, the data indicated PK similarity between all 3 treatments.

The study demonstrated that the safety profile was similar across the 3 treatment groups. The most common treatment related adverse events (AEs) were headache, upper respiratory tract infection, oropharyngeal pain and injection site haematoma and were reported for similar numbers of subjects in each treatment group, with the exception of injection site haematoma which was reported for more subjects in the FKB327 treatment

group (4 subjects) than in the EU- and US-Humira treatment groups (1 and 2 subjects, respectively). Most AEs were mild or moderate in intensity.

Two subjects experienced serious adverse events (SAEs): 1 subject receiving FKB327 experienced loss of consciousness 11 days after dosing and 1 subject receiving US-Humira developed a psychotic disorder 8 days after dosing, the same day that he was discharged from the study unit. These 2 subjects were in the same dosing cohort and were dosed consecutively. Both SAEs resolved and were considered to be possibly related to study drug due to the temporal relationship with study dosing. There were no deaths, other significant AEs or AEs leading to withdrawal. Two months after study dosing, 1 subject reported he had unprotected sex and his partner became pregnant. The outcome of this pregnancy was successful.

In total, 9 subjects had clinically significant (CS) abnormal laboratory results during the study: 3 subjects in the FKB327 treatment group, 2 subjects in the EU-Humira treatment group and 4 subjects in the US-Humira treatment group. The most common CS abnormal laboratory result was low neutrophil count, which was reported as an AE of neutropenia for 4 subjects overall (2 on FKB327 and 2 on US-Humira); 2 of the subjects (1 on FKB327 and 1 on US-Humira) had abnormally low neutrophil counts at Screening which was not considered to be of clinical significance. None of the CS abnormal laboratory test results was associated with any clinical signs or symptoms. There were no other notable results for any of the other safety parameters.

The distribution of ADA titre results at the last sampling time point was consistent between treatments: approximately 31.7%, 26.7% and 30.0% of subjects on FKB327, EU- and US-Humira, respectively, had negative ADA titres, and there were similar proportions of subjects in each treatment group at each positive ADA titre level. Of all positive titres (non negative screening results) measured at the last sampling time point, approximately 82.7% were positive in the neutralising antibody assay, with a further 10.2% considered to be inconclusive due to interference from high levels of drug (>500 ng/mL).

Study FKB327-002, a randomised, double-blind, active-controlled, 26-week Phase 3 study comparing the efficacy and safety of FKB327 and Humira in patients with RA who have had an inadequate response to MTX is scheduled to start in Q2 2014. Study FKB327-002 will enrol approximately 680 patients (340 patients per arm). Only patients who have completed Study FKB327-002 will be eligible to enter this open-label extension (OLE) study (FKB327-003).

1.5.2 Clinical Studies with Humira

Humira has been studied in >8,000 patients in pivotal controlled and open-label studies for up to 60 months or more. The most commonly reported AEs were infections (nasopharyngitis, upper respiratory tract infection, and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. Clinical response rate of 63.3% was observed for RA in combination therapy with MTX (American College of Rheumatology [ACR]20 at 6 months). Other response rates observed for autoimmune indications were 58.0% for CD and 70.9% for psoriasis.[4] It is

expected that the efficacy and safety profiles of FKB327 will be similar to those of Humira in clinical studies.

1.6 Potential Risks and Benefits

The mode of action and risks for FKB327 are expected to be the same as those for Humira since the active ingredient of both products is adalimumab. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1).[5] In the context of this OLE study, the benefit is to provide patients that benefited from adalimumab therapy with a long-term treatment option. Patients should have completed Study FKB327-002, which means they did not show any adverse reaction that prevented them from receiving long term therapy. The main risk is decreased immune surveillance, leading to increased incidence of infections (including reactivation of latent infections) and potentially tumour formation.

Humira is immunogenic. In pivotal studies in RA and psoriatic arthritis, anti-adalimumab neutralizing antibodies were identified in 5.5% and 10% of patients, respectively,[6] although these rates were lower in patients who were also receiving MTX, 1% and 7%, respectively. Formation of neutralising ADAs is associated with a higher clearance of Humira and reduced efficacy. Formation of ADA can also be associated with hypersensitivity reactions including anaphylaxis. There is a risk that patients taking part in this study may develop ADAs. If such patients subsequently required treatment with Humira in the future, therapeutic benefit might be reduced and the risk of hypersensitivity reactions increased.

The most common adverse effects of Humira are injection site reactions and infections. The majority of injection site reactions are mild to moderate and reversible.[6] The most common infections seen in patients given repeated doses of Humira are upper respiratory tract infections, which are easily monitored and treatable. Patients with a history of chronic or acute infection, including a positive result for hepatitis or untreated latent tuberculosis (TB), were not permitted to enter Study FKB327-002 and so will not be included in this OLE study. Patients will be monitored during the study for development of such infections and, when required, study treatment will be promptly discontinued.

1.7 Rationale for Study

This Phase 3 open-label extension study will compare the long-term safety, efficacy, immunogenicity and multiple-dose PK of FKB327 with Humira in patients with RA. This study will commence once a patient completes Study FKB327-002 and opts to enter this extension study.

In order to make a long-term treatment comparison, a proportion of patients in the first part of this open-label extension study will receive Humira, and the findings in that treatment arm will be compared to those for patients receiving FKB327. Therefore, in addition to providing longer term data regarding the safety, immunogenicity and efficacy of FKB327, the study will provide the opportunity for a descriptive and objective

comparison of these parameters between FKB327 and Humira over longer term treatment (approximately 1 year in total from the start of Study FKB327-002 to the end of Study FKB327-003). Furthermore, the study will also permit an evaluation of these parameters in patients switching between the products after randomisation and could therefore provide relevant data for subsequent clinical practice.

1.8 Study Conduct

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

1.9 Population to be Studied

The study will enrol only patients who completed Week 24 visit procedures and 22 weeks of treatment of the double-blind study FKB327-002 (with a minimum of 9 doses of study drug received).

Inclusion and exclusion criteria are presented in Sections 4.1 and 4.2, respectively.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the safety of long-term treatment with FKB327 and Humira in patients with RA.

2.2 Secondary Objectives

- To compare the efficacy of long-term treatment with FKB327 and Humira in patients with RA.
- To compare the proportions of patients developing ADAs on long-term treatment with FKB327 and Humira in patients with RA.
- To compare the PK of long-term treatment with FKB327 and Humira in patients with RA.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who are switched from Humira in the preceding FKB327-002 double-blind study to FKB327 in the FKB327-003 OLE study, and of patients who are switched from FKB327 to Humira, respectively.
- To evaluate safety, changes in efficacy, and changes in PK and immunogenicity in patients who are switched from FKB327 in the preceding FKB327-002 double-blind study to Humira in the FKB327-003 OLE study, and then switch back to FKB327 in the second part of the FKB327-003 OLE study (from Week 30; double switch).

3 STUDY DESIGN

3.1 Primary Endpoint

- Safety will be evaluated using the following assessments: AEs; SAEs including serious infections and malignancies, vital signs, and clinical laboratory tests.

3.2 Secondary Endpoints

- ACR20, ACR50 and ACR70 response rates from baseline (Week 0 from Study FKB327-002).
- Changes in Disease Activity Score 28 based on C-reactive protein (CRP) (DAS28-CRP) score compared to baseline (Week 0 from Study FKB327-002).

3.3 Other Endpoints

- Immunogenicity.
- PK.

3.4 Description of Study

The first part of this study is an open-label, randomised, comparative, multi-centre, 2-arm extension Phase 3 study in patients with RA who are taking a stable dose of MTX and folate who will continue from the preceding Study FKB327-002. Eligible patients who complete Study FKB327-002 and consent to this open-label extension study will be randomised to receive treatment with either FKB327 40 mg eow or Humira 40 mg eow from Week 0 to Week 28. Patients who received FKB327 in Study FKB327-002 will receive FKB327 or Humira in a 2:1 ratio and patients who received Humira in Study FKB327-002 will receive Humira or FKB327 in a 2:1 ratio. The second part of the study is an open-label, single arm extension in which all patients receive prolonged FKB327 treatment from Week 30 to Week 76, followed by a 4-week follow-up period. Scheduled clinic visits will be conducted at Weeks 0, 2, 4, 8, 12, 24, 30, 32, 34, 42, 54, 66, 76, and 80. The patient or carer will be allowed to administer interim doses of study drug at home (eow) between clinic visits. FKB327 in an Auto-Injector device presentation will be introduced during the open-label follow-up treatment period depending on availability of the Auto-injector relative to the patient's progress within the study.

At the Week 22 visit of Study FKB327-002 the investigator will discuss participation in this open-label extension study with the patient, if appropriate. If the patient is eligible for this study and gives informed consent to participate, the patient will be randomised into the study and Week 0 study drug dose for this study will be administered after the Week 24 study procedures for Study FKB327-002 have been performed. The first 3 doses of study drug (Weeks 0, 2, and 4 for all patients and Weeks 30, 32, and 34 for patients switching from Humira to FKB327 at that point) will be self-administered (or administered by a carer) at the study site after training has been given. Subsequent doses may be administered by the patient or carer at home, except when clinic visits for blood tests and efficacy assessments are scheduled when the dose must be given after blood samples are drawn.

