RISK MANAGEMENT PLAN
For
Hulio® (Adalimumab)

Data lock point (DLP) for RMP: 31-Oct-2025

Version Number 4.1

Dated: 29-Jul-2026

[redacted]

RMP Version to be assessed as part of this application:

Risk Management Plan for:	Adalimumab
RMP version number	4.1
Data lock point for this RMP	31-Oct-2025
Date of final sign off	29-Jul-2026
Rationale for submitting an updated RMP	To align the summary of safety concerns with the most up-to-date Risk Management Plan (versions 16.2 and 17.0) of Reference Biologics Humira® Change in the Marketing Authorisation Holder (MAH) name from Viatris to Biosimilar Collaborations Ireland Limited (BCIL).
Summary of significant changes in this RMP	**Module SIV – Sub-Section SIV.3: Table 8 updated.** The information on the Type of special population regarding the "Immunocompromised patients" was removed to align with the reference Biologics (Humira). **Module SV – Post-authorisation Experience:** Postmarketing exposure data were updated to the data lock point of 31 October 2025. **Module SVII – Identified and Potential Risks:** • The missing information of "Patients with immune-compromised conditions", "Long-term safety information in the treatment of children with uveitis" and "Long-Term Safety Information in the Treatment of Children aged from 6 years to less than 18 years with UC" were removed to align with the reference Biologics RMP (Humira). • The missing information "Episodic treatment in psoriasis, ulcerative colitis, and juvenile idiopathic arthritis (Ps, UC, and JIA)" was updated as "Episodic treatment in UC" to align with the reference Biologics RMP (Humira). **Module SVIII – Summary of the Safety Concerns:** Updated to reflect and align with the above changes in alignment with the Reference Biologics RMP (Humira)
Other RMP versions under evaluation: • RMP version number	Not applicable

• Submitted on • Procedure number	
Details of the current RMP • Version number • Approved with procedure • Date of approval	 4.0 EMEA/H/C/004429/IB/0037 13-Jul-2022
QPPV Name	Sanja Prpic
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List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AS	Ankylosing Spondylitis
AUC_{0-t}	Area under the concentration time curve from time 0 to the time of the last serum drug concentration sample taken
$AUC_{0-\infty}$	Area under the concentration time curve from time 0 to infinity
AUC0-360h	Area under the concentration time curve from time 0 to 360 hours
axSpA	Axial Spondyloarthritis
BCC	Basal Cell Carcinoma
Cmax	Maximum observed concentration
CD	Crohn's Disease
CHF	Congestive Heart Failure
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CRP	C-reactive Protein
CVA	Cerebrovascular Accident
DAS	Disease Activity Scores
DBT	Double Blind Trial
DMARD	Disease-modifying Anti-Rheumatic Drugs
DLBCL	Diffuse Large B-cell Lymphoma
EM	Erythema Multiforme
EMA	European Medicines Agency
Eow	Every other week
ERA	Enthesitis-related Arthritis
ESR	Erythrocyte Sedimentation Rate
EU	European
FKB	FUJIFILM KYOWA KIRIN BIOLOGICS Co., Ltd.
GBS	Guillain-Barré Syndrome
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

Abbreviation	Definition
GVP	Good Pharmacovigilance Practices
HBsAg	Hepatitis B Surface Antigen
HBV/HCV	Hepatitis B virus/Hepatitis C virus
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HS	Hidradenitis Suppurativa
HSTCL	Hepatosplenic T-cell Lymphoma
ILD	Interstitial Lung Disease
IR	Incidence Rate
JIA	Juvenile Idiopathic Arthritis
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
mAb	Monoclonal Antibody
MCC	Merkel Cell Carcinoma
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTX	Methotrexate
NHL	Non-Hodgkin's Lymphoma
NMSC	Non-Melanoma Skin Cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OLE	Open Labelled Extension
PE	Pulmonary Embolism
pedPs	Paediatric Plaque Psoriasis
PFP	Pre-filled Pen
PFS	Pre-filled Syringe
PK	Pharmacokinetics
PL	Package Leaflet
Ps	Plaque Psoriasis
PsA	Psoriatic Arthritis
PTD	Patient Treatment Days

Abbreviation	Definition
RA	Rheumatoid Arthritis
RABBIT	"Rheumatoide Arthritis: Beobachtung der Biologika-Therapie"
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
Sc	Subcutaneous
SCC	Squamous Cell Carcinoma
SIR	Standardised Incidence Rate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
t½	Elimination half life
Tmax	The time to maximum observed concentration (Cmax)
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TNF	Tumour Necrosis Factor
TSE	Transmissible Spongiform Encephalopathy
UC	Ulcerative Colitis
UK	United Kingdom
WCB	Working Cell Bank
WHO	World Health Organization

Part I: Product(s) Overview

Table 1 Part I.1 – Product overview

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants; tumour necrosis factor alpha (TNF-α) inhibitors (L04AB04)
Marketing Authorisation Applicant	Biosimilar Collaborations Ireland Limited
Invented name(s)	Hulio®
Brief description of the product:	**Chemical Class:** Hulio (FKB327) is a biosimilar medicinal product to Humira® containing the active ingredient adalimumab, which is a recombinant human monoclonal antibody directed against tumour necrosis factor alpha (TNF-α). (ATC Code: L04AB04). Adalimumab belongs to the pharmacotherapeutic group "Immunosuppressants; tumour necrosis factor alpha (TNF-α) inhibitors." **Summary of mode of action:** Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 0.1-0.2 nM). **Important information about its composition:** Biosimilar adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary (CHO) cells.
Hyperlink to the Product Information	Hulio Product information (Module 1.3.1)
Indication(s) in the EEA	**Rheumatoid Arthritis (RA)** Hulio® in combination with methotrexate (MTX), is indicated for: • the treatment of moderate to severe, active RA in adult patients when the response to disease-modifying anti- rheumatic drugs (DMARDs) including MTX has been inadequate.

	• the treatment of severe, active and progressive RA in adults not previously treated with MTX. Hulio® can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX. **Juvenile idiopathic arthritis (JIA):** • *Polyarticular juvenile idiopathic arthritis* Hulio® in combination with MTX is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Hulio® can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Adalimumab has not been studied in patients aged less than 2 years. • *Enthesitis-related arthritis (ERA)* Hulio® is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. **Axial Spondyloarthritis (axSpA)** • *Ankylosing spondylitis (AS)* Hulio® is indicated for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy. • *Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA)* Hulio® is indicated for the treatment of adults with severe nr-axSpA but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). **Psoriatic Arthritis (PsA)** Hulio® is indicated for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. Hulio® reduces the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and improves physical function. **Psoriasis (Ps)**

	Hulio® is indicated for the treatment of moderate to severe chronic plaque Ps in adult patients who are candidates for systemic therapy. **Paediatric plaque psoriasis (pedPs)** Hulio® is indicated for the treatment of severe chronic plaque Ps in children and adolescents from 4 years of age who have had an inadequate response to, or are inappropriate candidates for, topical therapy and phototherapies. **Hidradenitis Suppurativa (HS)** Hulio® is indicated for the treatment of active moderate to severe HS (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. **Crohn's Disease (CD):** Hulio® is indicated for treatment of moderately to severely active CD, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to, or have medical contraindications, for such therapies. **Paediatric Crohn's Disease:** Hulio® is indicated for the treatment of moderately to severely active CD in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to, or have contraindications, for such therapies. **Ulcerative Colitis (UC):** Hulio® is indicated for treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to, or have medical contraindications, for such therapies. **Uveitis** Hulio® is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid- sparing, or in whom corticosteroid treatment is inappropriate. **Paediatric Uveitis (pedUV):** Hulio® is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to

	conventional therapy, or in whom conventional therapy is inappropriate. **<u>Paediatric ulcerative colitis (pedUC):</u>** Hulio is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6- mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
Dosage(s)	***<u>Rheumatoid Arthritis</u>*** The recommended dose of Hulio® for adult patients with RA is 40 mg adalimumab administered every other week (eow) as a single dose via subcutaneous (sc) injection. MTX should be continued during treatment with Hulio®. Glucocorticoids, salicylates, NSAIDs, or analgesics can be continued during treatment with Hulio®. In monotherapy, some patients who experience a decrease in their response to Hulio® 40 mg eow may benefit from an increase in dosage intensity to 40 mg adalimumab every week or 80 mg eow. Available data suggests that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. Hulio® may be available in other presentations depending on the individual treatment needs. <u>Dose interruption</u> There may be a need for dose interruption, for instance before surgery or if a serious infection occurs. Available data suggest re-introduction of Hulio® after discontinuation for 70 days or longer should result in the same magnitudes of clinical response and similar safety profile as before dose interruption. • *<u>Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and psoriatic arthritis</u>* The recommended dose of Hulio® for patients with AS, nr-axSpA and for patients with PsA is 40 mg adalimumab administered eow as a single dose via sc injection. Available data suggests that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. ***<u>Psoriasis</u>***

	The recommended dose of Hulio® for adult patients is an initial dose of 80 mg administered sc, followed by 40 mg given sc eow starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response to Hulio® 40 mg eow may benefit from an increase in dosage to 40 mg every week or 80 mg eow. The benefits and risks of continued 40 mg weekly or 80 mg eow therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week or 80 mg eow, the dosage may subsequently be reduced to 40 mg eow. Hulio® may be available in other presentations depending on the individual treatment needs. ***Hidradenitis Suppurativa*** The recommended Hulio® dose regimen for adult patients with HS is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29), continue with a dose of 40 mg every week or 80 mg eow (given as two 40 mg injections in one day). Antibiotics may be continued during treatment with Hulio if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Hulio®. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hulio® 40 mg every week or 80 mg eow may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated. Hulio® may be available in other presentations depending on the individual treatment needs. ***Crohn's Disease*** The recommended Hulio® induction dose regimen for adult patients with moderately to severely active CD is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), 80 mg at week 2 (given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events (AEs) is higher during induction. After induction treatment, the recommended dose is 40 mg eow via sc injection. Alternatively, if a patient

	has stopped Hulio® and signs and symptoms of disease recur, Hulio® may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Hulio® 40 mg eow may benefit from an increase in dosage to 40 mg. Hulio® every week or 80 mg eow. Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. Hulio® may be available in other presentations depending on the individual treatment needs. ***Ulcerative Colitis*** The recommended Hulio® induction dose regimen for adult patients with moderate to severe UC is 160 mg at week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg eow via sc injection. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Hulio® eow may benefit from an increase in dosage to 40 mg Hulio® every week or 80 mg eow. Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Hulio® therapy should not be continued in patients failing to respond within this time period. Hulio® may be available in other presentations depending on the individual treatment needs ***Uveitis*** The recommended dose of Hulio® for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given eow starting one week after the initial dose. There is limited experience in the initiation of treatment with adalimumab alone. Treatment with Hulio® can be initiated in combination with corticosteroids and/or with other non- biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Hulio®. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Hulio® may be available in other presentations depending on the individual treatment needs.

