# Statistical Analysis Plan

## Protocol Number: FKB327-003

## 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)

**Customer: Fujifilm Kyowa Kirin Biologics Co., Ltd (FKB), Tokyo 100-8185, Japan**
**Compound: FKB327 (adalimumab)**
**Study Phase: Phase 3**

**Version: 4.0.0**
**Date: 10 JUL 2018**
**Author:**

**VERSION CONTROL**

| Version | Date | Author(s) | Changes/Comments |
|---|---|---|---|
| Version 1.0.0 | 25AUG2016 | | Version 1 issued |
| Version 2.0.0 | 05JUN2017 | | Updated section 1 on general features of the SAP + new IA rationale brief introduction.<br>Specified Auto-Injector as part of the secondary objectives.<br>Added rationale for second Interim Analysis to Section 5.4.<br>Added details to Section 6 relevant subsections related to all additional analyses included after finalisation of SAP v1.0.0.<br>Created a Section 7 related to outputs to be produced only for the final analysis.<br>Details on changes from V1.0.0 of the SAP to 2.0.0 added in Section 8.2. |
| Version 3.0.0 | 19OCT2017 | | Updated section 1 with new IA rationale brief introduction.<br>Details on changes from V2.0.0 of the SAP to 3.0.0 added in Section 8.3 |
| Version 4.0.0 | 10JUL2018 | | Added in Additional D120 tables requested for CSR, which consider summaries of Adverse Events, Neutralizing Antibody, Anti-Drug Antibody Titres and Injection site reactions stratified by administration method (pre-filled syringe or auto-injector) whilst exposed to FKB327.<br>Introduction section is also updated to reflect most recent SAP versioning, purpose and DBL date.<br>Sections 6.8.2, 6.9.4 and 6.9.5 are also updated to reflect the above summaries. |

| | | | |
|---|---|---|---|
| | | | Add additional column for outputs which are included in final analysis and update abbreviation list with Auto-Injector<br><br>Details on changes from V3.0.0 of the SAP to 4.0.0 added in Section 8.3<br><br>Update the title of table 14.3.1.2.10, as per FKB request, and change mentions of drug-related to treatment related where appropriate. |

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ACR | American College of Rheumatology |
| ADAs | Anti-drug antibodies |
| AE | Adverse event |
| AESI | Adverse Events of Special Interest |
| AI | Auto-Injector |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| ATC | Anatomical Therapeutic Chemical |
| BLA | Biologics Licence Application |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence interval |
| CRP | C-reactive protein |
| CS | Clinically significant |
| CV | Coefficient of variation |
| DAS28 | Disease Activity Score 28 |
| DMARD | Disease modifying anti-rheumatic drug |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eow | Every other week |
| ESR | Erythrocyte sedimentation rate |
| EU | European Union |
| EULAR | European League Against Rheumatism |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GGT | Gamma glutamyl transferase |
| GH | Global Health |
| HAQ-DI | Health Assessment Questionnaire Disability Index |
| Hb | Haemoglobin |
| 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 |
| MTX | Methotrexate |
| NEC | Not elsewhere classified |
| NCS | Not clinically significant |
| NSAID | Non-steroidal anti-inflammatory drug |
| OLE | Open-label extension |
| PDF | Portable Document Format |
| PFS | Pre-filled syringe |
| PK | Pharmacokinetics |
| PKAS | PK Analysis Set |
| PRO | Patient reported outcomes |
| PT | Preferred Term |
| RA | Rheumatoid arthritis |

| | |
|---|---|
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| sc | Subcutaneous |
| SD | Standard deviation |
| SI | Système Internationale |
| SJC | Swollen joint count |
| SLE | Systemic lupus erythematosus |
| SMQ | Standardised MedDRA Queries |
| SOC | System Organ Class |
| $t_{1/2}$ | Elimination half-life |
| TB | Tuberculosis |
| TJC | Tender joint count |
| $t_{max}$ | Time of maximum concentration |
| TNF-α | Tumour necrosis factor-alpha |
| US(A) | United States of America |
| VAS | Visual analogue scale |
| WBC | White blood cell |

# 1 Introduction

This statistical analysis plan (SAP) is being updated from the FKB327-003 study SAP version 3.0.0 dated 19 OCT 2017and based on protocol FKB327-003 Version 4.4/4.5 (based on Global amendment 5) dated 19 MAY 2017. This SAP contains a complete and detailed specification of the statistical and pharmacokinetic (PK) analyses for interim and final analyses and should be used and authorised in conjunction with the document 'FKB327-003 Final Run shells V4.0.0', dated XX JUL 2018.

A Marketing Authorisation Application (MAA) for FKB327 was submitted to the European Medicines Agency (EMA) in April 2017 using data from a planned interim analysis of study FKB327-003 whose rationale, timing and content were detailed in FKB327-003 Statistical Analysis Plan Version 3.0.0. FKB decided that a further interim analysis of study FKB327-003 should be performed in order to be able to provide updated safety, efficacy, PK and immunogenicity data on the ongoing FKB327-003 study, should this be requested. The need for this additional interim analysis and its regulatory implications were documented in the internal "Document Revision Assessment Form" (FKB Form 302) signed off on 28th April 2017. A Non-substantial Global Amendment to the study protocol was then prepared and signed off on 19th May 2017. A data-base lock and subsequent interim analysis was planned for July 2017 based on data collected for all patient visits that occurred from the beginning of the study up until the 30th April 2017. Following this additional interim analysis, the final DBL took place on 13APR2018, and during the reporting process that followed it was agreed to create additional tables to complement assessments of safety, efficacy and immunogenicity, following specific requirements from the regulators during the review process. The present SAP version includes details for the creation of such tables.

This version of the statistical analysis plan has only been used for the final analysis of FKB327-003 study, although guidance is provided in the Attachments section with respect to which outputs have been created for which analysis (i.e. either interim and/or final).

## 1.1 Rationale

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 rheumatoid arthritis (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 Visit 7 (Week 30) of Study FKB327-003). Post Week 30, all patients will transition on to FKB327 in order to gain further long-term exposure on FKB327. Furthermore, the study will also permit an evaluation of the above mentioned parameters in patients switching between the products after randomisation and could therefore provide relevant data for subsequent clinical practice.

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

# 2 Summary of the Protocol

## 2.1 Study Objectives

### 2.1.1 Primary Objective

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

### 2.1.2 Secondary Objectives

The secondary efficacy objectives of the study comprise the following:

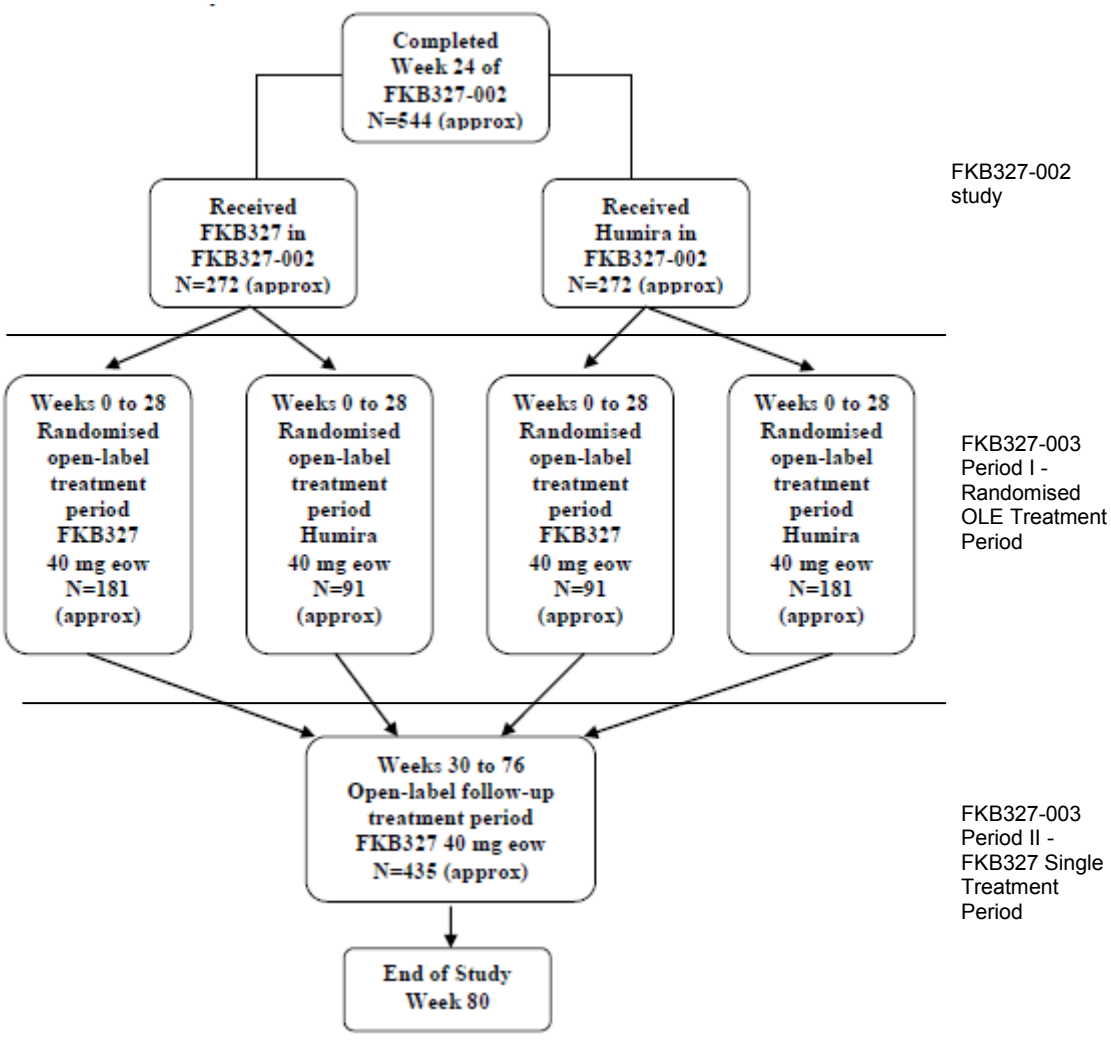
- To compare the efficacy of long-term treatment with FKB327 and Humira in patients with RA.
- To compare the proportion of patients developing anti-drug antibodies (ADAs) on long-term treatment with FKB327 and Humira in patients with RA.
- To compare the PK of long-term treatment with FKB327 and Humira 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, 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).
- To evaluate safety and PK profile of patients switching to administration of FKB327 using an Auto-Injector (AI) device during Period II (i.e. on or after Week 30) as opposed to the Pre-filled Syringe (PFS) device used during Period I.