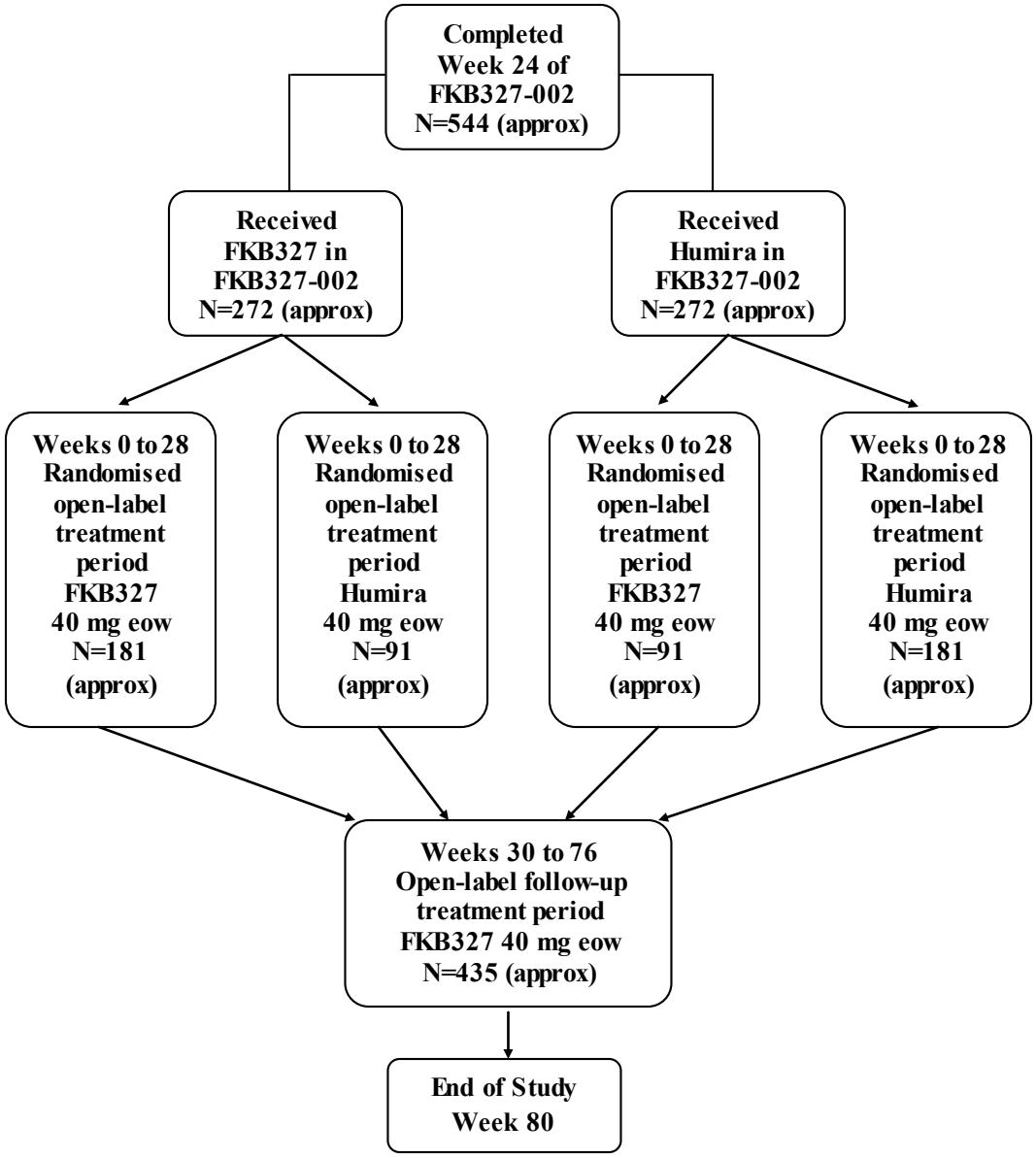
If, for any reason, it is not possible to conduct Week 24 visit procedures for study FKB327-002 and Week 0 procedures for this study on the same day, the maximum permitted interval between study drug doses in the 2 studies (Week 22 dosing in Study FKB327-002 and Week 0 dosing in this study) will be 4 weeks. If Week 24 visit procedures for Study FKB327-002 and Week 0 procedures have an interval of 2 weeks or

more between them then some procedures will need to be repeated prior to dosing at Week 0 for this study (see Table 1 – all procedures marked with an asterisk).

The study schema is presented in Figure 1; this schema assumes that approximately 544 patients out of 680 (80%) complete Study FKB327-002 and are eligible for Study FKB327-003. A drop-out rate of approximately 20% is anticipated in the present study by the time all remaining patients are switched to FKB327 at Week 30, so an estimated 435 patients will enter the single-arm part of the study. However, all patients who are eligible to enter this study from FKB327-002 may do so even if the estimated numbers are exceeded.

An interim analysis of planned endpoints for all patients will be performed once 100 patients randomised to FKB327 in study FKB327-002 and also to FKB327 in the randomised phase of study FKB327-003 plus 100 patients randomised to Humira in study FKB327-002 and also to Humira in the randomised phase of study FKB327-003 have reached Week 30 in this study. This will provide more than 100 patient-years of exposure to FKB327 and to Humira across studies FKB327-002 and FKB327-003 for comparison.

Figure 1: Overall Study Schema



3.5 Randomisation and Blinding

3.5.1 Randomisation

The first part of this study is a comparative, randomised, open-label extension study. Patients who complete Week 24 of Study FKB327-002 and meet inclusion and exclusion criteria for this open-label extension study will be eligible to enrol in this study. Patients will attend the Week 0 visit of this study (which is the same clinic visit as Week 24 from Study FKB327-002), and will be randomised to receive either FKB327 40 mg eow or

Humira 40 mg eow from Week 0 to Week 28, according to the scheme presented in Figure 1.

Consequently, patients who received FKB327 in Study FKB327-002 may receive Humira in this study, and patients who received Humira in Study FKB327-002 may receive FKB327 in this study, whilst some patients will receive either FKB327 or Humira for the entire duration of the randomised period of the combined studies.

Randomisation will be carried out using the Medidata Balance® randomization and trial supply management system, which is directly linked to the electronic case report form (eCRF).

After this period of randomised treatment, all patients will then receive FKB327 40 mg eow from Weeks 30 to 76.

3.5.2 Blinding

As this is an open-label study no blinding is required.

3.6 Duration of Patient Participation

For each patient, the study is expected to last 80 weeks.

3.7 Identification of Source Data

All data recorded for the study must be supported by appropriate source documents.

Source documents are considered to be all information in original records (and certified copies of original records) of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data should be recorded contemporaneously with the activities performed.

All study data are to be captured on the eCRF with the exception of clinical laboratory, PK and immunogenicity data, which will be provided electronically by the laboratories, electronic patient-reported outcomes (ePRO, recorded using the SitePRO device), and joint and disease evaluations data. Reports received by the site from the central laboratory should be printed, retained as source documentation and signed by a medically qualified Investigator, indicating which values are considered CS and to be reported as AEs. All data recorded on the SitePRO device will be regarded as source data.

4 PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Have completed all 24 weeks of study procedures (including dosing) according to protocol FKB327-002, with a minimum of 9 doses of study drug received, and are continuing with stable concomitant MTX and folate.
2. In the investigator's opinion, the patient showed a clinical response to treatment during Study FKB327-002.

3. Are willing to participate in the study and have provided written informed consent.
4. Females of childbearing potential must have a negative pregnancy test prior to study dosing. Both sexes must be willing to take adequate contraceptive precautions throughout the study period and continuing for at least 5 months post study. Acceptable methods of contraception in this study are: surgical sterilisation, intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptives, partner's vasectomy, or a double-protection method (condom or diaphragm with spermicide).

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Evidence of an SAE ongoing from Study FKB327-002 at entry to this study, including a serious infection, malignancy, or any other condition that may put patients at increased risk when receiving treatment with adalimumab.
2. Presence of active and/or untreated latent TB as detected by QuantiFERON test at Week 22 combined with chest X-ray at Week 24 in Study FKB327-002. Latent TB, treated with prophylactic anti-mycobacterial therapy for at least 3 weeks before study dosing is resumed, is acceptable (see Appendix 16.2). Patients may have up to a maximum of 4 weeks interruption of dosing between the last dose in Study FKB327-002 and Week 0 dosing in study FKB327-003 for this purpose.
3. Were non-compliant with FKB327-002 study procedures, or with any condition or circumstances, which, in the opinion of the Investigator, makes them unlikely or unable to comply with study procedures and requirements.
4. ACR Functional Class IV (see Appendix 16.1).
5. Acute infection requiring antibiotic treatment within 2 weeks of Week 0 dosing. Patients may have up to a maximum of 4 weeks interruption of dosing between the last dose in Study FKB327-002 and Week 0 dosing in Study FKB327-003 in order to recover from infection requiring antibiotic treatment (see Section 5.7).
6. Presence of serious, uncontrolled disease of another body system including cardiovascular, neurological, pulmonary, renal and hepatic disease.
7. Presence of New York Heart Association (NYHA) Class III/IV heart failure (see Appendix 16.3).
8. Presence of any uncontrolled disease for which steroid treatment is regularly required for flares, eg, asthma.
9. Patients with demyelinating diseases (eg, multiple sclerosis).
10. Pregnant or breastfeeding women.

4.3 Patient Withdrawal Criteria

Patients are free to withdraw consent to the study at any time without giving reasons. Furthermore, the Investigator must withdraw a female patient in the event of pregnancy. The Investigator may also withdraw a patient for medical reasons such as intercurrent illness, need for medication which is contraindicated and poor compliance or any other

safety issues. The Investigator will assess reasons for withdrawal as far as possible and will fully record the circumstances and medical details.

5 STUDY TREATMENT

5.1 Allocation to Treatment

At entry to this open label study, patients will be randomised to receive either FKB327 40 mg eow or Humira 40 mg eow from Week 0 to Week 28 using the Medidata Balance® randomization and trial supply management system. Patients who received FKB327 in Study FKB327-002 will be randomised to FKB327 or Humira in a 2:1 ratio and patients who received Humira in Study FKB327-002 will be randomised to Humira or FKB327 in a 2:1 ratio.

From Week 30 onwards, all patients will receive FKB327 40 mg eow.

5.2 Blinding

This is an open-label study; therefore, no blinding is required.

5.3 Drug Supplies

FKB327 will be manufactured by Kyowa Hakko Kirin Co., Ltd. (KHK), Japan.

FKB327 will be supplied by the Sponsor in a plastic PFS with a safety device for single use only. FKB327 in an Auto-Injector device presentation for single use only will be introduced during the open-label follow-up treatment period depending on availability of the Auto-Injector relative to the patient's progress within the study. In both presentations, the dose will be 40 mg in 0.8 mL. Training in the use of the Auto-Injector device for 1 or more doses will be provided at the point of switching to this device; patients may be required to attend additional clinic visits for this to occur (unscheduled visit forms should be used if the switch training does not fit with the specified visit schedule).