Paediatric population

- *Juvenile idiopathic arthritis*

Polyarticular juvenile idiopathic arthritis from 2 years of age

The recommended dose of Hulio® for patients with polyarticular JIA from 2 years of age is based on body weight as presented in the table below. Hulio® is administered eow via sc injection.

Hulio® Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of adalimumab in patients aged less than 2 years for this indication.

Hulio® may be available in other presentations depending on the individual treatment needs.

Enthesitis-related arthritis

The recommended dose of Hulio® for patients with ERA from 6 years of age is based on body weight as presented in the table below. Hulio® is administered eow via sc injection.

Hulio® Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week, starting one week after the initial
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week, starting one week after the initial

Adalimumab has not been studied in patients with ERA aged less than 6 years.

Hulio® may be available in other presentations depending on the individual treatment needs.

Paediatric plaque psoriasis

The recommended Hulio® dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight as

presented in the table below. Hulio® is administered via sc injection.

Hulio® Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week, starting one week after the initial
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week, starting one week after the initial

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with Hulio® is indicated, the above guidance on dose and treatment duration should be followed.

The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months. There is no relevant use of adalimumab in children aged less than 4 years for this indication.

Hulio® may be available in other presentations depending on the individual treatment needs.

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with adalimumab in adolescent patients with HS. The posology of Hulio® in these patients has been determined from pharmacokinetic modelling and simulation.

The recommended Hulio® dose is 80 mg at week 0 followed by 40 mg eow starting at week 1 via sc injection. In adolescent patients with inadequate response to Hulio® 40 mg eow, an increase in dosage to 40 mg every week or 80 mg eow may be considered. Antibiotics may be continued during treatment with Hulio if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Hulio®.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hulio® may be re-introduced as appropriate. The benefit and risk of continued long-term treatment should be periodically evaluated. There is no relevant use of adalimumab in children aged less than 12 years in this indication.

Hulio® may be available in other presentations depending on the individual treatment needs.

Paediatric Crohn's Disease

The recommended dose of Hulio® for patients with Crohn's disease from 6 to 17 years of age is based on body weight as presented in the table below. Hulio® is administered via sc injection.

Hulio® Dose for Paediatric Patients with Crohn's Disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
< 40 kg	• 40 mg at week 0 and 20 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 80 mg at week 0 and 40 mg at week	20 mg every other week
≥ 40 kg	• 80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 160 mg at week 0 and 80 mg at week 2	40 mg every other week

Patients who experience insufficient response may benefit from an increase in dosage:

- < 40 kg: 20 mg every week

• ≥ 40 kg: 40 mg every week or 80 mg eow

Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of adalimumab in children aged less than 6 years for this indication.

Hulio® may be available in other presentations depending on the individual treatment needs.

Paediatric uveitis

The recommended dose of Hulio® for paediatric patients with uveitis from 2 years of age is based on body weight as presented in the table below. Hulio® is administered via subcutaneous injection. In paediatric uveitis, there is no experience in the treatment with Hulio® without concomitant treatment with methotrexate.

Hulio® Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	20 mg every other week in combination with methotrexate
≥ 30 kg	40 mg every other week in combination with methotrexate

When Hulio® therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Hulio® loading dose in children < 6 years of age. There is no relevant use of adalimumab in children aged less than 2 years in this indication. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. Hulio® may be available in other presentations depending on the individual treatment needs.

Paediatric ulcerative colitis

The recommended dose of Hulio for patients from 6 to 17 years of age with ulcerative colitis is based on body weight. Hulio is administered via subcutaneous injection.

Hulio® Dose for Paediatric Patients with Ulcerative Colitis

Patient weight	Induction dose	Maintenance dose
< 40 kg	80 mg at week 0 (given as two 40 mg injections in one day) and 40 mg at week 2 (given as one 40 mg injection)	40 mg every other week

<table>
<tr><td></td><td>
<table>
<tr><td>≥ 40 kg</td><td>160 mg at week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as two 40 mg injections in one day)</td><td>80 mg every other week</td></tr>
</table>
*Paediatric patients who turn 18 years of age while on Hulio should continue their prescribed maintenance dose.
Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.
Psoriatic arthritis and axial spondyloarthritis, including ankylosing spondylitis
There is no relevant use of adalimumab in the paediatric population for the indications of AS and PsA.
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td> Solution for subcutaneous injection (40 mg/0.8 mL) in a pre-filled syringe (PFS), pre-filled pen (PFP), or vial. Solution for subcutaneous injection (20 mg/0.4 mL) in a pre-filled syringe (PFS) </td></tr>
<tr><td>Is the product subject to additional monitoring</td><td>No</td></tr>
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Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

According to Table V.5 of Section V.C.1.1 (Summary of minimum RMP requirements for initial marketing authorisation applications) of the Guideline on good pharmacovigilance practices (GVP) – Module V (Rev 2) this section can be omitted for a biosimilar product. [1]

Part II: Module SII - Non-clinical part of the safety specification

FKB327 has been developed as a proposed biosimilar to Humira®, containing a recombinant human monoclonal antibody (adalimumab) directed against tumour necrosis factor-alpha (TNF-α) as an active substance. FKB327 is the internal company code for the biosimilar recombinant adalimumab which is used throughout this RMP.

The non-clinical programme to support European (EU) Marketing Authorisation Application (MAA) is based on recommendations described in the European Medicines Agency (EMA) guideline on "Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)". The guidance document recommends a risk-based approach to evaluate the biosimilar monoclonal antibody (mAb) and in determining the choice and extent of in vitro and in vivo studies to be conducted. In accordance with EMA/CHMP/BMWP/403543/2010, FUJIFILM KYOWA KIRIN BIOLOGICS Co., Ltd. (FKB), who initiated the development of FKB327, conducted the following comparative in vitro studies to evaluate similarity:

- Binding to the target antigen (recombinant human TNF-α [rhTNF-α] and transmembrane TNF-α [mTNF-α]);
- Binding to Fcγ receptors (I, IIa, IIb, IIIa(F), III(V), IIIbNA1, IIIbNA2) and neonatal Fc receptor (FcRn).
- Binding to complement component C1q.
- Fab-associated functions (neutralization of rhTNF-α-dependent cell killing, induction of apoptosis); and
- Fc-associated functions (Antibody-Dependent Cellular Cytotoxicity [ADCC] and Complement-Dependent Cellular Cytotoxicity [CDC] assays).

In line with the guidance, specific non-clinical in vivo studies were not considered necessary in terms of the non-clinical development of FKB327, as no "trigger" was observed from the in vitro pharmacology studies. However, during early development, FKB conducted a comparative in vivo study in a mouse model of arthritis mediated by human TNF-α (once weekly sc dosing for 5 weeks at 1 and 10 mg/kg; FKB327 versus EU-approved Humira®) and a comparative in vivo study in male cynomolgus monkeys to compare the PK of FKB327 (research lot) and EU-approved Humira® following a single sc dose of 3 mg/kg. Both studies showed comparative pharmacodynamics and pharmacokinetics between FKB327 and Humira®. In addition, to support development of FKB327 for registration in Japan and the US, the in vitro studies were supplemented with an in vivo Good Laboratory Practise (GLP) 4-week comparative repeat-dose toxicity study in male cynomolgus monkeys. In this study, no differences in toxicity were noted between the FKB327 and Humira® groups other than slight cell infiltration at the sc injection site. The change at the sc injection site noted at the end of the dosing period in the FKB327 group was reversed by the end of the 8-week recovery period.

Table 2: SII.1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies No single-dose toxicity studies have been performed. A 4-week comparative repeat-dose toxicity in male cynomolgus monkeys has been conducted	It is important to keep in mind that adalimumab neutralises both human TNF-α as well as cynomolgus monkey (non-human primate [NHP]) TNF- α, but does bind to rat TNF-α. Therefore, toxicological studies in the NHP can assess potential mechanistic (on-target) and non- mechanistic effects (off target) of adalimumab. Studies in rats will assess primarily non-mechanistic effects.
Reproductive/developmental toxicity Comparative reproductive studies between FKB327 and Humira® have not been performed in line with the EU guidance on biosimilar products (EMEA/CHMP/BMWP/42832/2005 Rev1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues), which states that studies regarding reproduction toxicology are not required for non-clinical testing of biosimilars.	FKB327 (adalimumab) has been developed as a similar biological medicinal product to Humira®. Consequently, the reproductive/ developmental toxicity package developed for Humira® should be considered when assessing this type of toxicity.
Genotoxicity Genotoxicity studies were not conducted as they are not applicable to biotechnology-derived proteins	None
Carcinogenicity Carcinogenicity studies were not conducted as they are not applicable to biotechnology-derived proteins	None
Safety pharmacology	
Safety pharmacology studies were not performed in line with the EMEA/CHMP/BMWP 42832/2005 Rev1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, and the CHMP Guideline on similar biological similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).	None

Cardiovascular system, including the potential effect on the QT interval No evidence of cardiotoxicity in the repeat dose study was observed. Consequently, no cardiotoxicity studies have been conducted in support of the safety profile of FKB327.	
Central Nervous System No evidence of neurotoxicity in the repeat dose study was observed. Consequently, no neurotoxicity studies have been conducted in support of the safety profile of FKB327.	None
Mechanisms for drug interactions	
On the basis of the known information for adalimumab and the extensive clinical experience with the reference product, no nonclinical studies pertinent to drug interaction were conducted	None

There are no safety concerns for FKB327 identified from the non-clinical development programme. Overall, the Applicant considers that any differences observed within the comparative *in vitro* and *in vivo* studies will not impact on the clinical safety and efficacy of the product. With regards to the reference product, all nonclinical safety findings were adequately addressed for the safety of adult and paediatric patients in the approved indications. There are no additional non- clinical studies considered necessary at this time for FKB327.