## 2.2 Study Design

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 Methotrexate (MTX) and folate who will continue from the preceding Study FKB327-002. Eligible patients who complete Study FKB327-002 and consent to participate in this open-label extension study will be randomised to receive treatment with either FKB327 40 mg every other week (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, where Week 0 is intended as the Baseline visit occurring within this extension study (see Table 3). The patient or carer will be allowed to administer interim doses of study drug at home (eow) between clinic visits (see Table 3). FKB327 in an AI 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.

The study design is presented in Figure 1.

**Figure 1 Study Schema**




End of Period I is defined as just before treatment at Week 30.

Randomised patients will be administered the Week 0 study drug dose after the Week 24 study procedures for Study FKB327-002 have been performed.

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 4 – all procedures marked with an asterisk).

The study schema presented in Figure 1 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.

Tables 1 and 2 present the treatment group and sequence labels that will be used in all outputs. The choice of presenting the 2-term or 3-term treatment sequence will depend on the output, as detailed in the shells.

**Table 1 Study Treatments**

| Actual Treatment | Treatment Label |
|---|---|
| US-licensed Humira 40 mg | Humira |
| FKB327 40 mg | FKB327 |

**Table 2 Treatment Sequence**

| Treatment Groups | | | Treatment Sequence | |
|---|---|---|---|---|
| FKB327-002 | FKB327-003 (Period I) | FKB327-003 (Period II) | 2-Term | 3-Term |
| FKB327 | FKB327 | FKB327 | F-F | F-F-F |
| FKB327 | Humira | FKB327 | F-H | F-H-F |
| Humira | FKB327 | FKB327 | H-F | H-F-F |
| Humira | Humira | FKB327 | H-H | H-H-F |

Table 3 presents the visit labels that will be used in all outputs.

**Table 3 Study Visits**

| Visit Week | Visit Type | Visit label |
|---|---|---|
| Week 0 (from Study FKB327-002) | Clinic | Baseline_002 |
| Week 0 | Clinic | Baseline_003 |
| Week 2 | Clinic | Week 2 |
| Week 4 | Clinic | Week 4 |
| Week 6 | Home | Week 6 |
| Week 8 | Clinic | Week 8 |

| Visit Week | Visit Type | Visit label |
|---|---|---|
| Week 10 | Home | Week 10 |
| Week 12 | Clinic | Week 12 |
| Week 14 | Home | Week 14 |
| Week 16 | Home | Week 16 |
| Week 18 | Home | Week 18 |
| Week 20 | Home | Week 20 |
| Week 22 | Home | Week 22 |
| Week 24 | Clinic | Week 24 |
| Week 26 | Home | Week 26 |
| Week 28 | Home | Week 28 |
| Week 30 | Clinic | Week 30 |
| Week 32 | Clinic or Home** | Week 32 |
| Week 34 | Clinic or Home** | Week 34 |
| Week 36 | Home | Week 36 |
| Week 38 | Home | Week 38 |
| Week 40 | Home | Week 40 |
| Week 42 | Clinic | Week 42 |
| Week 44 | Home | Week 44 |
| Week 46 | Home | Week 46 |
| Week 48 | Home | Week 48 |
| Week 50 | Home | Week 50 |
| Week 52 | Home | Week 52 |
| Week 54 | Clinic | Week 54 |
| Week 56 | Home | Week 56 |
| Week 57 | Home | Week 57 |
| Week 58 | Home | Week 58 |
| Week 60 | Home | Week 60 |
| Week 62 | Home | Week 62 |
| Week 64 | Home | Week 64 |
| Week 66 | Clinic | Week 66 |
| Week 68 | Home | Week 68 |

| Visit Week | Visit Type | Visit label |
|---|---|---|
| Week 70 | Home | Week 70 |
| Week 72 | Home | Week 72 |
| Week 74 | Home | Week 74 |
| Week 76 | Clinic | Week 76 |
| Week 80 | Clinic | Week 80 |
| End of Study | Clinic | End of Study (EOS) |
| Auto-Injector Start | | AIS |

** The Week 32 and 34 visits are to be performed in the clinic for patients who have switched from Humira to FKB327 (treatment sequences F-H-F and H-H-F) only. Patients remaining on FKB327 can dose at home.

## 2.3 Sample Size Determination

As this is an open-label extension of Study FKB327-002, no formal sample size has been calculated. The number of patients 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.

## 2.4 Schedule of Events

Table 4 presents the schedule of study events for the randomised OLE part of the study (Period I) and Table 5 presents the study schedule for the treatment follow up period (Period II).

**Table 4 Schedule of Study Events – 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) |

| 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 |
| Concomitant MTX and folate | → | → | → | → | → | → | → | → | → | → |
| Haematology | (●)* | | ● | | ● | | ● | | ● | |
| Serum chemistry | (●)* | | ● | | ● | | ● | | ● | |
| Dipstick urinalysis[e] | (●)* | | ● | | ● | | ● | | ● | |
| Pregnancy testing[f] | (●)* | | ● | | ● | | ● | | ● | |
| QuantiFERON test[g] | | | | | | | | | ● | |
| CRP[h,i] | (●)* | | ● | | ● | | ● | | ● | |
| ESR[j] | (●)* | | | | | | | | | |
| 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] | (●)* | | ● | | ● | | ● | | ● | |

| 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 |
| Physician global assessment of disease activity VAS[i] | (●)* | | ● | | ● | | ● | | ● | |

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; DAS = disease activity score; MMP-3 = matrix metalloproteinase 3.

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.

[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 5 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] |

| 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 |
| CRP[h,i] | ● | | | ● | | ● | | ● | | ● | ● |
| Serum drug concentration | ● | | | | | ● | | | | ● | ● |
| ADA test | ● | | | | | ● | | | | ● | ● |
| Injection site assessment (including injection site pain VAS)[j] | ● | | | | | | | | | | |
| 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; DAS = disease activity score.
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.
[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 AI during the open-label follow up treatment period

# 3 Patient Analysis Sets

## 3.1 Safety Analysis Set

The safety set will comprise all patients who gave consent for this study and received at least 1 dose of treatment in the FKB327-003 study. The safety analysis will be based on the Safety Analysis Set. Patient safety data will be analysed according to treatment actually received (for both studies).

## 3.2 Full Analysis Set (FAS)

The FAS 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. Patients will be analysed according to their randomised treatment sequence (for both studies) or randomised treatment group (see Table 2).

## 3.3 Pharmacokinetic Analysis Set (PKAS)

The 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. Patients will be analysed according to the treatment they actually received in the FKB327-003 study.

# 4 Study Measures

This section describes the measures that were collected and/or derived during the study at the time points specified in the Schedule of Events (Table 4 and Table 5). This includes efficacy, safety, immunogenicity and patient characteristics data.

## 4.1 Assessment of Efficacy

### 4.1.1 Secondary Efficacy Variables

#### 4.1.1.1 Measured Variables

*4.1.1.1.1 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 4 and Table 5 using standardised techniques recommended by the European League Against Rheumatism (EULAR). XXX will send SAS (Statistical Analysis System) datasets of the joint counts.

If, at any visit, a joint is not evaluable for any reason, this will be recorded on the patient-reported outcomes devices, SitePRO. 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. Missing or unevaluable joints will be treated as follows:

- If the joint assessment is missing, then the joint will be regarded as non-tender and non-swollen at Baseline and tender and swollen at post-Baseline.

- If the joint is assessed as unevaluable due to prior surgery at any visit, then the joint will be counted as non-tender and non-swollen at Baseline and all post-Baseline assessments.
- If the joint is unevaluable due to surgery conducted during the study, then the joint will be counted as tender and swollen from that point onwards.
- If the joint is unevaluable due to steroid injection, then the joint will be counted as tender and swollen for 12 weeks after the date of injection.
- If the joint is unevaluable due to other conditions or procedures at any visit post-Baseline, then the joint will be counted as swollen and tender at that visit.