From Week 0 to Week 28 only, patients randomised to Humira will be supplied US-licensed Humira in a glass PFS by the Sponsor. The dose will be 40 mg in 0.8 mL. Note: The needle cover of the Humira PFS contains dry rubber (latex) which should not be handled by persons sensitive to this substance without using latex-free gloves.

It is planned that all patients will be introduced to treatment by self-injection (or injection by a carer) in order to be able to dose at home between scheduled clinic visits.

Further details on drug supplies can be found in the Pharmacy Manual.

5.3.1 Preparation and Dispensing

The Medidata Balance® system will be used to indicate to site staff which study drug kit(s) to select to dispense to each patient.

During the randomised part of this study FKB327 and Humira will be provided as PFSs ready for injection. At a suitable point during the open-label study all patients will be provided with FKB327 in an Auto-Injector presentation.

As the patient or carer will be administering doses at home, they must have the facility to refrigerate study drug at home and will be provided with the means to keep study drug chilled while transporting between the site and home. Along with these supplies, patients will be given a Patient Instruction Leaflet, describing how study drug should be kept refrigerated at home, and a Dosing Diary to record the dates on which study drug was administered and any problems with dosing.

All used study drug must be disposed of into the disposal container provided and returned by the patient to the study site together with any unused study drug at each visit for drug accountability and dosing compliance purposes.

Further details on the preparation and dispensing of study drug at site can be found in the Pharmacy Manual.

5.3.2 Administration

FKB327 and Humira will be administered via sc injection. Drug will be administered by subcutaneous injection either into the anterior thigh or anterior abdominal wall (within a 10-cm radius around the umbilicus, but not closer to the umbilicus than approximately 5 cm). Injection sites should be changed between dosing occasions to minimise local side effects.

The first 3 doses (Weeks 0, 2, and 4 for all patients and Weeks 30, 32, and 34 for patients switching from Humira to FKB327 at that point) will be administered by the patient or carer, under supervision by study site staff, at the study site and after appropriate training by study site staff. Subsequent doses may be administered by the patient or carer at home, except when clinic visits for blood tests and efficacy assessments are scheduled when the dose must be given after blood samples are drawn.

The maximum interval permitted between doses of study drug is 4 weeks. This also applies to the transition from FKB327-002 into this study. Study drug may need to be interrupted for treatment of serious infection, latent TB or other AE (see Section 5.7). In this case the maximum permitted gap between study drug doses is 4 weeks. If it is necessary, in the investigator's judgement, to interrupt study drug treatment for longer than 4 weeks, the patient will be withdrawn from study treatment but will be followed for resolution of the AE. The minimum permitted gap between study drug doses is 8 days.

5.3.3 Treatment Compliance

Written records of study medication administration will be kept at the study site. Patients will be asked to keep a diary card recording dates and times of dosing. This information will be transcribed into the eCRF by site staff. PK and ADA samples are taken at intervals during the study.

Unused study drug will be returned to the site by the patient and retained at the study site for compliance checks but need not be refrigerated.

5.3.3.1 Product Complaints

Product complaints might include malfunctions or breakages of the FKB327 injection device (PFS), safety issues with the device, problems with the labelling or instructions.

Issues with the quality of the investigational medicinal products (eg, cloudiness or precipitation of the drug product solution) might also be considered product complaints. Any such product complaints should be entered on the Device Complaint Form and submitted to the Sponsor via email as soon as possible. The faulty product should be retained for return at the Sponsor's request.

If the product complaint results in an AE, it must be documented on the AE page of the CRF, and if it meets any of the serious criteria it needs to be reported through to the Sponsor's pharmacovigilance department on an SAE form (see Section 8.6.2).

5.4 Drug Storage and Accountability

The study drug and supplies will be refrigerated at the site in a locked facility with monitored temperature. Only authorised personnel will be allowed access. An inventory, including the description and quantity of study medication received will be maintained. A record of study medication dispensed, along with the patient number and date and time of administration will be kept in the separate pharmacy section of the Investigator Site File (ISF) and filed with the main body of the ISF after database lock. When doses are self-administered by the patient (or carer) at home, the Dosing Diary will be completed to record the administration.

At the end of the study, any unused study drug kits will be returned to the Sponsor or designee, or destroyed in accordance with the Sponsor's instructions.

5.5 Concomitant Medication

5.5.1 Permitted Concomitant Medication

Patients will be taking MTX (oral or parenteral) at a stable dose of 10-25 mg/week from Study FKB327-002, and will continue to take MTX during this OLE study. The route of administration of MTX should not change throughout the study. The patient's MTX dose can be reduced for toxicity only. If toxicity occurs, this should be recorded as an AE. The patient's MTX dose may also be increased if an RA flare occurs, although attempts should be made to reduce it back to the Baseline dose if possible.

Patients should also continue to take accompanying folic/folinic acid (at a dose of at least 5 mg/week) during this OLE study.

Oral corticosteroids (≤10 mg/day prednisone or equivalent) are permitted during the study. A temporary increase in oral steroid dose (≤10 mg/day prednisone or equivalent) is permitted to treat concomitant conditions, eg, asthma. The reason for any such increase in dose should be recorded as an AE (eg, asthma flare). The dose must be tapered back down as soon as medically viable. The oral steroid dose may also be increased if an RA flare occurs although attempts should be made to taper it back to the Baseline dose if possible. A short course of oral steroids (≤10 mg/day prednisone or equivalent) may also be initiated in patients who had not previously been taking them, if an RA flare occurs.

If a patient's RA is adequately controlled and stable on study treatment, the Investigator may start to taper the concomitant oral steroid dose at their discretion. A comment in the

eCRF 'Comments page' that oral steroid reduction is being initiated should be created. All changes (increases or decreases) to oral steroid use should be carefully documented in the concomitant medication section of the eCRF.

Inhaled and topical steroids are permitted during the study. Treatment with intra-articular steroids is allowed during the study; however, repeated requirement for joint injection could be considered evidence of lack of efficacy and the investigator should consider withdrawing the patient from study treatment. A joint which has been injected with intra-articular steroids should be excluded from joint counts (marked as unassessable on the SitePRO) for 12 weeks after the injection.

Non-steroidal anti-inflammatory drugs (NSAIDs) up to the maximum approved dose are permitted during the study. NSAID dose may be increased (not above the maximum approved dose) although attempts should be made to taper it back to Baseline level if possible. Additional NSAIDs may also be added in this circumstance, according to local approved prescribing instructions. Topical NSAIDs are permitted during the study.

Analgesics up to the maximum approved dose are permitted during the study but should not be taken in the 24 hours prior to efficacy evaluations.

All concomitant medications (including over-the-counter medications, herbal medications, preventative vaccines, vitamins and food supplements) and procedures must be recorded in the eCRF. Concomitant medications for chronic conditions should be kept stable throughout the study wherever possible.

Prophylactic anti-mycobacterial treatment may be given to patients found to have latent TB on completion of Study FKB327-002. This treatment should be given prior to Week 0 of the present study (see Appendix 16.2).

5.5.2 Prohibited Concomitant Medication

Immunisation with a live or attenuated vaccine is prohibited for the duration of this study, including the follow-up period, and for 3 months after administration of the last dose.

Treatment with an investigational agent is prohibited for the duration of this study.

Treatment with parenteral steroids for RA is prohibited for the duration of this study. If the patient requires parenteral steroids to manage their RA they should be withdrawn from the study for lack of efficacy. However, a short course (maximum of 3 days) of parenteral steroid treatment for another condition, eg, allergy (not related to study treatment) or asthma, is permitted.

Treatment with other DMARDs (apart from MTX) is prohibited for the duration of the study. In the event the Investigator wishes to treat a patient with a DMARD (other than MTX or adalimumab) during the study, the patient must be withdrawn from study treatment and the reason for withdrawal documented.

5.6 Study Restrictions

All patients must use a reliable method of contraception during the study, and for 5 months after the last dose of study medication unless they (or their partners) are women

who are not of childbearing potential. Acceptable methods of contraception are: surgical sterilisation, intrauterine devices, oral contraceptives, contraceptive patch, long-acting injectable contraceptives, partner's vasectomy, or a double-barrier protection method (condom or diaphragm with spermicide). Women who are not of childbearing potential are defined as: post-menopausal women (no menstrual periods for at least 12 consecutive months); or women who have undergone a hysterectomy, a bilateral oophorectomy or a bilateral salpingectomy.

All patients will be strongly advised (in the ICF) that they (or the female partners of male patients) should not become pregnant while on study treatment or for 5 months after the last dose. Female patients will be advised that if they believe they may be pregnant, they must report immediately to the study site for pregnancy testing and appropriate management.

5.7 Safety Precautions

All patients will be given an alert card stating that they are taking part in a clinical study involving administration of adalimumab, in accordance with the prescribing information for Humira.

Patients will be advised that if they experience symptoms of infection, such as cough, loss of weight or fever, they should report this to study site staff immediately by telephone (a contact number will be provided). This may necessitate an unscheduled visit to the study site for investigations, at the discretion of the investigator, and initiation of treatment. If severe infection develops, study treatment may need to be interrupted, again at the discretion of the Investigator and in discussion with the study Medical Monitors. If it is necessary to interrupt study dosing for more than 4 weeks despite antibiotic treatment, the patient will be discontinued from the study.

Patients will also be advised that if they experience any symptoms suggestive of anaphylaxis, they should seek immediate local medical assistance then contact the study site.

The needle cover of the Humira PFS contains dry rubber (latex), which should not be handled by persons sensitive to this substance without using latex-free gloves.

If a patient is diagnosed with any of the following conditions during the study, they may be discontinued from the study, again involving discussion with the Medical Monitors:

- Malignancy (with the exception of carcinoma in situ of the cervix or basal cell carcinoma of the skin that has been fully excised)
- Anaphylactic reaction
- Significant haematological or biochemical abnormality
- Newly diagnosed or worsening heart failure
- Newly diagnosed lupus-like syndrome with positive test for antibodies to double-stranded DNA
- Newly diagnosed demyelinating conditions
- Pregnancy (see Section 8.8).

- Any severe or opportunistic infection

Patients needing to undergo surgery during the study will be monitored closely for infection. If evidence of infection develops following surgery it may be necessary to interrupt study dosing as described above.