Part II: Module SIII - Clinical trial exposure

FKB327 has been developed as a biosimilar medicinal product. The reference product is Humira® (adalimumab). Adalimumab was first approved for the treatment of RA in September 2003 in the EU and was subsequently launched globally under the brand name Humira®. FKB327 is a recombinant human mAb expressed in CHO cells. The similarity between FKB327 and Humira® (both EU-approved and US-licensed Humira®) has been assessed in a range of characterisation studies. In addition, in vitro non-clinical studies have demonstrated similarity in terms of pharmacological activity between FKB327 and Humira®, and the results of in vivo non-clinical studies support the conclusion.

The Applicant initiated the FKB327 clinical programme with a 3-arm randomized, double-blind, parallel-group Phase 1 study in the UK, comparing the PK and safety of FKB327 with EU- approved and US-licensed Humira® after a single 40 mg sc injection in healthy subjects (FKB327- 001). A total of 180 subjects were randomly assigned to receive a single 40 mg sc injection of EU- sourced Humira®, US-licensed Humira® or FKB327, in a 1:1:1 ratio (i.e. 60 subjects per treatment) and were followed up 64 days after dosing.

The primary endpoints were Cmax, AUC0-t, AUC0-∞ and safety. The secondary endpoints were AUC0-360h, t1/2, tmax, additional PK parameters (conducted in a subpopulation excluding anti- drug antibodies [ADA] positive cases), immunogenicity (ADA to FKB327/Humira® and neutralizing ADA), injection site reaction, and injection site pain. Serum concentrations of adalimumab, ADA levels, and safety findings confirmed bioequivalence of FKB327 with both EU-approved and US-licensed Humira® and also confirmed the bioequivalence of EU-approved and US- licensed Humira®.

Subsequently, the Applicant initiated two Phase 3 studies, which were a double-blinded study

(DBT) (FKB327-002) and an open-label extension (OLE) study (FKB327-003):

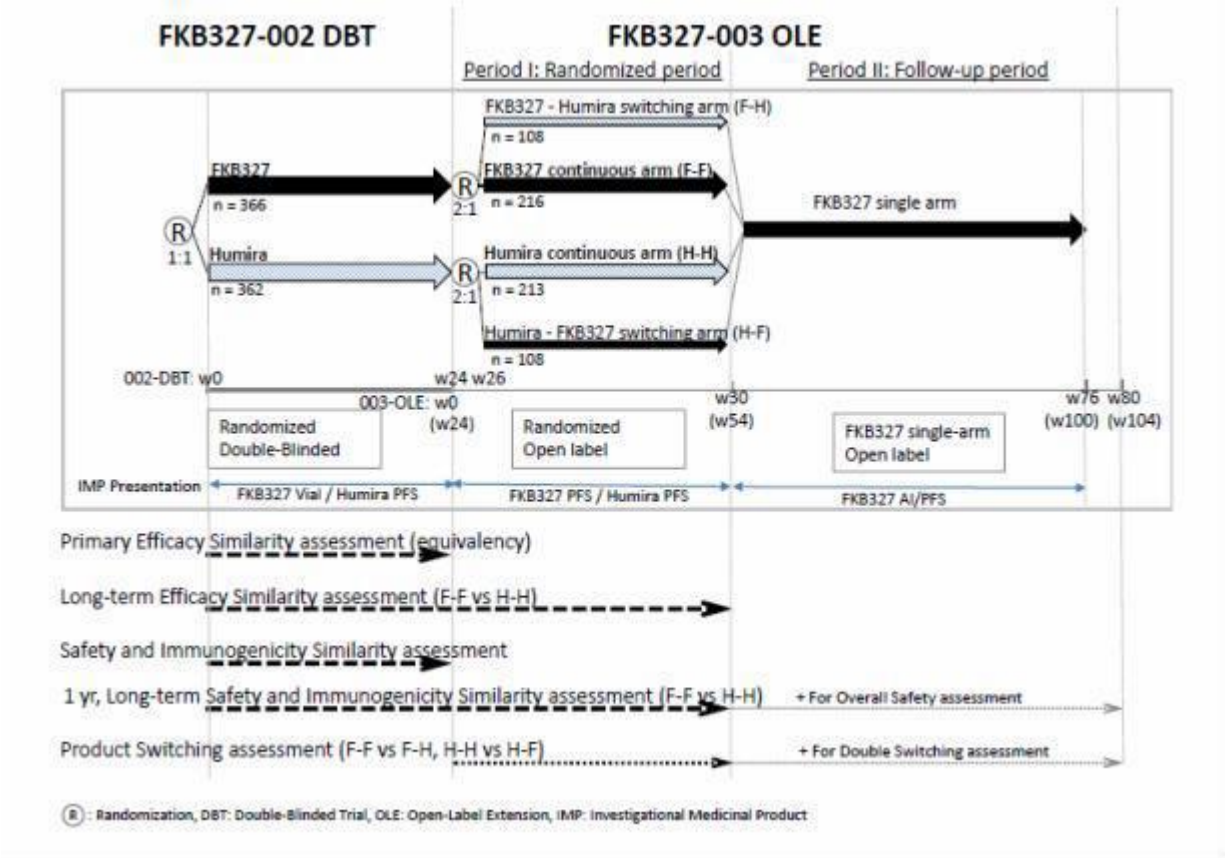
- **FKB327-002:** A Randomized, Blinded, Active Controlled Study to Compare FKB327 Efficacy and Safety with the Comparator Humira® in Rheumatoid Arthritis Patients Inadequately Controlled on Methotrexate (ARABESC);
- **FKB327-003:** An Open-label Extension Study to Compare the Long-term Efficacy, Safety, Immunogenicity and Pharmacokinetics of FKB327 and Humira® in Patients with Rheumatoid Arthritis on Concomitant Methotrexate (ARABESC-OLE).

A total of 730 patients were enrolled in FKB327-002 and randomized 1:1 to receive either FKB327 40 mg or Humira® 40 mg eow. The primary efficacy endpoint was ACR20 response rate at Week 24 and the key secondary efficacy endpoint was DAS28 score at Week 24.

Eligible patients completing the DBT were subsequently moved into the OLE study designed to compare the long-term efficacy, safety, immunogenicity and multiple-dose PK of FKB327 with Humira®. The patients moving into the OLE were randomised to receive treatment with either FKB327 40 mg eow or Humira® 40 mg eow from Week 0 to Week 28. The second part of the OLE study (follow-up period) was an open-label, single-arm extension in which all patients from the first part would receive prolonged treatment with 40 mg FKB327 eow from Week 30 to Week 46. The FKB327-003 extension study is now completed (Annex 2). For the MAA filing, an interim data cut for FKB327-003 was performed on 07 October 2016 to include more than 100 patients who were under continuous treatment for at least one year (from the start of FKB327-002 to the end of Period I of FKB327-003) with FKB327 and with Humira®.

An overview of the Phase 3 studies is presented in Figure 1.

Figure 1: Summary of Phase 3 Clinical Program



In addition, a PK similarity study between FKB327 and Humira® in Japanese healthy male subjects was also conducted:

- **FKB327-004:** A Phase 1, Randomized, Single-Blind, Single-Dose Study to Compare Pharmacokinetic Characteristics and Safety of FKB327 with those of Humira® in Japanese Healthy Subjects.

Study FKB327-004 is mentioned here for completeness since the results of this supportive study are included in the MAA dossier.

Furthermore, a relative bioavailability study to compare the pharmacokinetics of the three FKB327 delivery presentations was completed:

- **FKB327-005:** A Phase 1, Randomized, Open-Label, Single-Dose Study to Assess the Relative Bioavailability of a Subcutaneous Dose of FKB327 when Administered Using Either a Pre-Filled Syringe, a Pre-Filled Autoinjector or a Vial with Disposable Syringe (Vial) in Healthy Subjects.

FKB327 is provided as: pre-filled syringe (PFS), pre-filled pen (PFP) and vial. The vial presentation was used in the Phase 1 study (FKB327-001) and the Phase 3 DBT (FKB327-002). The PFS presentation was used in the Phase 3 OLE study (FKB327-003) and PFP presentation was used during the follow-up period of the Phase 3 OLE study (FKB327-003).

Another PK similarity study between FKB327 and Humira® in Japanese healthy male subjects was conducted:

- **FKB327-006:** A Phase 1, Randomized, Single-Blind, Single-Dose Study to Compare Pharmacokinetic Characteristics and Safety of FKB327 with those of Humira® in Japanese Healthy Subjects.

Study FKB327-006 is mentioned here for completeness.

An overview of the global clinical development plan is given in Table 3.

Table 3. Global clinical development plan

Study No. (region)	Phase	Objective	Subject	Design	No. of Subjects Enrolled	Dose, treatment period	FKB327 Presenta-tion
FKB327-002 (EU, US, and others) Completed	III	To compare FKB327 Efficacy and safety with the comparator Humira® in RA patients inadequately controlled on MTX	RA	Randomized, double blinded, active control	FKB327: 366 subjects US-Humira®: 362 subjects **Total of 728 patients**	40 mg, sc, 24 weeks (eow)	Vial

FKB327-003 (EU, US, and others)	III	To compare the long-term efficacy, safety, immunogenicity and PK of FKB327 and Humira® in Patients with RA on concomitant MTX	RA	Randomized, open-label extension, active control	FKB327: 324 subjects US-Humira®: 321 subjects **Total of 645 patients**	40 mg, sc, 28 weeks (eow)	PFS
				Single-arm, open label extension,	FKB327 (PFP): 507 subjects FKB327 (PFP): 65 subjects (all US patients) **Total of 572 patients**	40 mg, sc, up to 46 weeks (eow)	PFP/PFS

Key: US-Humira= US-licensed Humira, eow= every other week, MTX=methotrexate, PFS= pre-filled syringe, PFP= pre- filled pen, PK= pharmacokinetic, RA= rheumatoid arthritis, sc=subcutaneous

The overall patient exposure by duration of treatment, dose, age and gender, ethnic or racial origin, and special populations for FKB327 are summarized in Table 4, Table 5, Table 6, and Table 7.

The 664 patients included in this exposure analysis are from the FKB327-002/003 Safety Analysis Set (see Figure 1). This total of 664 comprises 366 patients who were treated following randomization to receive FKB327, 108 patients initially randomized to receive Humira® who were then randomly switched at Week 24 to receive FKB327, and 190 Humira® patients who were switched at Week 54 to receive FKB327 for the final follow-up period.