*4.1.1.1.2 C-reactive Protein (CRP)*

Analysis of serum CRP concentrations for inclusion in the American College of Rheumatology 20%/50%/70% improvement criteria (ACR20/50/70) and disease activity score 28 (DAS28-CRP) will be performed by XXX laboratory and transferred to the clinical database.

*4.1.1.1.3 Visual Analogue Scales (VAS)*

Patient global assessment of disease activity VAS (global health [GH]; ranging from very well to extremely bad), patient assessment of pain (ranging from no pain to intolerable pain) 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 4 and Table 5. These VASs must be completed by the patient/physician themselves on a SitePRO tablet. All these VASs will contribute to the calculation of ACR20, ACR50 and ACR70 response (see Section 4.1.1.2.1), whereas the patient global assessment of disease activity VAS only will contribute to the calculation of the DAS28 (see Section 4.1.1.2.2). Patient-recorded data will not be corrected or revised in any way. Patient assessment of pain is collected from the health assessment questionnaire – disease index (HAQ-DI) . XXX will send SAS datasets of the VAS scores.

*4.1.1.1.4 Health Assessment Questionnaire – Disease Index (HAQ-DI)*

The HAQ-DI 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. This scale is sensitive to change and is a good predictor of future disability. The HAQ-DI questionnaire will be completed on the SitePRO device by the patients themselves at the time points indicated in Table 4 and Table 5, following which XXX would send SAS datasets with the results. Patient-recorded data will not be corrected or revised in any way.

The score for each category is the single response within the category with the highest score (greatest difficulty). If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s). However, if any "aids or devices" and/or "help from another person" items at the bottom of each page are checked, all the categories for

- Group 1: Dressing and grooming, getting up, eating and walking, or
- Group 2: Personal care, reaching, gripping and usual activities

are adjusted upward to "2", depending on which group this has been selected for. If the basic score is already "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can only change a category's score to "2"; they do not change the score to a "1" or a "3". For the 'Aids or devices' option, these are the possible responses (i.e. the specific aid or device used) for each group:

- Group 1: Cane, Walker, Crutches, Wheelchair, Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.), Built up or special utensils, Special or built up chair, Other.
- Group 2: Raised toilet seat, Bathtub seat, Jar opener (for jars previously opened), Bathtub bar, Long-handled appliances for reach, Long-handled appliances for in bathroom, Other.

The score for the disability index is the mean of the eight category scores, presented to 1 decimal place. If more than two of the categories, (i.e., >25%), are missing, the score is not calculated. If 2 or fewer of the categories are missing, the sum of the categories is divided by the number of answered categories. The higher score indicates greater disability.

#### 4.1.1.2 Derived variables

##### *4.1.1.2.1 ACR20, ACR50 and ACR70*

The ACR response criteria will be derived and used as secondary efficacy variables. These criteria look at improvement in tender joint count (TJC), swollen joint count (SJC) (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, see Section 4.1.1.1.2).
- Patient global assessment of disease activity (see Section 4.1.1.1.3).
- Physician global assessment of disease activity (see Section 4.1.1.1.3).
- Patient pain scale (see Section 4.1.1.1.3).
- Disability/functional questionnaire (patient completed HAQ-DI, see Section 4.1.1.1.4)

An ACR20 positive response means that the patient achieved a 20% improvement in tender and swollen joint counts and a 20% improvement 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 a 50% improvement 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 a 70% improvement in at least 3 of the other 5 criteria.

If either the tender or the swollen joint counts at Baseline or at a given post-Baseline visit are missing, the ACR20 will be set to missing. If both joint counts are not missing at Baseline and post-Baseline and the available data allow a proper ACR20 estimation (e.g. only 3 components are available but either a ≥20% or <20% improvement is observed for all of them such that the missing components do not have an impact on the ACR20 value), then the ACR20 will be assessed following the rule described above. Otherwise, if the available components data is not sufficient for an ACR20 assessment (e.g. 4 components are available but for 2 of them there's a <20% improvement and for the other 2 a ≥20% improvement, so that the last missing component would be crucial in determining the ACR20 status), the ACR20 will be set to missing. Similar logic will be applied for the estimation of the ACR50 and ACR70 scores.

The percentage of patients achieving ACR20, ACR50 and ACR70 response from Baseline will be assessed at the time points detailed in Table 4 and Table 5. The Baseline Visit used for the ACR response derivation will be the Week 0 visit of Study FKB327-002 (Baseline_002).

*4.1.1.2.2 Disease Activity Score 28 (DAS28)*

The DAS28 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. DAS28 will refer to the DAS28-CRP, unless otherwise specified. The DAS28 assessment involves evaluating the TJC and SJC (out of 28 specified joints), serum CRP and patient global assessment of disease activity (see Section 4.1.1.1.3). The results are then used to calculate the DAS28 using the following formula:

DAS28-CRP = 0.56*sqrt(TJC) + 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; DAS28 in the range of >3.2 to 5.1 indicates moderate disease activity; whereas a DAS28 ≤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 4 and Table 5. The Baseline DAS28, obtained at Week 0 from Study FKB327-002 (Baseline_002), will be used to calculate the change from Baseline.

If any one of the 4 components (28 tender joint counts, 28 swollen joint counts, CRP and VAS GH) is missing, the DAS28 cannot be derived.

Joint count results (28 joints) will be derived by Programming 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 XXX central laboratory.

The 28-joint counts will be derived from the 68/66 joints using the specified joints (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees) with a score of 1 (=Pain/Tender only) and 3 (=Pain/Tender and Swollen) being included in the tender joint count and scores of 2 (=Swollen only) and 3 (=Pain/Tender and Swollen) being included in the swollen joint count. The joints that assessed as part of the 68/66 and 28 joint counts are highlighted in Appendix 8.2.

A joint will be counted as tender and/or swollen if the tender and/or swelling code(s) is 'Present' or as described in Section 4.1.1.1.1 if the joint count is missing or the joint is unevaluable.

## 4.2 Safety Measures

In this study, safety will be assessed by evaluating the following: AEs, physical examination findings, vital signs measurements, and clinical laboratory test results.

### 4.2.1 Exposure to Study Medication

Exposure to study medication in this study will happen in 2 periods. In the first period (Period I), eligible patients will be randomised to either FKB327 (40 mg) or Humira (40 mg) eow from Week 0 (Baseline_003) to Week 28. In the second period of the study (Period II), all patients receive FKB327 (40 mg) eow from Week 30 through to Week 76. Exposure to study medication will be recorded in the eCRF. Patient's concomitant doses of MTX and folic/folinic acid will also be recorded.

### 4.2.2 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient 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.

Patients will be carefully monitored for AEs from signing of the 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 the 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. Clinically significant (CS) changes in the findings of physical examination, and CS abnormalities in the results of objective tests (eg, laboratory parameters, X-ray and electrocardiogram [ECG]) may also be recorded as AEs.

#### 4.2.2.1 Adverse Event Definitions

A serious adverse event (SAE) is an AE which is fatal, life threatening, requires or prolongs inpatient treatment, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is a medically important event that may jeopardise the patient.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity after the first dose of study medication was taken.

A treatment-related TEAE is defined as a TEAE where the relationship to study drug was recorded as "Possibly related" or "Related".

A treatment-emergent serious adverse event (TESAE) is defined as a SAE occurring or increasing in severity after the first dose of study medication was taken.

An AE leading to treatment interruption will be defined as an AE where the response to the question "What action was taken with regard to study medication?" was recorded as "Temporarily Interrupted" on the Adverse Event Log case report form (CRF) page.

An AE leading to treatment discontinuation will be defined as an AE where the response to the question "What action was taken with regard to study medication?" was recorded as "Permanently Discontinued" on the Adverse Event Log CRF page.

#### 4.2.2.2 Coding of Adverse Event Terms

The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high level term (HLT), a high level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, Version 17.1.

Although there can be multiple SOCs for a PT, each PT will be linked with 1 SOC, namely the primary SOC which is automatically assigned by MedDRA via 1 HLT, HLGT route.

The following coding data will be presented:

- LLT (Investigator term).

- PT.

Coding data per primary SOC:

- HLT.
- HLGT.

In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in all summary tables.

Adverse events will be reported on a per-patient basis and per-event. On a per-patient basis this means that even if a patient reported the same event repeatedly (ie, events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst severity and the strongest relationship to the study medication. The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

#### 4.2.2.3 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.

#### 4.2.2.4 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.

### 4.2.3 Clinical Laboratory Tests

Laboratory testing will be performed by a central laboratory facility with the exception of erythrocyte sedimentation rate (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 4 and Table 5.

For the laboratory parameters, if a re-test was performed prior to a study medication administration at any visit, all values will be included in the listings, and will be clearly identified as unscheduled with the time of the repeat measurement. If a test is repeated, the initial value will be used in the summaries, unless the result is missing or non-evaluable (for example, due to haemolysis of a blood sample) in which case the repeat result will be used.

For each laboratory test (quantitative and qualitative), the Baseline value is defined as the result at Week 0 for study FKB327-002 (Baseline_002), in general. However, if the result at this visit is missing, the last non-missing measurement collected/derived prior to the first study medication administration from study FKB327-002 will be imputed as the Baseline value, i.e. the last measurement taken at the Screening visit from FKB327-002. For quantitative laboratory tests, the change from Baseline value at each post-Baseline visit will be calculated as the difference between the value obtained at the specific post-Baseline visit, and the Baseline value.