6 STUDY PROCEDURES

Study procedures and assessments with their timings are summarised in Table 1 for the randomised treatment period and Table 2 for the follow-up treatment period.

For visits when dosing is performed, all procedures will be performed prior to dosing except for injection site assessment and recording of any post-injection AEs.

Patients will have been taking MTX for at least 3 months prior to screening for Study FKB327-002 and for the duration of that study; consequently, continuous MTX therapy (with concomitant folate) is assumed and is not detailed in each of the following sections.

6.1 Procedures for Baseline Visit (Week 0 [Visit 1])

Patients who have completed Week 24 of Study FKB327-002 will be eligible to enrol into this study at the discretion of the investigator. The Baseline (Week 0) visit for this study is the same as the Week 24 visit in Study FKB327-002. Procedures on that day up until confirmation of eligibility for this study will be considered part of Study FKB327-002. Procedures from confirmation of eligibility onwards will be considered part of this study. Patients will be identified by the same number as in Study FKB327-002 (4-digit site number, a hyphen then the 4-digit patient number, eg, 0001-0001). It will be necessary to confirm in the eCRF for study FKB327-002 that the patient will transition to this study (FKB327-003) in order for the patient identifier number to be available within this study (and site) database. A signed and dated informed consent form will be obtained before procedures specific to this study commence. After informed consent is obtained, and eligibility is confirmed, patients will be randomised by the Medidata Balance® system.

The following procedures will be performed. Some of these procedures will have been performed as part of the Week 24 visit of Study FKB327-002 and so will not be repeated specifically for this study and are presented below in parentheses. NOTE: Procedures marked with an asterisk need to be repeated if there is a delay of 2 weeks or more between Week 24 of study FKB327-002 and Week 0 of study FKB327-003, for example, due to the need to interrupt study drug while serious infection or latent TB is treated.

- [Record concomitant medication].*
- Review and record medical history and current conditions, including AEs that were ongoing from Study FKB327-002 and any possible contact with individuals with active TB since Screening in Study FKB327-002.*
- [Perform physical examination including weight].
- [Perform vital signs measurements (blood pressure, pulse and temperature)].
- [Perform 12-lead electrocardiogram (ECG)].

- [Perform chest X-ray unless patient has negative QuantiFERON test at Week 22 of study FKB327-002 with no signs/symptoms of clinically significant lower respiratory infection].
- [Perform clinical laboratory tests: haematology, serum chemistry, dipstick urinalysis (at site), CRP and erythrocyte sedimentation rate (ESR)].*
- [Perform urine pregnancy test at site (females of childbearing potential only)].*
- [Take blood sample for assessment of serum blood concentrations of adalimumab].*
- [Take blood for ADA sampling].*
- [Perform test for matrix metalloproteinase (MMP)-3].
- [Administer patient assessment of physical function questionnaire (Health Assessment Questionnaire Disability Index [HAQ-DI])].*
- [Assess tender/swollen joints (68/66 joints)].*
- [Administer patient global assessment of disease activity visual analogue scale (VAS) and patient assessment of pain VAS].*
- [Perform physician global assessment of disease activity VAS].*
- Obtain written informed consent before any other study-related procedures specific to FKB327-003 are performed.
- Randomise patient using the Medidata Balance® system.
- Train patient and/or carer in self-administration of study drug
- Supervise self-administration of study medication (or administration by carer) at study site.
- Perform injection site assessment including injection site pain VAS.

6.2 Procedures during Treatment Period

Note: for Visit 2 and Visit 3 there will be a window of ±3 days. For example, the Week 2 visit (Visit 2) should take place on Day 15, but could be as early as Day 12 or as late as Day 18. From Visit 4 (Week 8) onwards, a window of ±7 days is permissible.

6.2.1 Week 2 (Visit 2)

- Supervise self-administration of study medication (or administration by carer) at study site.
- Record AEs.

6.2.2 Weeks 4, 8, and 12 (Visits 3, 4, and 5)

- Record concomitant medications.
- Perform vital signs measurements (blood pressure, pulse and temperature).
- Perform clinical laboratory tests (haematology, serum chemistry, urinalysis and CRP).
- Perform urine pregnancy test at site (females of childbearing potential only).

- Week 12 only: take blood sample for assessment of serum blood concentrations of adalimumab.
- Week 12 only: take blood for ADA sampling.
- Record AEs.
- Administer patient assessment of physical function questionnaire (HAQ-DI).
- Assess tender/swollen joints (68/66 joints).
- Administer patient global assessment of disease activity VAS and general assessment of pain VAS.
- Perform physician global assessment of disease activity VAS.
- Week 4 only: supervise self-administration of study medication (or administration by carer) at study site.
- Dispense study medication for patient/carer to administer at home and Dosing Diary.
- Instruct patient/carer (i) to dose at home (specify dates), (ii) to complete Dosing Diary card, (iii) to keep study drug refrigerated and secure at home, and (iv) to seek immediate local medical advice or contact study site staff in case of any AEs, depending on the severity of the event.
- Provide Patient Instruction Sheet.

6.2.3 Weeks 6, 10, 14, 16, 18, 20, 22, 26, and 28

- Patient/carer to administer study drug at home and complete Dosing Diary.
- Contact study site staff in case of any AEs.

Note: Week 28 will be the last administration of randomised treatment.

6.2.4 Week 24 (Visit 6)

- Record concomitant medication.
- Record weight.
- Perform vital signs measurements (blood pressure, pulse and temperature).
- Perform clinical laboratory tests (haematology, serum chemistry, urinalysis, CRP).
- Perform urine pregnancy test at site (females of childbearing potential only).
- Perform QuantiFERON test (may be omitted if patient is receiving anti-mycobacterial treatment for latent TB).
- Take blood sample for assessment of serum blood concentrations of adalimumab.
- Take blood for ADA sampling.
- Record AEs.
- Administer patient assessment of physical function questionnaire (HAQ-DI).
- Assess tender/swollen joints (68/66 joints).
- Administer patient global assessment of disease activity VAS and general assessment of pain VAS.

- Perform physician global assessment of disease activity VAS.
- Supervise self-administration of study medication (or administration by carer) at study site.
- Dispense study medication for patient/carer to administer at home and Dosing Diary.
- Instruct patient/carer (i) to dose at home (specify dates), (ii) to complete Dosing Diary card, (iii) to keep study drug refrigerated and secure at home, and (iv) to seek immediate local medical advice or contact study site staff in case of any AEs, depending on the severity of the event.
- Provide Patient Instruction Sheet.

6.2.5 Weeks 30, 54, and 76 (Visits 7, 11, and 13)

Note: from Week 30, all patients will receive FKB327.

- Record concomitant medication.
- Perform clinical laboratory tests (haematology, serum chemistry, urinalysis and CRP).
- Perform urine pregnancy test at site (females of childbearing potential only).
- Week 76 only: perform QuantiFERON test (may be omitted if patient is receiving anti-mycobacterial treatment for latent TB).
- Take blood sample for assessment of serum blood concentrations of adalimumab.
- Take blood for ADA sampling.
- Week 30 only: chest X-ray, performed only in the event of a new positive or confirmed (ie, repeated) indeterminate QuantiFERON test result (eg, from Week 24) and/or signs/symptoms of lower respiratory infection (see Appendix 16.2).
- Record AEs.
- Administer patient assessment of physical function questionnaire (HAQ-DI).
- Assess tender/swollen joints (68/66 joints).
- Administer patient global assessment of disease activity VAS and general assessment of pain VAS.
- Perform physician global assessment of disease activity VAS.
- Supervise self-administration of study medication (or administration by carer) at study site.
- Week 30 only: perform injection site assessment including injection site pain VAS (Note: an additional injection site assessment will be performed at the time of switching to the Auto-Injector during the open-label follow-up treatment period).
- Dispense study medication for patient/carer to administer at home and Dosing Diary.
- Instruct patient/carer (i) to dose at home (specify dates), (ii) to complete Dosing Diary card, (iii) to keep study drug refrigerated and secure at home, and (iv) to seek immediate local medical advice or contact study site staff in case of any AEs, depending on the severity of the event.

- Provide Patient Instruction Sheet.

6.2.6 Weeks 32 and 34 (Visits 8 and 9)

For patients switched from Humira to FKB327, the Weeks 32 and 34 visits must be performed at the clinic:

- Record AEs.
- Supervise self-administration of study medication (or administration by carer) at study site.

For patients continuing with FKB327, the patient or carer can administer at home:

- Patient/carer to administer study drug and complete Dosing Diary.
- Contact study site staff in case of any AEs.

6.2.7 Weeks 36-40, 44-52, 56-64, and 68-74

- Patient/carer to administer study drug at home and complete Dosing Diary.
- Contact study site staff in case of any AEs.

6.2.8 Weeks 42 and 66 (Visits 10 and 12)

- Record concomitant medication.
- Perform clinical laboratory tests (haematology, serum chemistry, urinalysis and CRP).
- Perform urine pregnancy test at site (females of childbearing potential only).
- Record AEs.
- Administer patient assessment of physical function questionnaire (HAQ-DI).
- Assess tender/swollen joints (68/66 joints).
- Administer patient global assessment of disease activity VAS and general assessment of pain VAS.
- Perform physician global assessment of disease activity VAS.
- Supervise self-administration of study medication (or administration by carer) at study site.
- Dispense study medication for patient/carer to administer at home and Dosing Diary.
- Instruct patient/carer (i) to dose at home (specify dates), (ii) to complete Dosing Diary card, (iii) to keep study drug refrigerated and secure at home, and (iv) to seek immediate local medical advice or contact study site staff in case of any AEs, depending on the severity of the event.
- Provide Patient Instruction Sheet.

6.2.9 Week 80 or End-of-study (Visit 14)

In the event of early treatment discontinuation, patients will be asked to attend an end-of-study visit. Early treatment discontinuation is defined as withdrawal from the

study prior to Week 80. The reason for early treatment discontinuation should be recorded in the eCRF.