Table 4: SIII.2 Duration of Exposure

Total exposed population (N=664)		
Duration of exposure*	**Persons (%)**	**Person time (person-years)**
≥2 weeks to <8 weeks	12 (1.8)	1.05
≥8 weeks to <16 weeks	14 (2.1)	3.23
≥16 weeks to <24 weeks	16 (2.4)	6.31
≥24 weeks to <42weeks	60 (9.0)	32.30
≥42 weeks to <54 weeks	193 (29.1)	177.61
≥54 weeks to <66 weeks	10 (1.5)	11.30
≥66 weeks	359 (54.1)	605.47

Total	**664 (100.0)**	**837.26**

* Data is presented by interval and not cumulatively: minimum individual duration of exposure = 14 days; maximum individual duration of exposure = 725 days.

Table 5: SIII.3 By Dose

Total population (N=664)		
Dose of exposure	**Persons (%)**	**Person time (person-years)**
40 mg	664 (100)	837.26
Total	**664 (100)**	**837.26**

Table 6: SIII.4 By Age Group and Gender

Total population (N=664)				
Age group (years)	**Persons (%)**		**Person time (person-years)**	
	M (%)	**F (%)**	**M**	**F**
<40	23 (15.6)	71 (13.7)	33.54	94.69
40 to 64	107 (72.8)	347 (67.1)	143.11	439.82
65 to 74	15 (10.2)	83 (16.1)	17.53	89.29
75 to 84	1 (0.7)	15 (2.9)	1.49	16.01
≥85	1 (0.7)	1 (0.2)	0.88	0.91
Total	**147 (100.0)**	**517 (100.0)**	**196.54**	**640.72**

Table 7: SIII.5 By Ethnic or Racial Origin

Total population (N=664)		
Ethnic/racial origin	**Persons (%)**	**Person time**
American Indian or Alaska Native	1 (0.2)	0.54
Asian	2 (0.3)	3.44
Black or African American	6 (0.9)	6.89
White	569 (85.7)	720.56
Other	86 (13.0)	105.84
Total	**664 (100.0)**	**837.26**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The main exclusion criteria of pivotal FKB327-002/003 studies are detailed below.

Exclusion criteria to ensure standardization of the trial population (i.e. to avoid bias or complication of interpretation of efficacy and safety results) that are common to the majority of clinical studies are not presented, including: prior treatment with the same active substance, other TNF inhibitors, or DMARDs (other than MTX) which may complicate or interfere with the study results; participation in another investigational clinical trial within 12 weeks of the study; and presence of another serious disease or condition (including abnormal laboratory test

values) which may interfere with the study results, confounding efficacy and safety assessments, or make patients unlikely or unable to comply with study procedures and requirements.

History of relevant allergy/hypersensitivity to monoclonal antibodies or any of the excipients of FKB327

Reason for exclusion: Patients with known hypersensitivity to adalimumab or excipients must not receive FKB327 (SmPC Section 4.3), since severe hypersensitivity may be life-threatening and require urgent medical attention.

Is it considered to be included as missing information? No

Rationale: As for all medicinal products, patients with a known hypersensitivity to the active substance or to any of the excipients are contraindicated and therefore it is unlikely that FKB327 will be used in this population.

Presence of chronic or acute infection, including positive result for human immunodeficiency virus (HIV) 1 or 2, hepatitis B (HBV), hepatitis C (HCV), and active tuberculosis (TB) or untreated latent TB where the patient is not willing to undergo prophylactic treatment.

Reason for exclusion: Patients with tuberculosis or other serious infections must not receive FKB327 in order to avoid any possible immunosuppressant impact on the treatment of a concurrent or recent infection, and/or to avoid reactivation of latent virus (SmPC Section 4.3).

Is it considered to be included as missing information? No

Rationale: Active tuberculosis or other severe infections such as sepsis, and opportunistic infections are a contraindication, since patients taking TNF-antagonists are more susceptible to serious infections and impaired lung function may increase the risk for developing infections. Treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. Patients must therefore be monitored closely for infections, including tuberculosis, before treatment with FKB327 (and also during and after treatment). Hence, it is unlikely that FKB327 will be used in this population.

Presence of New York Heart Association (NYHA) Class III/IV heart failure.

Reason for exclusion: Therapy with FKB327 is contraindicated for patients with moderate or severe heart failure, based on studies performed in patients with congestive heart failure and other TNF inhibitors, which showed an increased risk of worsening of congestive heart failure (SmPC Section 4.3).

Is it considered to be included as missing information? No

Rationale: Since therapy in patients with moderate to severe heart failure (NYHA class III/IV) is contraindicated, it is unlikely that FKB327 will be used in this population.

Immunisation with a live or attenuated vaccine within 4 weeks prior to study drug dosing.

Reason for exclusion: These should not be administered during treatment with TNF inhibitors as no data are available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

Is it considered to be included as missing information? No

Rationale: The absence of data about the secondary transmission of infection by live vaccines in patients receiving adalimumab is addressed in Section 4.4, “Special warnings and precautions for use,” of the SmPC and it therefore is unlikely that FKB327 will be used in this population.

Intra-articular or parenteral steroids within 28 days prior to Screening

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

Presence of active autoimmune disease or joint disease other than RA (e.g., mixed connective tissue disorder, gout), which may confound efficacy assessments such as joint count evaluations or CRP/erythrocyte sedimentation rate (ESR).

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

ACR functional Class IV.

Reason for exclusion: To exclude the most severe forms of disease that may complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

Major surgery (including joint surgery) within 8 weeks prior to Screening or planned to take place during the study period.

Reason for exclusion: To avoid any risk to patients and subsequent patient withdrawal from the study. Joint surgery may well interfere with interpretation of efficacy endpoints.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product. It is addressed in Section 4.4, "Special warnings and precautions for use," of the SmPC and therefore it is unlikely that FKB327 will be used in this population.

Acute infection requiring parenteral antibiotics within 4 weeks of study dosing or requiring oral/topical antibiotics within 2 weeks of study dosing.

Reason for exclusion: To avoid any possible impact of the immunosuppressant effect of adalimumab on the treatment of a current or recent infection, leading to worsening infection and patient withdrawal.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product. Treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. This point is addressed in Section 4.4, "Special warnings and precautions for use," of the SmPC. Therefore, it is unlikely that FKB327 will be used in this population.

Presence of any uncontrolled disease for which steroid treatment is regularly required for flares, e.g., asthma.

Reason for exclusion: Corticosteroids may complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

Presence of any malignancy or history of malignancy in the 5 years prior to Screening

which has not been curatively treated, with the exception of carcinoma in situ of the cervix or basal cell carcinoma (BCC) of the skin that has been fully excised.

Reason for exclusion: Patients may have an elevated risk of recurrence, leading to potential bias on the efficacy and safety results of the study and patient withdrawal.

Is it considered to be included as missing information? No

Rationale: There is an increased background risk for lymphoma and leukaemia in RA patients with long-standing highly active, inflammatory disease, which complicates the risk estimation. No studies have been conducted that include patients with a history of malignancy or in whom treatment with adalimumab is continued following development of malignancy. Thus, additional caution should be exercised in considering adalimumab treatment of these patients and this is addressed in Section 4.4, "Special warnings and precautions for use," of the SmPC.

Patients with demyelinating diseases (e.g., multiple sclerosis)

Reason for exclusion: Adalimumab use in patients with a history of demyelinating disease is not recommended.

Is it considered to be included as missing information? No

Rationale: TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of FKB327 in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of FKB327 should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non- infectious intermediate uveitis prior to the initiation of FKB327 therapy and regularly during treatment to assess for pre- existing or developing central demyelinating disorders. This is addressed in Section 4.4, "Special warnings and precautions for use," of the SmPC. It therefore is unlikely that FKB327 will be used in this population.

Pregnant or breastfeeding women.

Reason for exclusion: Standard exclusion criterion. Adalimumab has a Class B pregnancy rating, which means there is no information available on the effects of adalimumab on the pregnancy or unborn child. Taking adalimumab while pregnant is not recommended. Furthermore, human immunoglobulins are excreted in milk.

Is it considered to be included as missing information? Yes

Body weight >120 kg

Reason for exclusion: To avoid any potential bias on the efficacy and safety results of the study.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

Prior or current treatment with an agent which might confound efficacy or safety evaluation, e.g., RANKL inhibitors for osteoporosis, immunomodulators for asthma within 5 half-lives of the drug concerned prior to the first dose of study treatment.

Reason for exclusion: To avoid any potential bias on the efficacy and safety results of the study.

Is it considered to be included as missing information? No

Rationale: Not considered missing information for the reference product.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as uncommon or rare (≥1/1,000 to < 1/100; ≥1/10,000 to <1/1,000) adverse reactions, or those caused by prolonged exposure or adverse reactions with a long latency beyond the current maximum of 102 weeks continuous treatment in the FKB327 clinical development programme (i.e. the time of second interim data cut-off). Similarly, adverse reactions due to cumulative effects which require an exposure of longer than 102 weeks to manifest would not be detected in this safety data set at the completion of the FKB327-003 study.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 8: SIV.1 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Neither pregnant or breastfeeding women were included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic or renal impairment	Patients with hepatic or renal impairment have not been directly studied in FKB327 or Humira® clinical trials. Similarly, the effect of hepatic or renal impairment on exposure to FKB327 has not been studied. No recommendations regarding dose can be made. Adalimumab is a protein and is likely to be metabolized in a similar fashion to other human antibodies, the metabolism of which is not significantly impaired even in patients with end-stage liver or kidney disease.
Patients with cardiovascular impairment	Patients with the presence of NYHA Class III/IV heart failure were excluded from clinical studies conducted with FKB327. Cases of worsening congestive heart failure have been reported in patients receiving Humira®. The SmPC contraindicates the administration of Humira® to patients with moderate to severe heart failure. Treatment with Humira® must be discontinued in patients who develop new or worsening symptoms of congestive heart failure. Similar contraindications and warnings will be specified in the Hulio® SmPC.
Patients with a disease severity different from the inclusion criteria in clinical trials:	In accordance with the indications authorised for the reference product, Humira®, the efficacy and safety of FKB327 in patients diagnosed with RA (according to revised American College of Rheumatology [ACR] criteria; 2010 version) have been evaluated in the clinical studies FKB327-002 and FKB327-003. Patients with severe RA (ACR functional Class IV) were not included in the clinical development programme.