#### 4.2.3.1 Haematology

The following haematology tests will be performed: haemoglobin (Hb), red blood cell (RBC) 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 the FKB327-002 study) ESR.

#### 4.2.3.2 Serum Chemistry

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

#### 4.2.3.3 Urinalysis

Dipstick urinalysis (performed by local study site staff) will include testing for the following: protein, blood, glucose and leukocyte esterase. If the dipstick reveals any CS 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.

#### 4.2.3.4 Pharmacodynamic Markers

Serum MMP-3 will be analysed at the time points detailed in Table 4 and Table 5.

#### 4.2.3.5 Pregnancy Testing

Females of childbearing potential will take a urine pregnancy test (performed at site) at the time points detailed in Table 4 and Table 5.

#### 4.2.3.6 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 tuberculosis (TB). This may be repeated, at the discretion of the Investigator or to comply with local practices, at additional time points.

### 4.2.4 Vital Signs Evaluations

Vital signs will be collected in accordance with the Schedule of events (see Table 4 and Table 5). The following variables will be collected:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Temperature ($^{o}$C or F). All presentations will show the temperature in $^{o}$C.

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. For each vital signs variable, the Baseline value is defined as the last non-missing measurement collected prior to the first study medication administration in the FKB327-002 study (Baseline_002).

For each variable, the change from Baseline value at each post-Baseline time point will be calculated as the difference between the measurements obtained at the specific post-Baseline time point, and the Baseline value.

### 4.2.5 Physical Examination

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

### 4.2.6 Chest X-ray

Chest X-rays (posterior and lateral views) will be performed at Week 30 and Week 80 or EOS unless patient has a 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.

### 4.2.7 Injection Site Assessment

An injection site assessment will be performed within 30 minutes of dosing at Week 0 (Baseline_003) and Week 30, as well as at the time of switching to the AI 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 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 (Baseline_003), Week 30, or at the assessment conducted at the point of switching to the AI 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").

## 4.3 Other Measures

### 4.3.1 Patient Disposition

Patient disposition data was collected on the 'Study Discontinuation' CRF page when a patient completed or discontinued from the study.

The following data will also be presented:

- Date of informed consent
- Date of early termination of study medication
- Date of final study contact
- Whether patient completed study according to protocol
- Reason for early withdrawal

The analysis sets defined in Section 3 will be analysed and presented as part of the patient disposition data.

### 4.3.2 Baseline Patient Characteristics

Baseline patient characteristics include characteristics that patients presented with prior to the first administration of study medication in the FKB327-002 study. The last available vital signs variables, laboratory results and ECG results collected prior to the first administration of study medication in the FKB327-002 study will be presented in order to assess homogeneity of the treatments. ECG results will consist of the incidence (Yes or No) of clinically significant findings for ECG. The characteristics prior to study drug administration at Week 0 (Baseline_003) are also of interest.

### 4.3.3 Medical History

Medical history contains information about conditions that a patient might have suffered from prior to the first administration of study medication at Week 0 (Baseline_003), or conditions that were ongoing at the time of the first administration of study medication. Ongoing AEs from the FKB327-002 study will also be recorded as medical history. Any changes to medical history conditions during the course of the study that meet the criteria for an AE will be recorded as such.

Medical history data was collected at Week 0 (Baseline_003) on the 'Medical History and Medical Conditions' CRF page.

#### 4.3.3.1 Coding of Medical History Terms

The medical history term (Investigator term) is assigned to the LLT, and a PT will be classified by a HLT, a HLGT and a SOC according to the MedDRA thesaurus, Version 17.1.

Although there can be multiple SOCs for a PT, each PT will be linked with 1 SOC, namely the primary SOC which is automatically assigned by MedDRA via 1 HLT, HLGT route.

The following coding data will be presented:

- LLT.
- PT.
- Coding data per primary SOC:
- HLT.
- HLGT.

Medical history will be reported on a per-patient basis. This means that even if a patient suffered the same clinical event repeatedly (i.e., events mapped to the same PT) the event will be counted only once and the earliest date will be regarded as start date of the event and the latest date will be regarded as stop date of the event.

The same rule for counting applies for PTs mapped to the same HLT and for HLTs mapped to the same HLGT and for HLGTs mapped to the same SOC.

### 4.3.4 Prior and Concomitant Medications

Concomitant medications include all medications that a patient used at any stage during the study. Any medication started prior to Week 0 and used during the study, or medication started at any time after the first study medication administration, will be included.

Medications that started and ended before the first dose of study medication in the FKB327-002 study will be defined as prior medications.

Concomitant medications data are collected throughout the study on the 'Concomitant Medications' CRF page. Any new concomitant medication or change to an existing one will be recorded in the Concomitant Medication Log Form.

Missing concomitant medications data will be handled according to the rules specified in Section 5.3.2.5.

#### 4.3.4.1 Coding of Prior and Concomitant Medication Terms

Prior and Concomitant medications are classified according to active drug substance using the current version World Health Organization-Drug Dictionary (WHO-DD).

The WHO-DD drug identity (ID) has 11 characters. The preferred name, for example, the salt/ester of the substance is defined by the first 8 characters, and the WHO-DD name is defined by the 11 characters.

In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug ID. An ATC code has 7 characters. The first character gives the anatomical main group (1$^{st}$ level), the first 3 characters give the therapeutic main group (2$^{nd}$ level), the first 4 characters give the therapeutic subgroup (3$^{rd}$ level), the first 5 characters give a further level therapeutic subgroup (4$^{th}$ level), whereas the 7 characters give the subgroup for the chemical substance. In this study, ATC codes are defined to the 4$^{th}$ level.

Although there can be multiple ATC classes for some drugs, each drug will be linked with 1 ATC class which will be assigned manually during the coding process when more than 1 class is available, based on information about the indication and route in relation to the study therapeutic area. This 1 ATC class will be indicated as the 'primary' ATC class, and only the primary class will be presented.

### 4.3.5 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.

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.

The following data from clinic visits will be listed as a record of treatment administration:

- Date of administered study medication
- Whether full dose of study drug was administered or not

### 4.3.6 Immunogenicity Assessments

Blood samples for the assessment of ADAs will be collected prior to dosing at Week 0 (Baseline_003) and at the time points detailed in Table 4 and Table 5.

### 4.3.7 Pharmacokinetic Assessments

Blood samples for the quantification of adalimumab in serum will be collected prior to dosing at Week 0 (Baseline_003) and at the time points detailed in Table 4 and Table 5. Concentrations of MTX will not be assessed.

# 5 Statistical Methodology

## 5.1 General Statistical Methods

### 5.1.1 General Information

All analysis data sets and output, will be produced by the Biostatistics Department of XXX using the SAS® system Version 9.3 or higher.

### 5.1.2 Default Descriptive Statistics and Data Rules

Unless otherwise stated, summary statistics including the number of patients, mean, standard deviation (SD), median, minimum and maximum, will be presented for all continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to 1 more, and the standard deviation, to 2 more decimal places than the raw values.

For categorical variables, per category, the absolute counts (n) and percentages (%) of patients with data, and if appropriate, the number of patients with missing data, will be presented. All percentages will be presented to 1 decimal place.

For AEs reported on a per-patient basis, medical history and concomitant medications, the denominator for the percentage calculation will be the number of patients in each treatment arm in the Safety Analysis Set. A patient will be considered at risk if the patient is in the Safety Analysis Set.

For AEs reported on a per-event basis, the incident rate will be displayed, adjusting the number of AEs by the total exposure to each treatment in person-years.

## 5.2 Hypotheses and Decision Rules

### 5.2.1 Primary Hypothesis

No formal primary hypothesis will be tested.

### 5.2.2 Secondary Hypotheses

No formal secondary hypothesis will be tested.

## 5.3 Handling of Missing Data

In general missing data will not be imputed except the situations described below.

### 5.3.1 Safety endpoints

#### 5.3.1.1 Adverse Events

Missing or incomplete dates and times for AEs are imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking additionally into account that the start date and time should not be after the stop date and time. Stop dates and times will not be imputed if the AE is ongoing.

This will be done as follows:

For a missing/incomplete start date the minimum of the following will be imputed:

- The maximum of the earliest possible start date/time and the date of study medication administration.
- The latest possible start date.
- The latest possible stop date.

For a missing/incomplete stop date the maximum of the following will be imputed:

- The minimum of the latest possible stop date/time and the date/time of study medication administration.
- The earliest possible stop date.
- The earliest possible start date.

The earliest (latest) possible date is defined as:

- The date itself if it is complete.
- The date of the first (last) day of the month, if month and year are available but day is missing.
- The date of the first (last) day of the year, if year is available but day and month are missing.
- A very early (late) date, e.g., 01JAN1000 (01JAN3000), if the date is completely missing.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study medication.

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, ‘Severe’ will be imputed. If causality data is missing, ‘Related’ will be imputed.

In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncodable Event' in summary tables.

### 5.3.2 Other Endpoints

#### 5.3.2.1 Exposure

If the start of treatment date is missing, the latest possible time of all the pre-dose assessments, up to and including randomisation will be imputed as the start of treatment date.

If the end of treatment date is missing, the latest possible time of all the post-dose assessments will be imputed as the end of treatment date.