The following procedures will be performed at the Week 80 or end-of-study visit:

- Record concomitant medication.
- Perform physical examination.
- Perform vital signs measurements (blood pressure, pulse and temperature).
- Perform clinical laboratory tests (haematology, serum chemistry, urinalysis and CRP).
- Take blood sample for assessment of serum blood concentrations of adalimumab.
- Take blood for ADA sampling.
- EOS only: perform QuantiFERON test (may be omitted if patient is receiving anti-mycobacterial treatment for latent TB)
- Perform chest X ray unless patient has negative QuantiFERON test at Week 76 or EOS, as appropriate, with no signs/symptoms suggestive of lower respiratory infection (see Appendix 16.2).
- Record AEs.
- Administer patient assessment of physical function questionnaire (HAQ-DI).
- Assess tender/swollen joints (68/66 joints).
- Administer patient global assessment of disease activity VAS and general assessment of pain VAS.
- Perform physician global assessment of disease activity VAS.

7 ASSESSMENTS

7.1 Assessment of Efficacy

7.1.1 Primary Efficacy Variable

There are no primary efficacy variables.

7.1.2 Secondary Efficacy Variables

7.1.2.1 ACR20, ACR50, and ACR70

ACR20, ACR50 and ACR70 response rates are secondary efficacy variables. The ACR response criteria involve improvement in tender joint count, swollen joint count (68/66-joint count) and improvement in at least 3 of the following 5 other specified ACR Core Data Set elements:

- Acute phase reactant (CRP).
- Patient global assessment of disease activity.
- Physician global assessment of disease activity.
- Patient pain scale.

- Disability/functional questionnaire (patient completed HAQ-DI)

An ACR20 response means that the patient achieved a 20% improvement in tender and swollen joint counts and in at least 3 of the other 5 Core Data Set elements listed above. ACR50 response means that the patient achieved a 50% improvement in tender and swollen joint counts and in at least 3 of the other 5 criteria, and an ACR70 response means that the patient achieved a 70% improvement in tender and swollen joint counts and in at least 3 of the other 5 criteria.[7]

The percent of patients achieving ACR20, ACR50 and ACR70 response will be assessed at the time points detailed in Table 1 and Table 2 as the ACR response rate (%), calculated using the Core Set variables described below. The baseline used for the ACR response will be the baseline of Study FKB327-002.

7.1.2.1.1 Tender and Swollen Joint Counts (68/66 Joints)

Counts of tender and swollen joints from amongst 68/66 selected joints will be performed by a trained and qualified joint assessor as scheduled in Table 1 and Table 2 using standardised techniques recommended by the European League Against Rheumatism (EULAR). Results will be recorded immediately on the SitePRO tablet device provided (constituting source data). To maintain consistency in evaluating each patient, efforts will be made to use the same joint evaluator as in study FKB327-002 and at all FKB327-003 visits. Joint evaluators will have received standardisation training for FKB327-002 and any new or replaced joint evaluators should also be trained. The training opportunities will include, the site initiation visit, WebEx presentations, a video and written manual detailing how to perform the joint assessment. Training will be documented by certificates held on the site file. Additionally, the number of joint evaluators used across the study will be kept as low as is logistically possible.

If, at any visit, a joint is not evaluable for any reason, this will be recorded on the SitePRO device. If this is due to amputation, the joint will automatically be recorded as unevaluable for the remainder of the study. If a joint is not evaluable for any other reason (such as infection, injury or surgery), the joint should be reassessed for evaluability at each visit by the joint examiner. If the joint is not evaluable due to an injection into the joint it should be marked as not evaluable for a period of 12 weeks post injection. Criteria for excluding such joints from the joint count used to calculate the ACR20/50/70/DAS28 will be detailed in the Statistical Analysis Plan (SAP).

7.1.2.1.2 C-reactive Protein (CRP)

Analysis of serum CRP concentrations for randomisation stratification and inclusion in the ACR20/50/70 and DAS28-CRP scores will be performed by XXX laboratory.

7.1.2.1.3 Visual Analogue Scales (VAS)

Patient global assessment of disease activity VAS (ranging from very well to extremely bad), and physician global assessment of disease activity VAS (ranging from very low to very high) will be assessed on 100-point scales at the time points detailed in Table 1 and Table 2. These VASs must be completed by the patient/physician themselves on a SitePRO tablet. The patient global assessment of disease activity VAS will contribute to

the calculation of the DAS28 score. The patient global assessment of disease activity VAS, and physician global assessment of disease activity VAS will contribute to the calculation of ACR20, ACR50 and ACR70 response. Patient-recorded data will not be corrected or revised in any way. VAS data recorded on the SitePRO device will be regarded as source data.

7.1.2.1.4 HAQ-DI

The HAQ-DI[8] is a 20-question, self-administered instrument that measures the patient's functional ability on a 4-level difficulty scale (0-3, 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.[9] This scale is sensitive to change and is a good predictor of future disability.[10] The HAQ-DI questionnaire will be completed on the SitePRO device by the patients themselves at the time points indicated in Table 1 and Table 2. Patient-recorded data will not be corrected or revised in any way.

7.1.2.1.5 Disease Activity Score 28 (DAS28)

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.[11] The DAS28 assessment involves evaluating the tender joint count (TJC) and swollen joint count (SJC) (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 results are then used to calculate the DAS28 using the following formula:

DAS28-CRP = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC) + 0.36*ln(CRP+1) + 0.014*VAS + 0.96

The DAS28 is a number on a scale from 0 to 10 indicating the current activity of the patient's RA. A DAS28 above 5.1 means high disease activity whereas a DAS28 $\leq$3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6.

The DAS28 will be calculated using information from the assessments performed at the time points detailed in Table 1 and Table 2.

The baseline DAS28 score from Study FKB327-002 will be used to calculate the change from baseline.

7.1.2.1.6 Components of the DAS28-CRP

Joint count results (28 joints) will be extrapolated automatically in the SitePRO device from the results of the 68/66 joint counts performed for the purpose of ACR response calculation. Results of the patient global assessment of disease activity VAS will be the same as used for the ACR response. CRP values will be the results from samples analysed by central laboratory.

7.2 Assessment of Safety

In this study, safety will be assessed by evaluating the following: AEs, physical examination findings, vital signs measurements, and clinical laboratory test results. The process for reporting AEs is detailed in Section 8.

7.2.1 Clinical Laboratory Tests

Laboratory testing will be performed by a central laboratory facility with the exception of ESR testing and dipstick urinalysis, which will be performed locally. All clinical laboratory test results outside of the reference range will be flagged and interpreted by the Investigator according to the following categories:

- Abnormal, not clinically significant (NCS)
- Abnormal, CS

CS laboratory abnormalities will be recorded as AEs. Laboratory tests will be performed at the time points detailed in Table 1 and Table 2.

7.2.1.1 Haematology

The following haematology tests will be performed: haemoglobin (Hb), red blood cell count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), haematocrit, white blood cell (WBC) count and differential, platelets and (at Week 0 only, as part of Study FKB327-002) ESR.

7.2.1.2 Serum Chemistry

The following serum chemistry tests will be performed: urea, creatinine, uric acid, total bilirubin, total protein, albumin, globulin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), glucose, phosphate, cholesterol, triglycerides, potassium, sodium, calcium, and chloride.

7.2.1.3 Urinalysis

Dipstick urinalysis (by local study site staff) will include testing for the following: protein, blood, glucose and leukocyte esterase. If the dipstick reveals any clinically significant abnormalities a second sample (provided on the same day, if possible), should be sent to the central laboratory. Microscopy will be performed by the central laboratory in the case of abnormal results.

7.2.1.4 Pharmacodynamic Markers

Serum MMP-3 will be analysed at the time points detailed in Table 1 and Table 2.

7.2.1.5 Pregnancy Testing

Females of childbearing potential will take a urine pregnancy test (performed at site) as scheduled in Table 1 and Table 2. Female patients will be advised that, if they believe they may be pregnant, they must report immediately to the study site for pregnancy testing and appropriate management.

7.2.1.6 Other

The QuantiFERON-TB Gold In-Tube test will be performed at Weeks 24 and 76 or EOS although this may be omitted in patients receiving anti-mycobacterial treatment for latent TB. This may be repeated, at the discretion of the Investigator or to comply with local practices, at additional time points. The test is approved by the Food and Drug Administration (FDA) and is used to detect active or latent *Mycobacterium tuberculosis* infection. The test is based on the quantification of interferon-gamma (IFN-γ) released from sensitised lymphocytes in whole blood incubated overnight with purified protein derivative (PPD) from *M. tuberculosis* and control antigens.[12] A positive result for active TB (as determined in association with chest X-ray and clinical evaluation) or untreated latent TB (unless prophylactic treatment is started) will lead to the patient being excluded/withdrawn from the study (see TB testing flow chart in Appendix 16.2). Latent TB treated with prophylactic anti-mycobacterial therapy for at least 3 weeks (or longer if required by local guidelines) before study treatment is commenced/resumed is acceptable. If the result is indeterminate the test may first be repeated or combined with PPD testing. If confirmed indeterminate, the patient should be managed as though they have a positive test result or excluded from the study (see Appendix 16.2).

7.2.2 Physical Examination

Physical examination will be performed by the Investigator at Week 0 (Week 24 of study FKB327-002) and Week 80 or end-of-study visit. The following will be examined: general appearance; head; ears; eyes; nose and throat; thyroid; lymph nodes; heart; chest (including lungs); abdomen; urogenital system (optional); skin; breasts; extremities; musculoskeletal system and neurological system.

7.2.3 Vital Signs

Vital signs (blood pressure, pulse, and temperature) will be measured at the time points detailed in Table 1 and Table 2. Blood pressure and pulse rate will be measured prior to dosing after the patient has rested in a supine or semi-recumbent position for at least 5 minutes.

7.2.4 Chest X-ray

Chest X-rays (posterior and lateral views) will be performed at Week 30 and Week 80 or EOS unless patient has negative QuantiFERON test at Week 24 or 76 or EOS, respectively, with no signs/symptoms suggestive of lower respiratory infection. The chest X-ray will be examined by a qualified radiologist to ensure that there is no evidence of active TB, other chest infection or interstitial pneumonitis in particular. An additional X-ray will be performed at the Investigator's discretion at additional time points in the presence of signs/symptoms suggestive of lower respiratory infection.