Type of special population	Exposure
Population with relevant different ethnic origin	Humira® has been extensively studied in subject populations that included men and women of a variety of racial backgrounds and ages in clinical trials; no safety signals were identified for any particular racial groups in clinical trials or in post-marketing surveillance. Similarly, Table 7 (SIII) shows the numbers of patients by ethnicity treated with FKB327 in the clinical development programme. The majority of patients treated were white (n=569, 85.7%), with only 0.9% black (n=6, black or African American) and 0.3 %(n=2)/0.2% (n=1) for Asian and American Indian, respectively.
Subpopulations carrying relevant genetic polymorphisms	Patients with relevant genetic polymorphisms were not included in the clinical development programme. There are no known relevant genetic polymorphisms that affect metabolism, degradation or pharmacological effects of anti-TNF inhibitors, including the reference product, Humira®.

Part II: Module SV - Post-authorisation experience

The cumulative patient exposure data from the Hulio (Adalimumab) first launch date to 31 Oct 2025 are presented in the section below.

SV.1 post-authorisation exposure

SV.1.1 Method used to calculate exposure

The cumulative exposure data from the first launch date to the DLP* (31 Oct 2025) are calculated from sales data and mentioned in **Error! Reference source not found.** respectively.

**These figures cover the period up to Oct-2025 as sales data are only available for complete months.*

Table 9: Cumulative Patient Exposure from Post-Marketing Experience

Product	Formulation	Sales volume (No. of units*Unit strength)	Patient Exposure in terms of Patient Treatment Days (PTD) PTD= Sales volume/ DDD
Adalimumab	SC	279,905,761	96,519,228
Total			**96,519,228**

The Defined Daily Dose (DDD) of adalimumab as recommended by the World Health Organization (WHO) and published in the ATC Classification Index is 2.9 mg.

The estimated patient exposure is presented in terms of Patient Treatment Days (PTD). The methodology used for estimate of patient exposure is described below:

$$\text{Patient Treatment Days (PTD)} = \frac{\text{Volume of sales in units (no. of package sold x no. of units per package)}}{\text{DDD}}$$

Therefore, the total patient exposure globally in terms of PTD for the cumulative period is 96,519,228, respectively.

These figures are compiled from data available at the time of writing and may not represent exact patient consumption. They may include packs that are lodged with wholesalers, pharmacists, or representatives. No data from Biocon sponsored non-interventional studies, market research, or from other sources (e.g., registries) are available to estimate patient exposure in special populations (e.g., children, elderly, patients with relevant co-morbidities) or in patients with disease severity different from that studied in clinical trials, sub-populations carrying relevant genetic polymorphism(s), and patients of different racial and/or ethnic origins.

No particular patterns of use have come to the attention of the company which are considered relevant for the interpretation of safety data.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no anticipated potential for illegal use of adalimumab given the mechanism of action for adalimumab.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Overdose

No dose-limiting toxicity for the reference product was observed in any of its clinical programmes, as noted in the EU SmPC for Humira®, where the highest dose level evaluated was multiple intravenous doses of 10 mg/kg, being approximately 15 times the recommended dose. Only one concentration of FKB327 solution for injection, 50 mg active ingredient per mL, (40 mg/0.8 mL supplied in a PFS, PFP, or vial and 20 mg/0.4 mL supplied in a PFS) is proposed for registration. The SmPC provides the recommended dosing regimens for each proposed indication and the correct route (sc) of administration. Treatment with FKB327 should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of the authorised indications, minimizing the potential for overdose. There is no experience with overdose in FKB327 clinical trials; single doses of FKB327 greater than 40 mg have not been administered. There is currently insufficient evidence to support the inclusion of overdose as an important risk for FKB327.

Transmission of infectious agents

FKB327 has been developed as a biosimilar product that contains adalimumab, the same active ingredient as Humira®. FKB327 contains different excipients to those in Humira®. FKB327 (50 mg/mL) is formulated to provide a pharmaceutically clear, buffered, isotonic solution, comprised of monosodium glutamate (10 mmol/L), sorbitol (262 mmol/L), methionine (5 mmol/L), polysorbate 80 (1.0 mg/mL), diluted hydrochloric acid (to adjust to pH 5.2), and water for injection (q.s. to 0.8 mL).

Testing for qualification of the Master Cell Bank (MCB) and the resultant Working Cell Bank (WCB) has been performed in accordance with ICH Guideline (Q5A[R1], Q5B and Q5D). The results demonstrate that both the MCB and WCB are sterile and free from contamination by adventitious agents, are of high quality, and have the correct identity, and therefore, are suitable for manufacture of FKB327. In addition, in accordance with the EMA guideline on "Virus Safety Evaluation of Biotechnological Investigational Medicinal Products

(EMEA/CHMP/BWP/398498/2005)", testing for viral contaminants in the bulk harvest has been conducted. Furthermore, the genetic characterization of WCB was evaluated. FKB327 is manufactured under current Good Manufacturing Practice (GMP) and is supplied as a highly purified biological product, with appropriate steps for virus inactivation and removal, and there are no transmissible spongiform encephalopathy (TSE) risks.

Patients administered FKB327 are not recognised to be at increased risk for the transmission of infectious agents. There is currently insufficient evidence to justify the inclusion of transmission of infectious agents as an important risk for FKB327.

Drug interactions

Since adalimumab is a human anti-TNF-α monoclonal antibody, it is considered to be metabolized to peptides and amino acids in vivo similarly to endogenous human immunoglobulins. Accordingly, interactions due to effects on CYP enzymes and drug transporters are unlikely.

Humira® has been studied in patients taking Humira® as monotherapy and those taking concomitant MTX (Humira® SmPC, 08 December 2017). Antibody formation and clearance were lower when Humira® was given together with MTX in comparison with use as monotherapy, but with no impact on safety. Following subcutaneous administration of 40 mg of Humira® eow in adult RA patients the mean steady-state trough concentrations were approximately 5 µg/ml (without concomitant MTX) and 8 - 9 µg/ml (with concomitant MTX), respectively. Concomitant administration of Humira® with other biologic DMARDs (e.g., anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. In adult CD studies with Humira®, higher incidences of malignant and serious infection-related adverse events were seen in combination with azathioprine/6-mercaptopurine compared with Humira® alone. It is considered that FKB327 will display similar drug interactions.

Although there is a potential health risk of concurrent immunomodulation and subsequent increased risk of infection if FKB327 were to be administered concomitantly with anakinra, abatacept, or thiopurines, as highlighted in sections 4.4 and 4.5 of the SmPC, such identified or potential drug interactions are not considered to be an important risk for FKB327.

Furthermore, based on harmonization with originator RMP, the following risks are not considered important for inclusion in the list of safety concerns. Further details are provided in Section SV.II.

Known risks that require no further Characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers:

- Reactivation of Hepatitis B
- Vasculitis
- Amyotrophic lateral sclerosis (ALS)
- Pulmonary embolism
- Sarcoidosis
- Pancreatitis
- Congestive Heart Failure
- Myocardial infarction

- Cerebrovascular Accident (CVA)
- Interstitial lung disease
- Cutaneous vasculitis
- Stevens-Johnson syndrome
- Erythema multiforme (EM)
- Worsening and new onset of Psoriasis
- Haematologic disorders
- Intestinal perforation
- Intestinal stricture in Crohn's Disease
- Liver failure and other liver events
- Elevated alanine aminotransferase levels
- Autoimmune Hepatitis
- Immune reactions (including Lupus-like Reactions and Allergic reactions)
- Medication errors and maladministration
- Off label use
- Infections in infants exposed to adalimumab in utero (see new identified risk of BCG disease following live BCG vaccination in infants within utero exposure)

Other reasons for considering the risks are not important:

- Lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukaemia, non-melanoma skin cancer, melanoma, Merkel cell carcinoma (MCC) and other malignancies: these risks are covered under the identified risk of malignancies.
- Medication error with paediatric vial: this risk is covered under the identified risk of medication errors and maladministration.
- Colon cancer in UC patients: reclassified as adenocarcinoma of colon in UC patients.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Serious infections

The most common treatment-related treatment-emergent AEs (TEAEs) included bronchitis, nasopharyngitis and urinary tract infection. The IRs (incidence rates) of all TEAEs under the SOC “Infection and Infestations” were broadly comparable between treatments (0.80 and 0.63 per patient-year for Humira® and FKB327, respectively). The most frequently reported treatment- emergent serious AEs (TESAEs) were infections and infestations, which occurred with the same incidence rate (0.03 events per patient year) for both FKB327 and Humira®; the number of patients experiencing a serious infection was small (20 subjects [3.0%] on FKB327 and 10 subjects [2.1%] on Humira®). TESAEs that occurred in more than 1 patient were: pneumonia (7 patients [1.1%] with FKB327 and 1 [0.2%] with Humira®), acute pyelonephritis (4 patients [0.6%] with FKB327 and 2 [0.4%] with Humira®), sepsis (3 patients [0.5%], all with FKB327), erysipelas (2 patients [0.3%], both with FKB327), pyelonephritis (2 patients [0.3%], both with FKB327), urinary tract infection (2 patients [0.3%], both with FKB327), and bronchitis (2 patients, 1 [0.2%] in each treatment group). One (0.2%) case each of bronchopneumonia, cervicitis, gangrene, meningitis, and pyelonephritis occurred in the

FKB327 treatment group, but not in the Humira® treatment group.

Risk-benefit impact:

Serious infections may range in severity and potentially lead to sepsis and death in individual patients, depending on their initial general health status. However, the benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk that can be closely monitored (before, during and after treatment) to prevent serious complications. In addition, treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. The risk of serious infections will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Identified Risk 2: Tuberculosis [TB])

TESAEs that occurred in more than 1 patient were: Disseminated TB (2 patients, 1 [0.2%] in each treatment group), and latent TB (2 patients [0.3%], both with FKB327).

No case of pulmonary TB was reported on FKB327 compared to 2 cases [0.4%] on Humira®.

Risk-benefit impact:

Tuberculosis may range in severity and potentially lead to death in individual patients, depending on their initial general health status. However, the benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk that can be closely monitored (before, during and after treatment) to prevent serious complications. In addition, treatment should not be initiated in patients with active, chronic or localized tuberculosis until TB is controlled. The risk of TB will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Identified Risk 3: Malignancies

There have been no treatment-related cases of malignancies including hepatosplenic T-cell lymphoma, leukaemia, melanoma, Merkel cell carcinoma in the clinical studies conducted with FKB327.