#### 5.3.2.2 Pharmacokinetics

Missing data will be excluded from the PK analysis (i.e. values will not be interpolated or carried forward). Removal of anomalous data (outliers) will also be considered on an individual basis, and will be documented in the report, along with justification for the removal of data and an assessment of the impact on the study.

#### 5.3.2.3 Immunogenicity

Where ADA screen results are negative, confirmatory assays will not be performed therefore titre and Neutralising results will not be available. Confirmatory ADA assay results for all negative screens will therefore be considered to be negative and presented as Negative for all ADA analyses. In addition, the associated titre result will be imputed as 0.0625 in order to estimate the median and lower/upper quartiles and be included as a covariate in the secondary PK analyses. Values below the lower limit of quantification (<LLOQ or reported as 0) will be imputed as 0.25; 1, will be not imputed, ≥2, ≤4, will be imputed as 4; >4, ≤16 will be imputed as 16; >16, ≤64 will be imputed as 64; >64, ≤256 will be imputed as 256; >256, ≤1024 will be imputed as 1024; >1024, ≤4096 will be imputed as 4096; >4096, ≤16384 will be imputed as 16384 and values above 16384 will be imputed as 65536.

Missing ADA titre results at Week 30 (for Period I) and Week 80 (for Period II and Overall) will be imputed with values carried forward from the previous sampling time(s), as appropriate.

#### 5.3.2.4 Demographics

Date of birth is required to determine age. If date of birth is incomplete the following rules will be applied,

- If only day is missing, day will be imputed as the 15$^{th}$,
- If day and month are missing this will be imputed as the 2$^{nd}$ of July which is day 183 in the year.

#### 5.3.2.5 Concomitant Medications

Missing concomitant medication dates will be handled in a similar fashion as described for Adverse Events in Section 5.3.1.1.

## 5.4 Interim Analyses

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.

It is anticipated that the interim analysis would be performed after the FKB327-002 study has been locked and unblinded so that no extra precautions would be required to maintain the randomisation blinding for the FKB327-002 treatment assignments. The analysis will therefore be performed on the unblinded treatment allocations.

Following the first interim analysis, it's been decided to perform an additional interim analysis in order to provide a more robust and mature body of evidence related to safety, efficacy, PK and Immunogenicity profile of FKB327 during Period II of the study, with particular interest for the PK and safety profile following the switch to AI use for all applicable patients. Given the absence of formal hypothesis testing and the unblinded nature of the trial, this additional interim analysis should not introduce any unwanted issue in terms of study results interpretation.

All displays described in this SAP and accompanying shells will be produced for all patients in the interim analyses, following the scheme provided in Attachment 1 (Section 9.1). All outputs produced for either interim analysis will be produced also for the Final Analysis. A few additional outputs that weren't originally part of the study reporting will be created for the purpose of the Final Analysis only, to specifically address some remarks raised by the regulators during the application review process.

# 6 Statistical Analyses

## 6.1 Patient Disposition

Patient disposition will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of randomised patients. The following will be presented by treatment sequence and by treatment in Period I:

- Number of patients enrolled
- Number of patients randomised to treatment
- Number of patients with study drug administered
- Number of patients who completed Period I
- Number of patients still ongoing in Period I (only for interim analyses)
- Number of patients who prematurely discontinued the study during Period I (and primary reason for discontinuation)

The following will be presented by treatment sequence for Period II:

- Number of patients who started Period II
- Number of patients who started the AI
- Number of patients still ongoing in Period II (only for the interim analyses)
- Number of patients who completed Period II (only for the second interim analysis)
- Number of patients who prematurely discontinued the study during Period II and primary reason for discontinuation.

In addition, the number of patients in each analysis set and the reasons for exclusion will be summarised by treatment sequence and treatment in Period I.

The number and percentage of patients randomised will be displayed by geographical region (Europe, North America, Rest of World) and strata (screening DAS28-CRP ≤5.1/>5.1 and biologic naïve or not) as per study FKB327-002, and will be summarised by treatment sequence and treatment in Period I.

## 6.2 Protocol Deviations

Protocol deviations will be fully described in a separate document which will be finalised prior to database lock. Protocol deviations will be summarised by treatment sequence and treatment in Period I for all randomised patients, split by major and minor protocol deviations, as defined below:

- Major protocol deviations are protocol deviations that would significantly impact on patient safety, GCP compliance or analysis of efficacy or safety endpoints.
- Minor protocol deviations are protocol deviations which have less potential to affect the patient safety or integrity of the data.

Protocol deviations will also be listed.

## 6.3 Demographics

The age and height of patients from the Screening visit of the FKB327-002 study, and weight from Week 0 (Week 24 of the FKB327-002 study) of the FKB327-003 study will be summarised as a continuous variable. Sex, race and ethnicity will be summarised by absolute counts (n) and percentages (%). Percentages will be based on the number of patients in each analysis set. Summaries will be by treatment sequence and treatment in Period I.

Demographic data will also be listed.

## 6.4 Baseline Patient Characteristics

Baseline patient characteristics will be summarised by treatment sequence and treatment in Period I using standard summary statistics for each analysis set (see Section 5.1.2).

Baseline RA disease will be summarised using the following parameters collected at Week 0 of the FKB327-002 study (Baseline_002) and Week 0 of the FKB327-003 study (Baseline_003):

- Rheumatoid factor status (only for Baseline_002)
- Serum MMP-3 concentration
- Anti-CCP antibody status (only for Baseline_002)
- Swollen joint count (66 and 28 Joint Count)
- Tender joint count (68 and 28 Joint Count)
- Patients assessment of disease activity
- Physicians assessment of disease activity
- Patients assessment of pain
- HAQ-DI
- CRP
- ESR
- DAS28-CRP

- DAS28-ESR

ESR is only collected at Week 0, as part of the Week 24 assessments of the FKB327-002 study. The following formula will be used to derive the DAS28-ESR, similar to DAS28-CRP, as follows:

DAS28-ESR = 0.56*sqrt(TJC) + 0.28*sqrt(SJC) + 0.70*ln(ESR) + 0.014*GH

## 6.5 Medical History and Concurrent Medical Conditions

Medical history and Concurrent Medical Conditions will be separately summarised by SOC and PT by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients in the Safety Analysis Set by treatment sequence and treatment in Period I.

Medical history and concurrent medical conditions data will also be listed.

## 6.6 Prior and Concomitant Medication

Concomitant Medications and Prior Medications, including prior biologics, will be listed and summarised separately by PT for any medications taken for RA and by ATC and PT for medications taken for any other reason. These summaries will be by absolute counts (n) and percentages (%). Percentages will be calculated based on the number of patients in the Safety Analysis Set for the specific treatment sequence or treatment in Period I.

Specifically, the following will be summarised by treatment sequence and treatment in Period I for the Safety Analysis Set:

- Patients who have received DMARDs for RA prior to Screening in the FKB327-002 study. A summary will also be included for the number of prior DMARDs for RA (1, 2, 3, 4, etc).

- Patients who have received biologic treatment for RA prior to Screening in the FKB327-002 study

- Patients who have received anti-TNF treatment for RA prior to Screening in the FKB327-002 study

- Patients who used oral steroids for RA prior to Screening in the FKB327-002 study

- Patients who used NSAIDs for RA prior to Screening in the FKB327-002 study

- Concomitant use of oral steroids for RA

- Concomitant use of NSAIDs for RA

- Concomitant use of both oral steroids and NSAIDs for RA

- Concomitant use of commonest drugs for diseases other than RA. These drugs would be identified as those having a frequency of ≥5%.

- Duration of continuous MTX treatment prior to Screening from the FKB327-002 study

- Average dose of concomitant MTX during the study

- Route of concomitant MTX during the study

- Concomitant use of oral steroids for RA, by drug name (both overall and by geographical region)

- Concomitant use of NSAIDs for RA, by drug name (both overall and by geographical region)

## 6.7 Efficacy Analyses

### 6.7.1 Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the FAS.

#### 6.7.1.1 Tender and Swollen Joint Counts

Tender joint count, and swollen joint count, based on the 68/66 joint counts and their change from Baseline_002, will be summarised as continuous variables by treatment sequence and visit over the whole study period. The DAS28-CRP specific tender and swollen joint counts (28 joint count) and their change from Baseline_002 will be summarised similarly.

Individual tender and swollen joint data will be listed, along with the 68/66 joint counts.

The mean tender and swollen joint counts will also be plotted over time by treatment sequence alongside their 95% CI.

#### 6.7.1.2 CRP

Values and change from Baseline_002 for CRP will be summarised as continuous variables by treatment sequence and visit over the whole study period. CRP values will be listed and plotted over time alongside their 95% CI.

#### 6.7.1.3 VAS

Each of the scores for patient's assessment of disease activity, physician's assessment of disease activity, and patient's assessment of pain, together with their change from Baseline_002 will be summarised as continuous variables (the VASs on a scale from 0 to 100), by treatment sequence and visit over the whole study period. Values at each visit will also be listed and plotted over time alongside their 95% CI.

#### 6.7.1.4 HAQ-DI

Disability Index score and change from Baseline_002 will be summarised as continuous variables by treatment sequence and visit over the whole study period. The HAQ-DI individual categories scores will also be listed and the Disability Index Score will also be plotted over time alongside the 95% CI.