7.2.5 Injection Site Assessment

An injection site assessment will be performed within 30 minutes of dosing at Week 0 and Week 30, as well as at the time of switching to the Auto-Injector during the open-label follow-up treatment period. Study staff will apply light pressure at the injection site and record any tenderness, erythema and induration. Local reactions will be

assessed according to the FDA Guidance for Industry on Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products,[13] as follows:

0 = no evidence of irritation.

1 = minimal erythema, barely perceptible.

2 = definite erythema, readily visible; minimal oedema or minimal papular response.

3 = erythema and papules.

4 = definite oedema.

5 = erythema, oedema, and papules.

6 = vesicular eruption.

7 = strong reaction spreading beyond test site.

The size of any injection site reaction will be measured along its longest axis. If a patient has a CS local reaction, it will be recorded as an AE. Any evidence of an injection site reaction at visits other than Week 0, Week 30, or at the assessment conducted at the point of switching to the Auto-Injector will also be recorded as an AE.

As part of this assessment, an injection site pain VAS will be completed by the patient using the SitePRO tablet. To determine the extent of the pain, patients will be asked to place a small vertical mark on a horizontal scale from 0 to 100, the ends of which are labelled with the extreme responses to be measured ("No pain" and "Intolerable pain").

7.3 Immunogenicity Assessments

Blood samples for the assessment of ADAs will be collected prior to dosing at Baseline (Week 0) and at the time points detailed in Table 1 and Table 2.

Blood (10 mL) will be placed into 2 × 5 mL polymer gel tubes, and allowed to clot. Serum will be separated by centrifugation, and divided into 8 aliquots of approximately equal volume (about 0.5 mL per aliquot) in capped cryovials (2 mL polythene tubes). Serum samples will be stored at –70°C (-20°C if a -70°C freezer is not available). The ADA analysis will be done by inVentiv Health Clinical.

Specific details of the sample collection procedure, the storage conditions, and the shipping instructions will be detailed in the laboratory manual.

7.4 Pharmacokinetic Assessments

Blood samples for the quantification of adalimumab in serum will be collected prior to dosing at Baseline (Week 0) and at the time points detailed in Table 1 and Table 2. Concentrations of MTX will not be assessed.

Blood (3.5 mL) will be placed in a polymer gel tube, and allowed to clot. Serum will be separated by centrifugation, and divided into 2 aliquots of approximately equal volume (about 0.5 mL per aliquot) in capped cryovials (2 mL polythene tubes). Serum samples will be stored at –70°C (-20°C if a -70°C freezer is not available). The PK concentration measurement will be done by inVentiv Health Clinical.

8 REPORTING OF ADVERSE EVENTS

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with that treatment.

An AE can, therefore, be any unfavourable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study medication. A new condition or the worsening of a pre-existing condition will be considered an AE.

All overdoses should be recorded as an AE. An overdose is any dose of study treatment, including protocol prescribed concomitant medication, given to a patient or taken by a patient that exceeds the protocol prescribed amount. An overdose should be recorded as an AE even if it does not result in an adverse effect to the patient. An overdose that results in an AE that meets any of the outcomes defined as serious must be reported on an SAE form and sent to the Sponsor's pharmacovigilance department within 24 hours of becoming aware of the event (as described in Section 8.6.2).

8.2 Recording and Reporting an Adverse Event

Patients will be carefully monitored for AEs from signing of informed consent until the End of Study visit (Week 80) or Early Termination visit if the patient does not complete the study. Ongoing AEs from Study FKB327-002 will be recorded in the FKB327-003 eCRF as medical history/concurrent conditions. Any AE occurring or worsening after randomisation to the FKB327-003 study will be recorded in the FKB327-003 eCRF as an AE.

SAEs will be followed until resolution, the Investigator confirms the event is unlikely to resolve or the patient is recorded as lost to follow-up. The Investigator or delegate will question the patient about AEs using a non-leading question, such as 'How are you feeling?' The Investigator will also record AEs reported spontaneously by the patient.

CS changes in the findings of physical examination, and CS abnormalities in the results of objective tests (eg, laboratory parameters, X-ray and ECG) may also be recorded as AEs. The Investigator will use the following criteria when deciding whether or not to report an abnormal result as an AE:

1. The test result is associated with accompanying symptoms.
2. Results of additional diagnostic tests cause concern or necessitate medical intervention.
3. As a consequence of the test result, the patient is withdrawn or the patient is given concomitant treatment.
4. The Investigator considers the result to constitute an AE.

If any of the above criteria are met, the Investigator will report the result as an AE. A record of all AEs reported, regardless of causality, will be kept in the eCRF.

8.3 Follow-up of Adverse Events

All AEs, including CS laboratory values or physical examination changes relative to Baseline values, must be followed until the AE resolves, is no longer of clinical concern, has stabilised or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilises, resolves or is no longer an ongoing clinical concern. If resolved, a resolution date for the AE should be documented on the eCRF. The Principal Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals as considered clinically appropriate by the Principal Investigator.

8.4 Severity of an Adverse Event

The severity of each AE must be recorded according to the following categories:

Mild: the AE does not interfere with the patient's daily routine and does not require intervention; it causes slight discomfort.

Moderate: the AE interferes with some aspects of the patient's routine or requires intervention but is not damaging to health; it causes moderate discomfort.

Severe: the AE results in alteration, discomfort or disability which is clearly damaging to health.

8.5 Relationship of an Adverse Event to Study Medication

The relationship of each AE to study medication must be recorded according to the following categories:

Related: an event which occurs after exposure to the test product, has a reasonable temporal relationship to dosing and is likely to be caused by it. The event may or may not be a known side effect of the test product. The event is not easily attributable to another cause. There may be evidence of a positive de-challenge and/or re-challenge.

Possibly related: An event for which, after careful medical evaluation, a connection with study medication cannot be ruled out with certainty. The event occurs after exposure to the test product. The event may occur at a reasonable time in relation to the time of administration of study medication, but might also be attributable to a commonly occurring alternative cause. Alternatively, the event may not occur at a reasonable time in relation to the time of administration of study medication, but not be attributable to an alternative cause.

Unrelated: an event which occurs before exposure to the test product, which can clearly be attributed to another cause or is clearly unrelated to the study, eg, road traffic accident in which the patient is a victim.

8.6 Serious Adverse Events

8.6.1 Definition of a Serious Adverse Event

An SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

- Death.
- A life-threatening AE (ie, the patient was at immediate risk of death from the event as it occurred); it does not include an event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization (defined as an overnight stay) or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study, or for social reasons (eg, renewal of disease certification) will not be considered SAEs.
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Development of active TB, an opportunistic infection, or a malignancy should always be considered an important medical event. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

8.6.2 Reporting a Serious Adverse Event

In the event of any SAE which, in the Investigator's opinion, justifies termination or modification of the study, dosing will be stopped and the Sponsor will be informed immediately.

For all SAEs, the Investigator will complete an SAE form and provide it to the Sponsor's pharmacovigilance department within 24 hours of becoming aware of the event:

email: safety@XXX.com (Sponsor's pharmacovigilance department)
Fax: +XX XXX XXX XX (Sponsor's pharmacovigilance department)

The Sponsor's pharmacovigilance department will confirm receipt of the report within 1 business day. The Principal Investigator should re-send any report where acknowledgement of receipt is not provided.

The Principal Investigator will assess whether an event is causally related to study medication (see Section 8.5). The Sponsor will consider the Principal Investigator's assessment and determine whether an event meets the criteria for being reportable as a 7-day or 15-day safety report.

The Sponsor (or delegate) will notify the relevant Competent Authority(ies) of all suspected unexpected serious adverse reaction (SUSARs), and will be responsible for ensuring that the Central Ethics Committees (CEC)/Institutional Review Boards (IRBs) are notified of relevant SUSARs, as applicable. SUSARs that are fatal or life-threatening must be notified to the Competent Authority and CEC/IRB within 7 days after the Sponsor (or delegate) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant Competent Authority(ies) and CEC/IRB within 15 days after the Sponsor (or delegate) has first knowledge of them.

Documentation of all submissions must be retained within the Study Master File.

Following the initial report, any additional information received by the Principal Investigator about an SAE must be reported promptly to the Sponsor's pharmacovigilance department as above.

Details of the expectedness of an SAE can be found in the Investigator's Brochure.[2]

8.7 Withdrawals due to Adverse Events

The Investigator will assess the reason for withdrawal as far as possible and will fully record the circumstances and medical details. Provided that patients give written informed consent, they will undergo the standard medical examination and laboratory tests at withdrawal from the study which they would have undergone had they completed it (see Table 1 and Table 2). Any SAEs ongoing at the time of withdrawal will be followed until resolution or confirmation from the Investigator that the event is unlikely to resolve.

8.8 Pregnancy

Any patient who becomes pregnant during the study will be withdrawn from the study. All pregnancies (in patients and patient's partners) occurring during the study, or within 5 months of completion of the study, are to be reported immediately to the Sponsor's pharmacovigilance department on a Pregnancy Report Form and the Investigator will take reasonable steps to follow the patient (or patient's partner) until the outcome of the pregnancy is determined. Any premature termination of pregnancy must also be reported to the Sponsor's pharmacovigilance department by the Investigator.

The process for reporting a pregnancy is the same as that for reporting an SAE (see Section 8.6.2) except that the Pregnancy Report Form is used instead of the SAE form.

8.9 Device Complaints

Where the study site personnel becomes aware of an issue with the study device (PFS or auto-injector), a Device Complaint Report (DCR) form is to be completed by the Investigator or designee and forwarded to the contact whose details are provided in

Section 8.6.2. Such issues may include problems with the identity (labelling, packaging), quality, durability, reliability, safety, effectiveness or performance of the device. The issues may be detected at the study site by site personnel or reported by the patient via phone call to the site personnel or recorded on their home dosing diary card.

9 STATISTICAL METHODS

Detailed methodology for the statistical analyses, including details of the data summary tables and figures, will be documented in a SAP. The statistical methodology presented in this section of the protocol represents a broad outline of the analyses planned at the time of writing. More specific details of the statistical analyses will be presented in the SAP; and the contents of the SAP should be considered to be the definitive documentation of the planned analyses; superseding, where necessary, the information contained within the protocol. Where a protocol is amended for operational reasons only, such amendments may not always be updated to reflect the analyses planned in the SAP, even when the date of the protocol amendment is later than the date of the SAP. Methods for handling missing data will be detailed in the SAP.