There have been one case (0.2%) breast cancer and one case (0.2%) cervix carcinoma in the FKB327 treatment group but none in Humira treatment group in the clinical studies conducted with FKB327. Of the treatment-related TEAEs, one case (0.2%) of basal cell carcinoma (BCC) was reported in the clinical studies conducted with FKB327, with one case (0.2%) of squamous cell carcinoma (SCC) reported in the Humira® treatment group. According to Humira SmPC, skin cancer excluding melanoma has been reported to occur commonly (≥ 1/100 to < 1/10). One treatment-related case of lymphoma in the FKB327 treatment group was reported as post-study event.

Risk-benefit impact:

In clinical trials of TNF-antagonists, cases of malignancies including lymphoma have been observed among patients receiving a TNF antagonist; however, the occurrence was rare. Cases of leukaemia have been reported in patients treated with a TNF-antagonist. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded. Non-melanoma skin cancer (NMSC) can lead to disfigurement, and possibly death in rare cases of metastatic SCC, depending on the patient's health status as well as the stage of the NMSC. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh this risk that can be closely monitored to prevent serious complications. All patients should be examined for the presence of NMSC prior to and during

treatment by a physician on an annual basis. Sunscreen use and education concerning risk and prompt detection of lesions should also be implemented. The risk of malignancies in general will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Identified Risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis [ON])

There have been no treatment-related cases coded as a recognised demyelinating disorder, although one treatment-related TEAE (0.2%) of hypoaesthesia was reported in the clinical studies conducted with FKB327, with one report of peripheral sensory neuropathy in the Humira® treatment group. According to the Humira® SmPC, demyelinating disorders have been reported to occur rarely (≥ 1/10,000 to < 1/1,000).

Risk-benefit impact:

The severity of demyelinating disorders can range from transient disability and visual disturbance to serious disability, such as paralysis or blindness. This risk can be potentially life-threatening, depending on the patient's health status as well as the severity of the demyelinating disease. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the potentially rare risk of demyelination disorders that can be mitigated through appropriate screening and evaluation by a physician to prevent serious complications. The risk of demyelinating disorders will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Identified Risk 5: BCG disease following live BCG vaccination

There have been no treatment-related cases of BCG disease following live BCG vaccination in infants within utero exposure to adalimumab in the clinical studies conducted with FKB327.

Risk-benefit impact:

The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the potentially rare risk of BCG disease following live BCG vaccination in infants within utero exposure to Hulio® that can be closely monitored (before, during and after treatment) to prevent serious complications. Patients treated with adalimumab may receive concurrent vaccinations, except vaccines with live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in-utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. The risk will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Potential Risk 1: Progressive multifocal leukoencephalopathy (PML)

There have been no treatment-related cases of PML in the clinical studies conducted with FKB327.

Risk-benefit impact:

PML, although rare, primarily affects individuals with chronically and severely suppressed immune systems and is always very serious. It can lead to severe neurological disabilities and death, depending on the patient's health status as well as the severity of the PML. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the rare risk of PML. This risk will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Potential Risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)

There have been no treatment-related cases of RPLS in the clinical studies conducted with FKB327.

Risk-benefit impact:

PLS is always very serious and can lead to neurological disabilities, multisystem organ involvement and sequelae, blindness, and death, depending on the patient's health status as well as the severity of RPLS. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the rare risk of RPLS.

This risk will be further characterised in patients exposed to Hulio® via the proposed registry study.

Important Potential Risk 3: Adenocarcinoma of colon in ulcerative colitis (UC) patients

There have been no treatment-related cases of adenocarcinoma of colon in UC patients in the clinical studies conducted with FKB327 (*studies were conducted in RA patients*).

Risk-benefit impact:

The risk of adenocarcinoma of colon is known to be elevated in UC patients and can potentially be life- threatening, depending on degree and extent of bowel inflammation as well as the length of time a patient has the disease. However early detection can limit morbidity. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk of adenocarcinoma of colon in UC patients if screened routinely for dysplasia (pre-cancerous lesions) prior to and during therapy with adalimumab as recommended in the product label. This evaluation should include colonoscopy and biopsies per local recommendations. The risk will be monitored in accordance with routine pharmacovigilance procedures. Available literature will be monitored, as will spontaneous case reports.

Missing information 1: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)

Whilst the efficacy and safety of Hulio® have been evaluated in a total of 664 adult patients with RA, other indications and paediatric patients have not been evaluated. At the time of the second interim data cut-off, the maximum treatment duration in the clinical development programme was 102 weeks.

Risk-benefit impact:

More than 230 patients have been treated with Hulio® for ≥ 66 weeks. The long-term safety of Hulio® in pediatrics is limited but is not expected to differ from the known safety profile of Hulio®. As for the reference product, Humira®, long-term safety in the treatment of children aged from 6 to <18 years with CD is considered an area of missing information.

Missing information 2: Episodic treatment in ulcerative colitis (UC)

Whilst the efficacy and safety of Hulio® have been evaluated in a total of 664 adult patients with RA, other indications or episodic treatment have not been evaluated.

Risk-benefit impact:

As for the reference product, Humira® episodic treatment in ulcerative colitis (UC), is considered missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new important identified or potential risks have been added or reclassified since the previous RMP (version 4.0).

Missing Information 1: Patients with immune compromised conditions

Reason for removal: Patients with immune compromised conditions have been reviewed thoroughly through standard safety surveillance and in multiple previous PSURs with no new safety signals identified. The commitment was closed with the Innovator PSUR (reporting interval 01 Jan 2017 to 31 Dec 2019) in agreement with the PRAC (procedure number: EMEA/H/C/PSUSA/00010783/201912).

Missing Information 4: Long-term safety information in the treatment of children with uveitis

Reason for removal: Long-term safety information for children with uveitis has been reviewed thoroughly through standard safety surveillance, Innovator completed Study P10-262, and in multiple previous PSURs with no new safety signals identified.

Missing Information 5: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC.

Reason for removal: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC has been reviewed through the completion of Study M10-870. Overall, the long-term safety data in paediatric patients with UC were comparable to those observed in previous Humira clinical trials and in line with the observed safety profile for Humira. No new safety concerns were identified. The benefit-risk profile is favourable in paediatric patients with UC treated with Humira.

Reclassified Missing Information

Missing Information 3: From Episodic treatment in Ps, UC, and JIA reclassified to Episodic treatment in ulcerative colitis (UC)

Reason for Reclassification: Renamed to "Episodic treatment in UC" to reflect completion of Innovator Study P10-262 and Study P10-023. Intermittent treatment populations were included in both studies, with no unexpected safety trends observed.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Data from 664 subjects who were treated with FKB327 40 mg eow in the clinical trials FKB327 002 and FKB327-003 are included in the Safety Analysis Set to characterize the safety profile of FKB327 in patients with RA. This total of 664 comprises 366 patients who were treated following randomization to receive FKB327, 108 patients initially randomized to receive Humira® who were then randomly switched at Week24 to receive FKB327, and 190Humira® patients who were switched at Week 54 to receive FKB327 for the final follow-up period.

Important Identified Risk 1: Serious infections

Potential mechanisms:

Immunosuppression by modulation of TNFα

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). In the

clinical studies conducted with FKB327 to date, the most common treatment-related infections included bronchitis, nasopharyngitis and urinary tract infection, although the overall number of patients experiencing any serious infection was small (20 subjects [3.0%] receiving FKB327). Serious infections have been classed as an identified risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

In the FKB327-002/003 clinical trials, the most common treatment-related TEAEs in the FKB327 treatment group included nasopharyngitis, urinary tract infection, upper respiratory infection and bronchitis. The Irs of all and Infestations TEAEs were broadly comparable between treatments (0.80 and 0.63 per patient-year for Humira® and FKB327, respectively). The most frequently reported TESAEs were Infections and Infestations, which occurred with the same incidence rate (0.03 events per patient year) for both FKB327 and Humira®; the number of patients experiencing a serious infection was small (20 subjects [3.0%] on FKB327 and 10 subjects [2.1%] on Humira®). TESAEs that occurred in more than 1 patient were: pneumonia (7 patients [1.1%] with FKB327 and 1 [0.2%] with Humira®), acute pyelonephritis (4 patients [0.6%] with FKB327 and 2 [0.4%] with Humira®), sepsis (3 patients [0.5%], all with FKB327), erysipelas (2 patients [0.3%], both with FKB327), pyelonephritis (2 patients [0.3%], both with FKB327), urinary tract infection (2 patients [0.3%], both with FKB327), and bronchitis (2 patients, 1 [0.2%] in each treatment group). One (0.2%) case each of bronchopneumonia, cervicitis, gangrene and meningitis occurred in the FKB327 treatment group, but not in the Humira® treatment group.

Overall, 4 deaths occurred amongst the 664 patients (0.6%) treated with FKB327 (1 was considered to be unrelated to study treatment by both of the investigator and sponsor) and one death (0.2%) amongst the patients receiving Humira®. Of the 2 deaths associated with FKB327 treatment, one was due to pneumonia and sepsis.

TEAEs leading to study discontinuation were most frequently reported for the SOC Infections and Infestations and were experienced by 20 patients (3.0%) receiving FKB327 (0.03 events per patient year) and by 10 patients (2.1%) receiving Humira® (0.03 events per patient year).

According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10), systemic infections, skin and soft tissue infections, ear infections, oral infections, reproductive tract infections, urinary tract infections, fungal infections, and joint infections have been reported to occur commonly (≥ 1/100 to < 1/10), neurological infections, opportunistic infections and tuberculosis, bacterial infections, eye infections, and diverticulitis have been reported to occur uncommonly (≥ 1/1,000 to < 1/100).