#### 6.7.1.5 ACR20, ACR50 and ACR70 Response Rates

The percentage of patients (%) achieving ACR20, ACR50 and ACR70 response will be summarised by overall treatment sequence and visit as well as by treatment separately for each period (Period I, Period II). 95% exact binomial CIs, via the Clopper-Pearson method will also be given for these rates.

The percentage of patients (%) achieving ACR20, ACR50 and ACR70 response over the whole study period will be plotted by treatment sequence. Another set of 2-panel plots will be produced for the treatment sequence and treatment in Period I only.

A bar plot of the percentage of patients achieving ACR20, ACR50 and ACR70 response will also be presented by treatment sequence at Week 30..

ACR response values will also be listed.

#### 6.7.1.6 DAS28-CRP

DAS28-CRP and the change from Baseline_002 will be summarised by overall treatment sequence and visit as well as by treatment for each period (Period I, Period II).

The mean DAS28-CRP and mean change from Baseline_002 alongside their 95%CI over the whole study period will be plotted by treatment sequence. Another set of 2-panel plots will be produced for the treatment sequence and treatment in Period I only.

DAS28-CRP data will also be listed.

## 6.8 Safety Analyses

All safety analyses will be based on the Safety Analysis Set.

### 6.8.1 Treatment Compliance and Exposure to Study Medication

A full listing of study dosing dates (including missed or incomplete doses) and duration of exposure by patient will be produced.

The number and percentage of patients fully dosed with study drug at each visit will be summarised separately by treatment sequence and treatment group for both Periods I and II.

The duration of exposure to FKB327 and Humira will be summarised by treatment group both as continuous (in days) and categorical (in weeks) variables

The duration of exposure to FKB327 in days is defined as:

(Date of last FKB327 administration – Date of first FKB327 administration) + 14. If a patient misses a dose of FKB327, dosing will be assumed to be continuous.

The duration of exposure to Humira in days is defined as:

(Date of last Humira administration – Date of first Humira administration) + 14. If a patient misses a dose of Humira, dosing will be assumed to be continuous.

The duration of exposure to the AI is defined as:

(Date of last FKB327 AI administration – Date of first FKB327 AI administration) + 14. If a patient misses a dose of AI, dosing will be assumed to be continuous.

Overall exposure to each study drug (FKB327, Humira) will be calculated by treatment group in patient-years by summing the individual patient values.

The number and percentage of patients receiving full dosing (16 doses for Period I and 23 for Period II) will also be summarised separately by treatment sequence and treatment group for both Periods I and II along with the number of patients who received delayed or interrupted dosing. A summary of the number of doses received will also be included.

Overall exposure to AI will also be calculated by treatment sequences in patient-years by summing individual patient values,

### 6.8.2 Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarised by SOC and (PT using MedDRA by absolute counts (n) and percentages (%) for each period (Period I, Period II) and overall. Treatment-related TEAEs will also be summarised. Percentages will be calculated based on the number of patients in the Safety Analysis Set for the specific treatment sequence or treatment group. Non-treatment-emergent AEs will be listed only (separately). Any tables displaying coding information for Period II will display by treatment sequence summaries only at the Final Analysis due to the low number of patients available at Interim; for the Interim Analysis, the by treatment group summaries will be presented only with the percentages calculated out of the number of patients who have entered Period II by that point.

Results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

Summary statistics will be presented by treatment and relationship to treatment to provide an overview of the AEs for each period (Period I, Period II) and overall. This will include the number of deaths, the number of treatment-emergent deaths, the number of patients with at least 1 SAE, the number of patients with at least 1 TESAE, the number of TESAEs, the number of patients who prematurely discontinued the IMP treatment due to a TEAE, the number of patients who prematurely discontinued the IMP treatment due to a TESAE, the number of patients who had a treatment interruption due to a TEAE, the number of patients who had a treatment interruption due to a TESAE, the number of patients with at least 1 TEAE, the number of patients with at least 1 severe TEAE and the number of patients with at least 1 treatment-related TEAE. These summaries will also be presented by treatment sequence for each period (Period I, Period II) and overall.

Summary statistics will be presented based on the strongest relationship to study medication of the TEAEs for each period (Period I, Period II) and overall by treatment sequence and treatment group. Relationship to study medication is recorded as 'Related', 'Possibly related, or 'Unrelated'. Missing will be counted as 'Related'. This summary for Period II will be repeated using only patients that switch to the AI, including only AEs that start on or after the first date of AI treatment.

Summary statistics for TEAEs will be presented based on the maximum severity ('Mild', 'Moderate' or 'Severe') for each period (Period I, Period II) and overall by treatment sequence and treatment group. This summary for Period II will be repeated using only patients that switch to the AI, including only AEs that start on or after the first date of AI treatment.

Summary statistics will be presented for the incidence of TEAEs leading to treatment interruption and TEAEs leading to treatment discontinuation for each period (Period I, Period II) by treatment sequence and treatment group.

Individual TEAEs (including TESAEs) will be summarised by primary SOC then by PT for each period (Period I, Period II) by treatment sequence and treatment group. This summary for Period II will be repeated using only patients that switch to the AI, including only AEs that start on or after the first date of AI treatment. Individual TEAEs with an incidence of ≥5% will be tabulated for each period (Period I, Period II) by treatment sequence and treatment group. Individual treatment-related TEAEs with an incidence of ≥3% will also be summarised.

In addition TESAEs will be summarised by SOC and PT by treatment sequence and treatment group for each period (Period I, Period II).

The following treatment-emergent AEs of special interest (AESIs) will be summarised by SOC and PT using MedDRA by absolute counts (n) and percentages (%) by treatment sequence and treatment group for each period (Period I, Period II):

- Infections including SAEs identified by any PT within MedDRA SOC Infections and Infestations
- Serious infections (including TB) identified by any PT within MedDRA SOC Infection and Infestations classified as serious
- Malignancies and lymphoproliferative disorders identified using MedDRA SMQs Malignancies and Malignant Lymphomas
- Injection site reactions to study drug identified using all PTs within MedDRA HLT infusion and injection site reactions classified as possibly related or related to study drug

- Hypersensitivity reactions and anaphylaxis to study drug identified by Standardised MedDRA Queries (SMQs) Hypersensitivity (narrow) and Anaphylactic Reaction (narrow) classified as possibly related or related to study drug
- Haematological events identified using the MedDRA PTs pancytopenia and aplastic anaemia,
- Neutropenia identified using MedDRA HLT neutropenias and PTs neutrophil count decreased, neutrophil count abnormal and band neutrophil count decreased
- Thrombocytopenia identified using MedDRA HLT thrombocytopenias and PTs platelet count decreased and platelet count abnormal
- New or worsening congestive heart failure identified using MedDRA HLTs heart failures not elsewhere classifiable (NEC), left ventricular failures and right ventricular failures
- Demyelination identified using MedDRA SMQ Demyelination (narrow)
- Lupus-like reactions identified using MedDRA SMQ Systemic lupus erythematosus (narrow)

The number of patients with at least 1 of the AESIs mentioned above will also be summarised for each bullet of the list by both treatment sequence and treatment group for both periods (Period I and Period II) and overall.

The number of events and incidence rates (events per patient year) of TEAEs, TESAEs, TEAEs leading to treatment discontinuation and treatment-emergent AESIs will be displayed by treatment group, SOC and PT for the overall treatment period.

An overall summary of AEs by administration method for those that occurred whilst FKB327 was taken (PFS or AI) will be created, similar to the first summary detailed in this section, including counts and percentage at a subject level and counts and incidence rates at an event level. Adverse events will also be summarized by administration method , with exposure-adjusted IRs by SOC and PT. Similar summaries with incidence rates by administration method will be created for TEAES occurring whilst exposed to FKB327 , with separate summaries for TEAES which are treatment-related, serious, of special interest or are treatment-related treatment-emergent Hypersensitivity/Anaphylaxis AEs.

In addition to the above summaries, the following listings will also be presented:

- Listing of all AEs (both treatment-emergent and non-treatment emergent)

- Listing of SAEs

- Listing of AEs leading to permanent treatment discontinuation

- Listing of AEs leading to temporary treatment interruption

- Listing of AEs leading to death

- Listing of TEAEs

- Listing of non-TEAEs

### 6.8.3 Clinical Laboratory Parameters

Clinical Laboratory Parameters include collected and derived quantitative and qualitative parameters. Laboratory data will be converted to SI (Système Internationale) units during the creation of Clinical Data Interchange Standards Consortium(CDISC) datasets, where required and all will be listed showing flags for abnormal high and low values and assessments of clinical significance by the investigator. Parameters will be grouped by category (see Section 4.2.3.1 to

Section 4.2.3.64.2.3.6) Quantitative parameters will be summarised by the number of patients, mean, SD, median, minimum and maximum values. Qualitative parameters will be summarised by absolute counts (n) and percentages (%).

Mean (± SD) values over time will be plotted by treatment sequence over the whole study period as well as treatment sequence and treatment group for each period (Period I, Period II), for all continuous laboratory parameters.

Summary statistics (including absolute and change from Baseline_002 values), for all quantitative lab parameters will be presented by visit and treatment sequence over the whole study period as well as by treatment for each period (Period I, Period II).

Summary statistics will be presented by visit and treatment sequence over the whole study period as well as by treatment for each period (Period I, Period II) for all qualitative lab parameters based on the incidence of clinically significant abnormal values.