The data from this study will be analysed in 4 groups as detailed in Table 3.

Table 3 Analysis of Treatment Groups

Treatment in FKB327-002	Treatment in FKB327-003	Treatment Sequence for Analysis (from Week 0 in 002 study to Week 30 in 003 study)	Treatment Sequence for Analysis (across studies 002 and 003)
FKB327	FKB327-FKB327	FKB327-FKB327	FKB327-FKB327-FKB327
FKB327	Humira-FKB327	FKB327-Humira	FKB327-Humira-FKB327
Humira	FKB327-FKB327	Humira-FKB327	Humira-FKB327-FKB327
Humira	Humira-FKB327	Humira-Humira	Humira-Humira-FKB327

The safety population will comprise all patients who received at least one dose of randomised treatment in the FKB327-003 study. The safety analysis will be based on the safety population. Patient safety data will be analysed according to treatment actually received (for both studies).

The Full Analysis Set (FAS) population will comprise all patients who received at least 1 dose of the randomised treatment and who had at least 1 evaluable efficacy measurement after their first dose of randomised treatment in the FKB327-003 study. The efficacy analysis will be based on the FAS population. Patients will be analysed according to randomised treatment (for both studies).

The PK Analysis Set (PKAS) will include all patients who received at least 1 dose of the randomised treatment and have at least 1 serum adalimumab concentration result after receiving randomised treatment in the FKB327-003 study.

9.1 Sample Size

As this is an open-label extension of Study FKB327-002, no formal sample size has been calculated. The number of patients (see Section 3.4) is based on the assumed number of

patients expected to complete Study FKB327-002 and the number of expected drop-outs in Study FKB327-003.

9.2 Efficacy Analysis

The percentage of patients (%) achieving ACR20, ACR50 and ACR70 response from baseline in FKB327-002 will be summarised by treatment sequence and visit.

The percentage of patients (%) achieving ACR20, ACR50 and ACR70 response from baseline in Study FKB327-002 over time will be plotted by treatment sequence.

Mean DAS28 score and the change from Baseline (Week 0 from Study FKB327-002) in mean DAS28 score, and individual ACR core set variables (swollen joint count, tender joint count, CRP, patient's assessment of disease activity, physician's assessment of disease activity, patient's assessment of pain, HAQ-DI) will be summarised by treatment sequence and visit.

The mean DAS28 and change from baseline (from Study FKB327-002) in DAS28 over time will be plotted by treatment sequence.

9.3 Safety Analysis

Safety data including vital signs, haematology, serum chemistry and urinalysis will be summarised by treatment sequence for each visit.

Withdrawals from the study will be summarised by treatment sequence.

AEs will be summarised by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated by treatment sequence and relationship to treatment. SAEs, in particular infections and malignancies, will be summarised by treatment sequence.

The incidence and size of injection site reactions and injection site pain VAS scores will be summarised by FKB327-003 treatment using descriptive statistics.

9.4 Immunogenicity Analysis

All ADA activity will be listed and summarised for each treatment period (by treatment sequence during the randomised treatment period), and the proportion of ADA positive cases (in the confirmatory assay) during the randomised treatment period will be compared between treatment sequences.

The frequency (percentage) of titre results will be summarised for each treatment by day; summaries will include the median and upper and lower ADA quartiles for the overall safety population. In addition, ADA titre results will be presented graphically for each treatment group during the randomised treatment period.

The frequency (percentage) of ADA neutralising results (positive, negative, inconclusive) during the randomised treatment period will be summarised for each treatment.

9.5 Pharmacokinetic Analysis

Serum trough concentrations of adalimumab will be listed and summarised by treatment sequence, and individual and mean concentration-time profiles will be presented graphically on linear scales.

In addition to individual and mean concentration-time plots presented for each treatment, individual concentration-time plots will also be presented to illustrate graphically the effect of ADA activity on the PK profiles.

9.5.1 Primary Pharmacokinetic Analysis

For the PKAS (Section 9), a mixed model for repeated measures will be fitted to the log transformed PK trough concentrations at Weeks 12, 24 and 30 (ie, during the randomised treatment period) with patient included as a random effect and fixed effect terms for week, treatment sequence, week x treatment sequence interaction where treatment sequence is the 4-level term as shown in Table 3. The LSM for each treatment sequence will be estimated at each week and averaged over time with 95% CIs and plotted over time.

Provided the interaction term for week x treatment sequence is not significant at the 10% level, only differences in LSMs averaged over all time points will be estimated with 90% CIs. Otherwise, difference will be estimated at each time point. Estimates will be back-transformed to give geometric LSMs and ratios of geometric LSMs. The following comparisons will be of interest:

- FKB327 to Humira (based on treatment in Study FKB327-003).
- Sequence group FKB327-Humira relative to Humira-Humira.
- Sequence group Humira-FKB327 relative to Humira-Humira.

Different covariance structures may be considered to improve the fit of the model (eg, autoregressive).

PK samples collected during the non-randomised period (ie, at Weeks 54 and 76) will be listed and summarised only, as described in Section 9.5.

9.5.2 Secondary Pharmacokinetic Analysis

Due to the potential formation of ADAs, a secondary PK analysis will be performed with ADA titre results.

Full details of the primary and secondary analyses will be provided in the SAP.

9.6 Interim Analysis

An interim analysis of all planned endpoints for all patients will be performed once 100 patients randomised to FKB327 in study FKB327-002 and also to FKB327 in the randomised phase of study FKB327-003 plus 100 patients randomised to Humira in study FKB327-002 and also to Humira in the randomised phase of study FKB327 003 have reached Week 30 in this study (FKB327-003). This will provide more than 100 patient-years of exposure to FKB327 and to Humira across studies FKB327-002 and FKB327-003 for comparison. The analyses to be performed will be detailed in the SAP.

9.7 Data Monitoring Committee

Following due consideration of the available guidance, including International Conference on Harmonisation Note for Guidance E6(R1) (Good Clinical Practice) and the European Medicines Agency published Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr), this study will not require a Data Monitoring Committee (DMC).

The rationale for this decision includes consideration that (i) the indication under investigation is not a disease considered to be within the class of life-threatening diseases, or within a patient population of a specific vulnerability usually requiring a DMC; (ii) the potential risks with FKB327 treatment are expected to follow those associated with Humira which are described in detail within the Summary of Product Characteristics/Prescribing Information for Humira; and (iii) the processes to be used for the recording and reporting of adverse events as described within Section 8 are considered adequate to allow the timely identification and management of any unexpected safety event without the additional requirement of DMC oversight.

10 DIRECT ACCESS TO SOURCE DATA DOCUMENTS

The sponsor, medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

The Investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study medication label records, diary data, protocol required worksheets, and eCRFs/SitePRO data that are used as the source (see Section 3.7).

The Investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the Sponsor.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Protocol Amendments

After the protocol has been approved by the IEC/IRB, no changes may be made without the agreement of the Sponsor. Any changes to the protocol will be documented in a protocol amendment which will be signed and dated by the Investigator and Sponsor, and attached to the original protocol. The IEC/IRB must approve substantial amendments before they are implemented.

The Sponsor and Investigator may take appropriate urgent safety measures to protect the patients from any immediate hazard to their health and safety. Any such measures should be taken immediately and may be done without prior Competent Authority(ies) or

IEC/IRB approval. However, the Competent Authority(ies) and IEC/IRB must be informed in writing in the form of a substantial amendment within 3 days of the urgent safety measures being implemented.

11.2 Study Monitoring

The study will be monitored to ensure that the study is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site visits will be made at appropriate times during the period of the study and will be conducted by authorised representatives of the Sponsor. Monitors (eg, Clinical Research Associates [CRAs]) will be given direct access to source documentation in order to check the accuracy and consistency of the data recorded in the CRFs. Remote monitoring may be conducted by direct review of electronic data or by contact with site staff.

In addition, the investigator will work closely with the Monitors and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

The Investigator will ensure entry of CRF data, response to data queries, review/signature of source documentation and resolution of issues are completed in a timely manner.

11.3 Audit and Inspection

The Sponsor, or delegate, may perform a quality assurance audit, and regulatory authorities may inspect this study, at any time during or after the study. The Sponsor and Investigator agree to allow auditors and inspectors direct access to all relevant documents, and to allocate time to discuss findings with the auditors or inspectors.

12 ETHICS

12.1 Informed Consent

The Investigator, or a qualified person designated by the Investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IRB/IEC. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IRB/IEC requirements. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The Investigator will keep the original consent forms, and the patient will be given a copy of all written information and the informed consent. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

12.2 Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to each applicable IEC/IRB for review. As required, the study will not start at a given investigational site before the IEC/IRB have given written approval or a favourable opinion.

12.3 Confidentiality

All personal details of the participating patients and the results of the study will be kept strictly confidential. Each patient's General Practitioner (or equivalent physician) will be informed of the nature and timing of the study. All unpublished documents including the protocol, the eCRF, and the Investigator's Brochure are confidential. Those documents cannot be disclosed to a third party without the written consent of the Sponsor. However, submission of those documents to the IEC/IRB is expressly permitted. The Investigator agrees that the Sponsor maintains the right to use the results of this study, in their original form and/or in a global report, for submission to governmental and regulatory authorities of any country.

12.4 Declaration of the End of the Study

For clinical investigational centres located in the EU, a declaration of the end of the clinical study (defined as last patient, last visit) will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5 Investigator Signatory Obligations

The Clinical Study Report (CSR) will be signed by the Coordinating Investigator for this multi-centre study on behalf of all investigators. The Coordinating Investigator, identified by the Sponsor, will either be:

- A recognised expert in the therapeutic area.
- An investigator or expert who provided significant contributions to either the design or interpretation of the study.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection

Data management will be performed by XXX. The data will be entered into the eCRF within 2 working days of the visit by the designated staff at the site. Relevant electronic Data Clarification Forms (eDCF) will occur on the data once that particular data point is saved. Manual queries may be raised by the CRA as part of Source Data Verification (SDV), the Clinical Data Manager (CDM) as part of consistency review of the data, or as a result of the coding process. Patient Recorded Outcomes, joint counts, and physician VAS assessments will be recorded electronically at the site using an Electronic Patient Recorded Outcome device. This will be in the form of a SitePad provided by XXX. Data captured on this device will be automatically uploaded to the XXX database when the device is connected to the internet. In the event of limited internet access, the device will store the data offline and will then upload the data when a connection to the internet is restored.