Infections may vary from mild infectious processes to sepsis and potentially death depending on the patient's health status as well as the severity of the infection. RA is associated with an approximate doubling of the risk of infection; chest infection and generalized sepsis are particular risks (https://cks.nice.org.uk/rheumatoid-arthritis - accessed 26Jan2017). RA appears to increase the risk for bacterial, tubercular, fungal, opportunistic, and viral infections, with all infections being more common in more active and severe RA (Gabriel SE et al 2009l) [2]

The incidence of serious infections was investigated (Doran MF ET AL 2002) [3] in a US cohort of 609 RA patients aged >18 years who were first diagnosed as having RA between 1955 and 1994. The authors concluded that patients with RA were at increased risk (twice the risk) of developing infections compared with 609 non-RA subjects, but that this may be due to immunomodulatory effects of RA, or to agents with immunosuppressive effects used in the treatment of RA. Similarly, a cohort from the Norfolk Arthritis Register (NOAR), UK, consisting of 2108 RA patients recruited from 1990 to 1999, was shown to have an overall

incidence of infection more than two and a half times that of the general population (Franklin J et al 2007) [4]

A later US investigation (Ni Mhuircheartaigh O et al 2013) [5] studied a cohort of patients with incident RA between 1995 and 2007, comprised of 464 patients. These patients were compared with the above 609 patients with incident RA from 1955 to 1994 (Doran et al, 2002)[3]. The mean age at RA incidence for the early cohort was 58.0 years (73% female) and 56.0 years (69% female) for the later cohort. The mean follow-up time was 7,730 total person-years (PY) and 2,715 PY, for the early cohort and later cohort, respectively. Rates of smoking and comorbidities were similar in the two time periods, except for diabetes mellitus, which occurred more frequently among patients in the 1995-2007 cohort compared to the 1955-1994 cohort. The risk score for serious infections was significantly higher among patients with incident RA in 1995- 2007 compared to those with incident RA in 1955 1994 (p=0.015). The rate of serious infections declined from 9.6 per 100 PY in the 1955 1994 cohort to 6.6 per 100 PY in the 1995 2007 cohort. Among patients with a history of serious infection, the rate of subsequent infection increased from 16.5 per 100 PY in 1955-1994 to 37.4 per 100 PY in 1995-2007. There was an increase in the rate of serious infections in patients who received biologic agents, but this did not reach significance. Due to the limited number of patients (96 in the 1995-2007 cohort) on biologic agents in this study, a definitive conclusion about the use of biologic agents and the rate of serious infections could not be made.

Conducted a systematic review of literature ranging from January 1998 to November 2011. A total of 72 published studies met the inclusion criteria and were reviewed, including 44 clinical trials, open- label extension studies, or meta-analyses, and 28 observational studies. The incidence of serious infection was consistent across studies and biologic therapies, ranging from 0 to 11/100 PY but mainly clustered from 2 to 6/100 PY. Fewer incidence data were available for opportunistic infection and tuberculosis (Tran TN et al 2013) [6].

Risk factors and risk groups:

Standard-dose and high-dose biological drugs (with or without traditional DMARDs) have been shown to be associated with a statistically significant increase in serious infections in MTX-naïve RA patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh J A et al 2015) [7]

Other risks associated with serious infections include very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.

Preventability:

Patients must be monitored closely for infections, before, during and after treatment with FKB327. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Treatment should not be initiated in patients with active infections including chronic or localised infections until infections are controlled.

Impact on the risk-benefit balance of the product:

Serious infections may range in severity and potentially lead to sepsis and death in individual patients, depending on their initial general health status. However, the benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk that can be closely monitored (before, during and after

treatment) to prevent serious complications. In addition, treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. To educate prescribers and patients and hence minimise the risk of serious infections associated with the use of Hulio®, Patient Reminder Cards are utilized.

Public health impact:

The potential public health issue is that of increased rates of infections.

Important Identified Risk 2: Tuberculosis

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence Sources and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). Tuberculosis has been classed as an identified risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

No case of pulmonary TB was reported on FKB327 compared to 2 cases [0.4%] on Humira®. Of the 1 death associated with FKB327 treatment, one was due to disseminated TB.

TESAEs that occurred in more than 1 patient were: disseminated TB (2 patients, 1 [0.2%] in each treatment group) and latent TB (2 patients [0.3%], both with FKB327).

Risk factors and risk groups:

Standard-dose and high-dose biological drugs (with or without traditional DMARDs) have been shown to be associated with a statistically significant increase in serious infections in MTX-naïve RA patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh J A et al 2015) [7]

Other risks associated with serious infections include very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.

Preventability:

Patients must be monitored closely for tuberculosis (active or latent), before, during and after treatment with FKB327. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Impact on the risk-benefit balance of the product:

Serious infections like TB may range in severity and potentially lead to sepsis and death in individual patients, depending on their initial general health status. However, the benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk that can be closely monitored (before, during and after treatment) to prevent serious complications. In addition, treatment should not be initiated

in patients with active infections including chronic or localized infections until infections are controlled. To educate prescribers and patients and hence minimise the risk of TB associated with the use of Hulio®, Patient Reminder Cards are utilized.

Public health impact:

The potential public health issue is that of increased rates of TB and, therefore, increased possible risk of contagion. TB is highly contagious via airborne bacteria, unlike other infections, which are not likely to be transmitted by casual contact with an infected individual.

Important Identified Risk 3: Malignancies

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity, which may influence the appearance of malignancy, but the mechanism is unknown.

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, malignancies have been reported to occur uncommonly (≥ 1/1,000 to < 1/100) and common (1/100 to < 1/10). In clinical studies conducted with FKB327, of the treatment- related TEAEs, one case (0.2%) of basal cell carcinoma (BCC) was reported with FKB327, with one case (0.2%) of squamous cell carcinoma (SCC) reported in the Humira® treatment group. There have been one case (0.2%) breast cancer and one case (0.2%) cervix carcinoma in the FKB327 treatment group but none in Humira® treatment group in the clinical studies conducted with FKB327. In rare cases of metastatic SCC, the outcome may potentially be fatal. There have been no treatment-related cases of melanoma, Merkel cell carcinoma, leukaemia and hepatosplenic T-cell lymphoma in the clinical studies conducted with FKB327 to date. One treatment-related case of lymphoma in the FKB327 treatment group was reported as post-study event. Malignancies has been classed as an identified risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

The risk potentially includes death, depending on the patient's health status as well as the stage of cancer.

Simon et al (2015) performed a systematic literature review and analysis to quantify the incidence of malignancies in patients with RA and the general population. Patients with RA have a 10 % increase in overall malignancy risk compared with the general population. Furthermore, the SIR estimates for patients with RA continued to show an increased risk of lymphoma and lung cancer as previously observed. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk among patients with RA compared with the general population.

The WHO classifies lymphoma into 4 main types. The mature B cell neoplasms consist of high-grade lymphomas (e.g. diffuse large B-cell lymphoma [DLBCL; 30-58% of all NHL]) and low- grade lymphomas (e.g. follicular lymphoma [20-25% of all NHL]). The two most common types of NHL are DLBCL and follicular lymphomas. The overall annual incidence of DLBCL in Europe is 3.8/100,000 but the incidence increases with age and varies considerably across Europe, whilst the annual incidence of follicular lymphomas has increased from 2 3/100,000 during the 1950s to 5-7/100,000 recently [8]

Conducted a meta- analysis on the incidence data of malignancy in adult patients with RA [9], which had been reported since the meta-analysis by (. The conclusion was that patients with RA

are at an increased risk of lung and lymphoma malignancies compared with the general population, with a standardized incidence ratio (SIR) ranging from 1.75 to 12.82 across eight studies. The pooled SIR for HL was higher than for NHL. The total pooled SIR (95 % CI) for the studies reviewed was 2.46 (2.05–2.96) for malignant lymphoma, 3.21 (2.42–4.27) for HL and 2.26 (1.82–2.81) for NHL.

Risk factors and risk groups:

Sustained inflammatory activity seems to be the primary risk factor for malignancies in autoimmune diseases such as RA as well as the common aetiology between RA and malignancy, such as genetic factors, smoking-related tissue necrosis and viral infection (e.g. Epstein-Barr virus, retroviruses). However, it is difficult to separate disease-related mechanisms from the potential oncogenic properties of immunosuppressive drugs used in these autoimmune-inflammatory diseases (Szekanecz Z et al 2011) [11],

From an analysis of the British Society for Rheumatology Biologics Register (BSRBR)-RA (Silva-Fernández et al 2016) [12]. , showed that after an average follow-up of 5 years, patients with RA and prior malignancy selected to receive treatment with TNF inhibitors in the UK do not have an increased risk of recurrence or development of new incident malignancy.

Preventability:

Frequent monitoring should be undertaken to allow for early intervention as necessary.

Impact on the risk-benefit balance of the product:

Malignancies have potential to be life-threatening, depending on the patient's health status as well as the stage of malignancy. As per the reference product, Humira®, the benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the common/uncommon risk of malignancy. To educate prescribers and patients and hence minimise the risk of malignancies associated with the use of Hulio®, Patient Reminder Cards are utilized.

Public health impact: None.

Important Identified Risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON])

Potential mechanisms:

MS is thought to be an autoimmune disease where the immune system attacks the myelin, covering the nerves of the central nervous system. The mechanisms underlying the predisposition to demyelination or exacerbation of demyelination in patients treated with TNFα antagonists is not well-understood.

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, demyelinating disorders have been reported to occur rarely (≥ 1/10,000 to < 1/1,000). There have been no treatment-related cases coded as a recognised demyelinating disorder, although one (0.2%) treatment-related TEAE of hypoaesthesia was reported in the clinical studies conducted with FKB327. Demyelinating disorders have been classed as an identified risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

There have been no treatment-related cases coded as a recognised demyelinating disorder, although one (0.2%) treatment-related TEAE of hypoaesthesia was reported in the clinical

studies conducted with FKB327, with one report of peripheral sensory neuropathy in the Humira® treatment group. The medical significance of this risk can range from transient disability and visual disturbance to paralysis or blindness, and even death.

There is limited information available on the incidence of demyelinating disorders in RA patients (Kaltsonoudis E et al 2014) [13]. However, in a prospective study using magnetic resonance imaging (MRI) and neurophysiological tests in patients with RA, PsA or AS receiving anti-TNFα antagonists estimated the rate of neurological adverse events (Aes) in these patients to be 4%. Seventy-five patients received anti-TNFα (38 infliximab, 19 adalimumab and 18 etanercept), with three patients developing neurological Aes. It has been suggested that TNFα antagonists may increase the risk of demyelinating diseases in patients with RA by about 30% (Bernatsky S, et al 2010) [14] , but this is not supported by (Fernández-Espartero MC, et al, 2011) [15] who concluded that it was unclear whether TNFα antagonists increase the incidence of demyelinating diseases in patients with rheumatic diseases. A review by (Morís G et al 2014) [16] looked at neurologic disorders (including demyelinating disease) in patients with CD and UC and reported on results of retrospective cross-sectional studies where an increased incidence of demyelinating disease in IBD was reported by (de Lau LM et al 2009) [17] , whilst incidence of MS was reported to be higher in patients with UC than with CD (Gupta G, et al 2005) [18] Nunes et al (2013) [19] reported a case of demyelinating brain lesions in a patient with CD and treated with adalimumab for eighteen months.