### 6.8.4 Vital Signs

Vital signs parameters with change from Baseline_002 will be summarised by treatment sequence over the whole study period as well as by treatment for each period (Period I, Period II) for each visit.

Continuous variables will be summarised by the number of patients, mean, SD, median, minimum and maximum values. Percentages will be based on the Safety Analysis Set.

Mean (± SD) values over time will be plotted for all vital sign parameters for each treatment sequence and treatment group for each period (Period I, Period II) and for each treatment sequence for the overall treatment period.

## 6.9 Other Analyses

### 6.9.1 Physical Examination

Physical examination information from all applicable visits will be listed.

### 6.9.2 Chest X-ray

The number of patients with an abnormality will be presented for patients with any abnormality. Chest x-ray results (abnormal clinically significant or not abnormal clinically significant) will be summarised by overall treatment sequence and treatment group in terms of absolute counts (n) and percentages (%). Percentages will be based on Safety Analysis Set.

Chest x-ray information will also be listed.

### 6.9.3 QuantiFERON Test

QuantiFERON test results (Negative, Positive, Indeterminate) will be summarised by overall treatment sequence and treatment group for all the relevant visits in terms of absolute counts (n) and percentages (%). Percentages will be based on Safety Analysis Set.

Full QuantiFERON test data will be listed.

### 6.9.4 Injection Site Assessment

The proportion of patients experiencing an injection site reaction at Week 0 will be summarised both by treatment sequence and actual Period I treatment group, whereas the summary at Week 30 will be by treatment sequence only, using counts (n) and percentages (%), following the categories presented in Section 4.2.7. Similar summaries, by treatment sequence only, will be

displayed separately for patients switching and not-switching to the auto-injector, including Week 0 and, respectively, the switching time-point or Week 30. A summary of injection site reactions at Week 30 will also be provided by administration method, AI or PFS, based upon the actual administration method used at this visit.

The size of injection site reactions will be summarised for each of these categories by visit, following the same scheme as presented in the above paragraph (i.e. at Week 0 by actual Period I treatment group and sequence, at Week 30 by Sequence, at Week 0 and Auto-Injector start for patients switching to Auto-Injector and at Week 0 and 30 for patients not switching to the Auto-Injector), in terms of absolute counts (n) and percentages (%) for each of the following magnitudes: 0, 1-5, 6-10, 11-15, 16-20, and >20mm. These data will additionally be summarised as continuous variables.

Percentages will be based on the number of patients in the Safety Analysis Set, unless otherwise mentioned in the tables footnotes.

The injection site pain VAS (ranging from 0 “No pain” to 100 “Intolerable pain”) scores will be summarised as a continuous variable using the same scheme already described in the previous paragraphs.. Full listing of injection site assessment will be produced.

### 6.9.5 Immunogenicity Analysis

All ADA activity will be listed and summarised for each treatment sequence by time point during the overall treatment period as well as treatment group for each period (Period I, Period II). Descriptive statistics will include absolute counts (n) and percentages (%).

The titre results will be summarised as continuous variables, for each time point and the last sampling day by treatment sequence for the overall treatment period as well as treatment group for each period (Period I, Period II); summaries will include the upper and lower ADA quartiles for the overall safety population. The frequency (percentage) of titre results in each treatment sequence for the overall treatment period as well as treatment group for each period (Period I, Period II) will be summarised for each time point and the last sampling day using the following imputed categories: 0.0625, 0.25, 1, 4, 16, 64, 256, 1024, 4096, 16384, 65536 (the actual categories displayed may depend on the data). The maximum value across all time points will also be presented by treatment sequence for the overall treatment period as well as treatment group for each period (Period I, Period II).

In addition, ADA titre results at all time-points will be presented graphically (bar charts) for each treatment sequence for the overall treatment period and by treatment group for Period I.

The frequency (percentage) of ADA neutralising results (positive, negative, inconclusive) will be summarised for each treatment sequence for the overall treatment period, as well as treatment group for each period (Period I, Period II), by time point.

A summary of ADA activity as well as a summary of frequency of Nab results during Period II will be displayed by administration method (AI vs PFS).

The percentages will be based on the Safety Analysis Set.

### 6.9.6 Pharmacokinetic Analysis

Serum trough concentrations of adalimumab will be listed and summarised using descriptive statistics by treatment sequence for the overall treatment period as well as by treatment group for each period (Period I, Period II). Concentrations below the lower limit of quantification (<LLOQ) will be taken as zero for the calculation of descriptive statistics on adalimumab concentrations. Serum concentrations will be summarised by treatment sequence at each blood sampling time by the number of patients, arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV),

median, minimum and maximum values. The arithmetic CV will be displayed to 1 decimal place and all other values will be reported to 3 significant digits. A summary by visit of serum concentration data will also be provided for patients switching to the auto-injector. In addition, an overall summary by administration method (PFS vs auto-injector) will be provided pooling together records at different time-points after Week 0.

Individual and mean (±SD) concentration-time plots will be presented for each treatment sequence (on linear-linear scales) for the overall treatment period and Period I, individual trough concentration-time plots will be presented on linear scales to illustrate graphically the effect of ADA activity on the PK plots (according to ADA titre results); in particular, plots will be displayed in 3 panels according to whether the patient's last sampling day titre (Week 30 for Period I, Week 80 for Period II and overall or EOS visit for patients who prematurely discontinue the study) result is:

- Low: less than or equal to the lower quartile;
- Moderate: between the lower and upper quartile (both not included).
- High: greater than or equal to the upper quartile.

PK analysis will be based on PKAS.

#### 6.9.6.1 Primary PK Analysis

A mixed model for repeated measures (MMRM) will be fitted to the log transformed PK trough concentrations at Weeks 12, 24 and 30 (i.e., during the randomised treatment period) with patient included as a random effect and fixed effect terms for week, treatment group (or sequence) and week x treatment group (or sequence) interaction. The least squares mean (LSM) for each treatment group (or sequence) will be estimated at each week and averaged over time with 95% CIs and plotted over time. If the interaction term for week x treatment group (or 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).
- Treatment sequence group Humira-FKB327 relative to FKB327-Humira.
- Treatment sequence group FKB327-Humira relative to Humira-Humira.
- Treatment sequence group FKB327-FKB327 relative to Humira-FKB327.
- Treatment sequence group FKB327-FKB327 relative to FKB327-Humira.
- Treatment sequence group Humira-FKB327 relative to Humira-Humira.
- Treatment sequence group Humira-Humira relative to FKB327- FKB327.

Two models will be fitted. The first model will be using treatment group for the comparison FKB327 to Humira. The second model will be fitted using treatment sequences.

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

PK samples collected during the non-randomised period (i.e., at Weeks 54 and 76) will be listed and summarised only (see Section 6.9.6 for details).

#### 6.9.6.2 Secondary PK Analysis

Due to the potential formation of ADAs, a secondary PK analysis will be performed: the analysis in Section 6.9.6.1 will be repeated for the overall treatment period with ADA titre results at the last sampling time point (Week 80 or EOS visit for patients who prematurely discontinue the study) included as an additional covariate, along with an ADA titre × treatment sequence interaction term to test for differences in the effect of ADA activity on the PK data. Note that the overall period analysis will only present the treatment sequence comparisons for FKB327-Humira-FKB327 vs Humira-Humira-FKB327 and Humira-FKB327-FKB327 vs Humira-Humira-FKB327.

# 7 Final Analysis

The details of the analysis including analysis sets definitions, endpoints, statistical methodology and the displays of study results will be the same across the interim and the final analysis of FKB327-003 study, which will be performed when all the patients have either completed or discontinued the study and the database will have been locked, apart from a few additional outputs which will only be produced for the Final Analysis. These exceptions are detailed below.

## 7.1 Overall Disposition

An overall disposition table will be presented by treatment sequence including the following summaries:

- Number of patients enrolled
- Number of patients randomised to treatment
- Number of patients with study drug administered
- Number of patients who completed the study
- Number of patients who prematurely discontinued the study during any period (and primary reason for discontinuation)

## 7.2 ACR20/50/70 Response at Week 76

Similar to what described in Section 6.7.1.5, a bar plot of the percentage of patients achieving ACR20, ACR50 and ACR70 response will also be presented by treatment sequence at Week 76.

All outputs proposed for the final analysis are identified in Attachment 1.

# 8 Changes to the Planned Analyses

## 8.1 Changes to the Analyses Described in the Study Protocol and Protocol Amendments

According to Version 4.2 of the protocol (based on Global Amendment 4) dated 06 APR 2016 the "proportion of ADA positive cases (in the confirmatory assay) during the randomised treatment period will be compared between treatment sequences." This analysis will no longer be performed.

In addition, many additional summaries were introduced that were explicitly mentioned and described neither in the study protocol nor in Version 1.0.0 of the SAP. All these additional exploratory summaries have been detailed in Section 8.2, and no formal hypothesis has been specified nor has any statistical testing been performed.