13.2 Data Quality Control

As this study will be conducted using Electronic Data Capture (EDC), data cleaning will commence when First Patient First Visit data is entered into the EDC system.

Validation checks run on data which have been entered by site staff into the clinical database will be run as the page is saved. Once the page has been saved, queries will be visible for the site. The site is then able to answer the query at this stage or return to the page at a later date.

The RAVE system will be used to produce and track discrepancies and DCFs and details of this information will be automatically auditable.

13.3 Archiving of Case Report Forms and Source Documents

Upon completion of the study and post Database Lock, the eCRF (including all audit trails and eDCFs) will be copied using an open standard for electronic document exchange. In this case a Portable Document Format (PDF) will be used.

The PDF copies of the eCRFs will be stored in a DVD and the Study Master File will be sent to relevant parties within 3 months of the completion of the final CSR.

14 FINANCING AND INSURANCE

Details of financing and insurance will be presented in a separate document that will be retained within the Study Master File.

15 PUBLICATION POLICY

The Investigator and the Sponsor will discuss the preparation of a manuscript for publication in a peer-reviewed professional journal or an abstract for presentation, oral or written, to a learned society or symposium. Either party may undertake the task but both must agree to the strategy before the work is started. Each party will allow the other 30 days to comment before any results are submitted for publication or presentation. Authorship should reflect work done by the Investigators and personnel of the Sponsor, in accordance with generally recognised principles of scientific collaboration.

16 APPENDICES

16.1 American College of Rheumatology Revised Criteria for Classification of Functional Status in Rheumatoid Arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)[a]
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited ability to perform usual self-care, vocational, and avocational activities

[a] Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific

Source: Hochberg MC1, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992 May;35(5):498-502.

16.2 Interpretation of TB Screening Results

Immunosuppressant biologic treatments have been shown to increase risk of TB infection or to cause conversion from latent to active TB in some circumstances. Because of this, and in accordance with approved prescribing instructions of Humira, patients must be screened for active or latent TB prior to entry to this study.

Definitions

Active TB is a disease caused by *M. tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with *M. tuberculosis,* as evidenced by a positive Tuberculin Skin Test or Interferon Gamma Release Assay (such as QuantiFERON-TB Gold) but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic anti-mycobacterial treatment to eliminate the infection at least 3 weeks prior to randomisation in Study FKB327-002 (or longer, if local guidelines specify) and commit to completing the course of treatment.

TB screening

As part of recording the patient's medical history, the patient should be asked if they have presented with active or latent TB in the past and whether they have received a Bacillus Calmette–Guérin (BCG) vaccination. They should also be asked if they have been in contact with any individuals known to have active TB, or been placed in any circumstances that may have exposed them an increased risk of TB infection, such as travels to TB endemic regions, close contacts with persons with active TB, work at risk (prison, hospitals, etc).

A QuantiFERON test will be performed at Screening for Study FKB327-002. A chest X-ray should also be performed and reported by a qualified radiologist (if not done within 12 weeks prior to Screening for Study FKB327-002).

Patients will be screened for active or latent TB using QuantiFERON-TB Gold-In-Tube tests performed by the Central Laboratory and chest X-rays performed locally (see Table 1 and Table 2 and Sections 7.2.1.6 and 7.2.4). A combination of the results of the QuantiFERON test, chest X-ray and any other investigations deemed appropriate by the Investigator based on clinical signs and symptoms will therefore be used to determine study eligibility at transition from FKB327-002 to FKB327-003, and during the studies as detailed in Table 4.

Note: i) Positive results of the QuantiFERON test may be reduced by immune suppression. Indeterminate results are more common in this population than in healthy individuals.

ii) If an initial QuantiFERON test result is indeterminate, the investigator is advised to repeat the test to confirm the result.

iii) The QuantiFERON test should not usually be positive/indeterminate due to prior BCG vaccination. In this situation positive/indeterminate results should be taken to indicate possible active or latent TB.

iv) Whilst QuantiFERON test results should revert to negative after successful treatment for active or latent TB, results may remain positive/indeterminate during and for some time after completion of anti-mycobacterial therapy.

Table 4: Interpretation of QuantiFERON and Chest X-ray Results (Across Studies FKB327-002 and FKB327-003)

QuantiFERON Test Result	Chest X-ray (evidence of current, active TB)	Interpretation
Positive	Positive	Active TB present. Ineligible for entry to study FKB327-002 or -003. If already on study, withdraw patient from study treatment, report SAE and treat TB appropriately.
Positive	Negative	Possible latent TB or extra-pulmonary TB present. Exclude extra-pulmonary TB using further investigations appropriate to any sign/symptoms. Once extra-pulmonary TB has been excluded and if at Screening for FKB327-002, patient is only eligible for study entry after at least 3 weeks of prophylactic anti-mycobacterial therapy (or longer, if local guidelines specify) and if committed to completing this course of treatment. If these test results are found after Screening, discuss with the Medical Monitors and either interrupt study dosing until at least 3 weeks of anti-mycobacterial treatment have been completed (with a commitment to complete treatment) or withdraw patient from study treatment. If patient was found with latent TB in the past and can provide at Screening complete documentation of previous prophylactic treatment, they may be enrolled provided no signs of extrapulmonary TB are detected.
Negative	Positive	Likely anomalous QuantiFERON result. Repeat QuantiFERON test if in doubt. Ineligible for entry to study FKB327-002 or -003. If already on study, withdraw patient from study treatment, report SAE and treat TB appropriately.
Negative	Negative	Eligible for study FKB327-002 or -003
Indeterminate	Positive	Likely anomalous QuantiFERON result. Repeat tests if in doubt. Ineligible for entry to study FKB327-002 or -003. If already on study, withdraw patient from study treatment, report SAE and treat TB appropriately.
Indeterminate	Negative	Possible anomalous QuantiFERON result or latent TB. Either: a) Repeat QuantiFERON test. If negative, patient is eligible for study FKB327-002 or -003. If positive, patient is ineligible for either study. If result still indeterminate, manage patient as though they have a positive QuantiFERON result and negative chest X-ray (see above). If already on study, discuss with Medical Monitors. Consider prophylactic anti-mycobacterial treatment or withdrawal from study treatment. Or: b) Repeat QuantiFERON test and perform a PPD test*. If both are negative, patient is eligible for study FKB327-002 or -003. If either is positive, patient is ineligible for either study. If either is indeterminate exclude from the study.

* PPD injected intracutaneously into the volar surface of the forearm and the result measured as millimetres of induration after 2 to 3 days. A positive result requires ≥5 mm of induration.

Management of signs/symptoms of TB during the study

If new signs/symptoms of TB infection develop during the study, perform diagnostic tests as above, and any other additional investigation as deemed appropriate by the investigator or a TB specialist. If active TB infection (active or latent) is diagnosed, interrupt study treatment and consult the Medical Monitors. Report active TB infection as a medically important SAE. Treat appropriately.

Treatment of latent or active TB

Treatment should be according to local guidelines, which may vary depending upon the sensitivity of strains of *M. tuberculosis* present locally. As a guide, the US Centers for Disease Control and Prevention recommendations are at http://www.cdc.gov/TB/publications/LTBI/default.htm. Patients with latent TB at screening should have received appropriate treatment for at least 3 weeks (or longer, according to local guidelines) prior to commencement of study treatment and should be committed to completing the course of anti-mycobacterial therapy during the study. If latent TB is diagnosed during the study, study treatment should be interrupted until at least 3 weeks of anti-mycobacterial treatment have been completed (with a commitment to complete the treatment course) or the patient should be withdrawn from study treatment.

In case of any doubt as to the diagnosis of latent TB and the appropriate course of anti-mycobacterial therapy, it is advised that a local physician with expertise in the treatment of TB is consulted.

Although QuantiFERON test results may remain positive/indeterminate for some time after treatment of active or latent TB, patients with a positive test result at Screening should continue to undergo protocol scheduled QuantiFERON tests and chest X-rays in order to document TB status and monitor for reinfection/reactivation.

16.3 New York Heart Association Classification

Class I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
Class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
Class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

Source: The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. Boston: Little Brown; 1964.

17 REFERENCES

1. Chatzantoni K, Mouzaki A. Anti-TNF-alpha antibody therapies in autoimmune diseases. Curr Top Med Chem. 2006;6(16):1707-14.
2. Investigator's Brochure for FKB327. Fujifilm Kyowa Kirin Biologics Co., Ltd. Version 4, 18 June 2015.
3. Methotrexate. MedlinePlus. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682019.html [accessed 21 March 2014].
4. Summary of Product Characteristics (SmPC) for EU licensed Humira®. Available from: http://www.emea.europa.eu [accessed 21 March 2014].
5. den Broeder AA, Joosten LA, Saxne T, Heinegård D, Fenner H, Miltenburg AM, Frasa WL, van Tits LJ, Buurman WA, van Riel PL, van de Putte LB, Barrera P. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis. 2002 Apr;61(4):311-8.
6. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Expert Opin Drug Saf. 2011;10:655-73.
7. What Is ACR (American College of Rheumatology) Criteria? 18 November 2012. Available from: http://arthritis.about.com/od/trials/f/ACR_criteria.htm [accessed 21 March 2014].
8. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137 45.
9. Bruce B, Fries J. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. Health and Quality of Life Outcomes. 2003;1:20.
10. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: identifying reversible and irreversible components. Arthritis and Rheumatism. 2006;54:2784 92.
11. The DAS28 score website. Radboud University Nijmegen. 2013. Available from: www.das-score.nl [accessed 21 March 2014].
12. Mazurek GH, Villarino ME. Guidelines for Using the QuantiFERON®-TB Test for Diagnosing Latent *Mycobacterium tuberculosis* Infection. Centers for Disease Control and Prevention. 31 January 2003. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5202a2.htm [accessed 21 March 2014].
13. FDA Guidance for Industry on Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 1999