## 8.2 Changes from the Statistical Analysis Plan Version 1.0 to Version 2.0

The following table details the changes that occurred from Version 1.0.0 of the SAP to the current Version 2.0.0.

| Section | Details of Changes |
|---|---|
| 1 (Introduction) | Protocol numbering has been updated and the reasoning behind the second Interim Analysis has been described. |
| 2.1.2 (Secondary Objectives) | The Auto-Injector safety and PK profile has been added to the list of secondary objectives |
| 5.4 (Interim Analyses) | A rationale for the second interim analysis has been discussed and a reference to the new list of outputs (as presented in the Attachment 1) has been introduced. |
| 6.1 (Patient Disposition) | The summaries have been aligned to what was produced for the primary analysis, eventually detailing what needs to be summarised for the interim analyses only. |
| 6.5 (Medical History and Concurrent Medical Conditions) | The title has been changed to account for split summaries of medical history (prior to the study) and concurrent medical conditions (which start or end after the study Baseline). |
| 6.7.1.5 (ACR20, ACR50 and ACR70 Response Rates) | The bar plot at Week 76 has been removed from here and placed into a section specific for 'Final Analysis'-only outputs. |
| 6.6 (Prior and Concomitant Medication) | Additional summaries for concomitant medications have been included to account for reporting decisions made during the first interim analysis. In particular, summaries of concomitant use of NSAIDs and oral steroids for RA have been added, overall and by geographical region (including a drug preferred term breakdown). |
| 6.8.1 (Exposure and Compliance) | The formula for estimating exposure to the auto-injector has been added and an additional table for auto-injector exposure summary has been included. |
| 6.8.2 (Adverse Events) | Three additional tables have been added, summarising all TEAEs, TEAEs by maximum severity and by strongest relationship during Period II only for patients switching to the auto-injector. In addition, the full set of AE listings has been detailed as well, accounting for 3 additional listings: a listing of all AEs, a listing only for TEAEs and one only for non-TEAEs. |
| 6.9.4 (Injection Site Reactions) | The summaries related to injection site reactions have been amended to reflect what was done during the first interim. In particular, for all endpoints (number of patients with injection site reactions, size of injection site reactions and related VAS score) 4 different tables have been detailed: one by treatment sequence and group reflecting summaries at Week 0, one by sequence only reflecting summaries at Week 30, one only for patients switching to the auto-injector reflecting summaries at Week 0 and at the switching time-point and one for patients not switching to the auto-injector reflecting summaries at Week 0 and 30. |

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|---|---|
| 6.9.6 (Pharmacokinetic Analysis) | Two additional tables have been added, displaying a by-visit summary of serum concentration data only for patients switching to the auto-injector and an overall summary of serum concentration data for FKB327-related administration by injection method (auto-injector vs PFS). |
| 6.9.6.1 (Primary PK Analysis) | Four pair-wise sequence comparisons have been added to the 2 originally planned. The new ones added are the following: Humira-FKB327 vs FKB327-Humira, FKB327-FKB327 vs Humira-FKB327, FKB327-FKB327 vs FKB327-Humira and Humira-Humira vs FKB327- FKB327. |
| 7 (Final Analysis) | Newly created section to detail which outputs will only be created for the final analysis. Includes an overall disposition table and Week 76 ACR20/50/70 response bar plot. |

## 8.3 Changes from the Statistical Analysis Plan Version 2.0 to Version 3.0

In Section 1 (Introduction) the new scope of the additional Interim Analysis has been introduced, detailing the key role of this interim in the US BLA submission process.

## 8.4 Changes from the Statistical Analysis Plan Version 3.0 to Version 4.0

| Section | Details of Changes |
|---|---|
| Abbreviations | AI (Auto-Injector) has been added |
| 1 (Introduction) | Updated the SAP version numbers where appropriate, updated DBL date and removed interim analysis specific text that was no longer needed |
| 6.8.2 (Adverse Events) | Add in specific details of what type of Adverse events are to be summarized by administration method |
| 6.9.4 (Injection Site Assessment) | Add in specific details of timepoint for injection site summaries (Week 30) to be summarized by administration method |
| 6.9.5 (Immunogenicity Analysis) | Add in specific details for Anti-Drug Antibody activity and Neutralising Anti Body Results summary by administration method |
| 9.1 Attachment 1 List of Tables, Listings and Figures | Added the following tables<br>Table 14.2.2.1.4 Summary of Anti-Drug Antibody Activity during Period II, by Administration Method: Safety Analysis Set<br>Table 14.2.2.4.4 Summary of Frequency of Neutralising Antibody Results during Period II, by Administration Method: Safety Analysis Set<br>Table 14.3.1.5.1.5 Summary of Injection Site Reactions at Week 30, by Administration |

| | |
|---|---|
| | Method: Safety Analysis Set<br><br>Table 14.3.1.1.3 Summary of Adverse Events, by Administration Method: Safety Analysis Set<br><br>Table 14.3.1.2.9 Incidence of Treatment-Emergent Adverse Events, by Administration Method: Safety Analysis Set<br><br>Table 14.3.1.2.10 Incidence of Drug-Related Treatment-Emergent Adverse Events, by Administration Method: Safety Analysis Set<br><br>Table 14.3.2.1.4 Incidence of Treatment-Emergent Serious Adverse Events, by Administration Method: Safety Analysis Set<br><br>Table 14.3.2.4.2.4 Incidence of Treatment-Emergent Adverse Events of Special Interest, by Administration Method: Safety Analysis Set<br><br>Table 14.3.2.4.2.5 Incidence of Treatment-Related Treatment-Emergent Hypersensitivity and Anaphylaxis Adverse Events, by Administration Method: Safety Analysis Set<br><br>A column has been added which denotes if the table, figure or listing is used in the final analysis<br><br>Drug-Related is changed to Treatment-Related for Table 14.3.1.2.10, and drug-related is changed to treatment-related where appropriate. |

# 9 Attachments and Appendices

## 9.1 Attachment 1 List of Tables, Listings and Figures

Attachment 1 is redacted from the document.

## 9.2 Appendix 1 Joints Considered for the 68/66 and 28 Joint Counts

| Joint | Assessed for the 68 joint count (Tender) | Assessed for the 66 joint count (Swollen) | Assessed for the 28 joint count |
|---|---|---|---|
| Right Temporomandibular | x | x | |
| Right Sternoclavicular | x | x | |
| Right Acromio-clavicular | x | x | |
| Right Shoulder | x | x | x |
| Right Elbow | x | x | x |
| Right Hip | x | | |
| Right Wrist | x | x | x |
| Right Metacarpophalangeal I | x | x | x |
| Right Metacarpophalangeal II | x | x | x |
| Right Metacarpophalangeal III | x | x | x |
| Right Metacarpophalangeal IV | x | x | x |
| Right Metacarpophalangeal V | x | x | x |
| Right Proximal Interphalangeal I | x | x | x |
| Right Proximal Interphalangeal II | x | x | x |
| Right Proximal Interphalangeal III | x | x | x |
| Right Proximal Interphalangeal IV | x | x | x |
| Right Proximal Interphalangeal V | x | x | x |
| Right Distal Interphalangeal II | x | x | |
| Right Distal Interphalangeal III | x | x | |
| Right Distal Interphalangeal IV | x | x | |
| Right Distal Interphalangeal V | x | x | |
| Right Knee | x | x | x |
| Right Ankle | x | x | |
| Right Tarsus | x | x | |
| Right Metatarsophalangeal I | x | x | |
| Right Metatarsophalangeal II | x | x | |
| Right Metatarsophalangeal III | x | x | |
| Right Metatarsophalangeal IV | x | x | |
| Right Metatarsophalangeal V | x | x | |
| Right Interphalangeal I | x | x | |
| Right Interphalangeal II | x | x | |
| Right Interphalangeal III | x | x | |
| Right Interphalangeal IV | x | x | |
| Right Interphalangeal V | x | x | |
| Left Temporomandibular | x | x | |
| Left Sternoclavicular | x | x | |
| Left Acromio-clavicular | x | x | |
| Left Shoulder | x | x | x |
| Left Elbow | x | x | x |

| | | | |
|---|---|---|---|
| Left Hip | x | | |
| Left Wrist | x | x | x |
| Left Metacarpophalangeal I | x | x | x |
| Left Metacarpophalangeal II | x | x | x |
| Left Metacarpophalangeal III | x | x | x |
| Left Metacarpophalangeal IV | x | x | x |
| Left Metacarpophalangeal V | x | x | x |
| Left Proximal Interphalangeal I | x | x | x |
| Left Proximal Interphalangeal II | x | x | x |
| Left Proximal Interphalangeal III | x | x | x |
| Left Proximal Interphalangeal IV | x | x | x |
| Left Proximal Interphalangeal V | x | x | x |
| Left Distal Interphalangeal II | x | x | |
| Left Distal Interphalangeal III | x | x | |
| Left Distal Interphalangeal IV | x | x | |
| Left Distal Interphalangeal V | x | x | |
| Left Knee | x | x | x |
| Left Ankle | x | x | |
| Left Tarsus | x | x | |
| Left Metatarsophalangeal I | x | x | |
| Left Metatarsophalangeal II | x | x | |
| Left Metatarsophalangeal III | x | x | |
| Left Metatarsophalangeal IV | x | x | |
| Left Metatarsophalangeal V | x | x | |
| Left Interphalangeal I | x | x | |
| Left Interphalangeal II | x | x | |
| Left Interphalangeal III | x | x | |
| Left Interphalangeal IV | x | x | |
| Left Interphalangeal V | x | x | |

# 10 References

1. DAS28 – Twenty-eight joints: http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/twenty-eight-joints.html [accessed 31 January 2016]