Risk factors and risk groups:

Risk factors associated with an increased risk for MS are a combination of genetic susceptibility (HLA-DR15 haplotype) and environmental exposures (including latitude, vitamin D deficiency, season of birth, Epstein Barr virus infection, and smoking behaviour) (O'Gorman C et al 2012) [20] These factors appear to act synergistically, and the risk of MS is increased in individuals exposed to more than one factor (Disanto G et al 2012) [21] .Being Caucasian and female increases risk, as does having a family relative with MS [22]

Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus (Blázquez A-B et al 2016) [23] , vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease (HL)) (Ansar & Valadi 2015) [24] [25]. Risk factors for optic neuritis include female sex, race (more frequent in white Caucasians, genetic mutations (as per MS), bacterial/viral infections, sarcoidosis/lupus and some drugs (e.g. Quinine and some antibiotics) [26]

Preventability:

Screening and evaluation by a physician may help prevent demyelinating disorders.

Impact on the risk-benefit balance of the product:

The severity of demyelinating disorders can range from transient disability and visual disturbance to serious disability, such as paralysis or blindness. This risk can potentially be life-threatening, depending on the patient's health status as well as the severity of the demyelinating disease. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the potentially rare risk of demyelination disorders that can be closely screened and evaluated for by a physician to prevent serious complications. To educate prescribers and patients and hence minimise the risk of demyelinating disorders associated with the use of Hulio®, Patient Reminder Cards are utilised.

Public health impact: None.

Important Identified Risk 5: BCG disease following live BCG vaccination in infants

within utero exposure to Hulio

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence Sources and strength of evidence:

Data from reference product trials, registries and databases.

Characterisation of the risk:

Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Risk factors and risk groups:

Infants who are exposed to adalimumab intrauterine.

Preventability:

Live vaccines should not be given to patients using adalimumab, and infants exposed to adalimumab in utero should not receive live vaccines (e.g., BCG) for 5 months following mother's last adalimumab dose.

Impact on the risk-benefit balance of the product:

Appropriate risk minimization measures have been in place. Additional risk minimization tool language is being proposed with this RMP update. With these measures in place, the risk benefit balance remains positive. To educate prescribers and patients and hence minimise the risk of BCG disease following live BCG vaccination in infants within utero exposure to Hulio®, Patient Reminder Cards are utilized.

Public health impact:

There is no potential public health risk or impact.

Important Potential Risk 1: Progressive multifocal leukoencephalopathy (PML)

Potential mechanisms:

Emergence of the pathogenic prototype from the commonly acquired JC virus (JCV) archetype; this transformation, consisting of tandem repeats of a 98-bp element, is poorly understood (Pavlovic D et al 2015) [27]

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. There have been no reports of PML in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of PML in the clinical studies conducted with FKB327 to date. PML has been classed as a potential risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

There have been no treatment-related cases of PML in clinical studies conducted with FKB327 to date. PML is always serious if it occurs and may lead to severe neurological disabilities and death depending on the patient's health status as well as the severity of the PML.

PML is a rare but debilitating and frequently fatal viral disease of the CNS, caused by JCV, a polyomavirus. The virus is widespread among human populations throughout the world. The routes of transmission are not well established, but oral/faecal route seems most plausible. Mostindividuals are infected by age 30–40. Although JCV is commonly spread in the community, the JCV archetype is not pathogenic (Pavlovic et al, 2015) [27]. Patients (N=66,278) with adult-onset RA, exposure to biological agents, and a diagnosis of PML from 1999 through 2009, were identified from Swedish national registries. The incidence rate of PML in the overall RA population was 1.0 (95% CI 0.3 to 2.5) compared with 0.3 (95% CI 0.1 to 0.6) in the general population. Among all patients exposed to biological agents, only one patient was diagnosed with PML (Arkema EV et al 2012) [28]

Among 2,030,578 US patients with autoimmune diseases of interest (RA, PsA, Ps, JIA, IBD, and AS), a total of 53 PML cases were identified (2.6 per 100,000 patients). Most PML cases had HIV and/or cancer. PML occurred at an estimated incidence of 0.2 per 100,000 patients with autoimmune diseases who did not have HIV or malignancy (Bharat A et al 2012) [29] . The incidence rates in the HIV+ population declined from levels of 2–10 per 1000 PYs in the era prior to combined antiretroviral therapy (cART), to around 1 per 1000 PYs in the post-cART era. Between 1998 and 2005 (during the cART era) about 80% of 9,675 PML cases in the US were attributed to HIV (Pavlovic D et al 2015) [27]

Risk factors and risk groups:

PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or relapsing–remitting multiple sclerosis patients treated with natalizumab.

PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number of cases and together account for less than 10% of all reported PML cases(Pavlovic D et al 2015) [27]

Preventability:

Potentially preventable by reversal of immune suppression (e.g. by cART in HIV patients or removal of immunosuppressive/immunomodulating treatments such as natalizumab) and subsequent recovery of immune system function.

Impact on the risk-benefit balance of the product:

PML, although rare, primarily affects individuals with chronically and severely suppressed immune systems and is always very serious. It can lead to severe neurological disabilities and death, depending on the patient's health status as well as the severity of the PML. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the rare risk of PML.

Public health impact: None.

Important Potential Risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)

Potential mechanisms: Unknown.

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. There have been no reports of RPLS in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of RPLS in the clinical studies conducted with FKB327 to date. RPLS has been classed as a potential risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

There have been no treatment-related cases of RPLS in the clinical studies conducted with FKB327 to date. RPLS is always serious if it occurs, and may lead to neurological disabilities, multisystem organ involvement and sequelae, blindness, and death, depending on the patient's health status as well as the severity of the RPLS.

The background incidence and prevalence of RPLS is not well described.

Risk factors and risk groups:

Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee VH et al 2008) [30]

Preventability: Unknown.

Impact on the risk-benefit balance of the product:

RPLS is always very serious and can lead to neurological disabilities, multisystem organ involvement and sequelae, blindness, and death, depending on the patient's health status as well as the severity of RPLS. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the rare risk of RPLS.

Public health impact: None.

Important Potential Risk 3: Adenocarcinoma of Colon in ulcerative colitis (UC) patients

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

FKB327 is a biosimilar medicine to the reference product Humira®. There was only one case of colon cancer in UC patients treated in Humira® UC trials (a rate of < 0.1 event of colon cancer per 100 patient-years of exposure). There have been no treatment-related cases of adenocarcinoma of colon in UC patients in the clinical studies conducted with FKB327 (*studies were conducted in RA patients*). However, adenocarcinoma of colon has been classed as a potential risk for FKB327 in accordance with the reference product.

Characterisation of the risk:

UC patients have not been studied in the clinical studies conducted with FKB327 to date, so there have been no treatment-related cases of colon cancer in UC patients. Colon cancer may lead to death, depending on the patient's health status as well as the stage of the adenocarcinoma of colon. The risk of colorectal cancer for any patient with UC is known to be elevated, and is estimated to be 2% after 10 years, 8% after 20 years and 18%after 30 years of disease. The crude annual incidence rate of colorectal cancer in UC ranges from approximately 0.06% to 0.16% with a relative risk of 1.0-2.75 (Lakatos Plet al 2008) [31] ·More recently an average of 1.6% of patients with UC was diagnosed with colorectal cancer during 14 years of follow-up. SIRs ranged from 1.05 to 3.1, with a pooled SIR of 2.4 (95% CI, 2.1–2.7) (Jess T et al 2012) [32]

Risk factors and risk groups:

Risk factors for colon cancer include extent and duration of UC, primary sclerosing cholangitis,

a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis (Lakatos Pl et al 2008) [31]. The SIR for colorectal cancer was 8.6 (95% CI, 3.8 –19.5) in those of young age and 4.8 (95% CI, 3.9 –5.9) in those with extensive colitis. Men with UC had a greater risk of colorectal cancer (SIR, 2.6; 95% CI, 2.2–3.0) than women (SIR, 1.9; 95% CI, 1.5–2.3) (Jess T et al 2012) [32]

Preventability:

Not preventable, however early detection can limit morbidity. Whilst there is a known increased risk of adenocarcinoma of colon in UC patients that varies with degree and extent of bowel inflammation as well as the length of time a patient has the disease, with current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. As a result, the routine screening of UC patients for dysplasia (pre-cancerous lesions) prior to and during therapy with adalimumab is recommended in the product label. This evaluation should include colonoscopy and biopsies per local recommendations.

Impact on the risk-benefit balance of the product:

The risk of colon cancer is known to be elevated in UC patients and can potentially be life-threatening, depending on degree and extent of bowel inflammation as well as the length of time a patient has the disease. However, early detection can limit morbidity. The benefit of adalimumab for the treatment of various severe and progressive autoimmune conditions, such as RA, is considered to outweigh the risk of colon cancer in UC patients if screened routinely for dysplasia (pre-cancerous lesions) prior to and during therapy with adalimumab as recommended in the product label. This evaluation should include colonoscopy and biopsies per local recommendations.

Public health impact: None.

SVII.3.2. Presentation of the missing information

Missing information 1: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)

Evidence source:

The efficacy and safety of FKB327 have been evaluated in a total of 664 adult patients with RA (treated for a maximum of 102 weeks in the clinical development programme) in the FKB327 002/003 clinical studies. More than 230 patients have been treated with FKB327 for ≥ 66 weeks, but paediatric patients were not evaluated.

Population in need of further Characterisation

The safety of Hulio® in paediatrics is not expected to differ from the known safety profile of Hulio® in adults. Also, the safety of Hulio® in patients treated long-term is not expected to be different from the safety of Hulio® used for shorter periods of time. Long-term safety data in children aged from 6 to <18 years with CD and pedERA exposed to Hulio® will be through collection and evaluation of spontaneous reports in the post-marketing setting (routine pharmacovigilance).

Missing information 2: Episodic treatment in ulcerative colitis (UC)

Evidence source:

The efficacy and safety of FKB327 have been evaluated in a total of 664 adult patients with RA (treated for a maximum of 102 weeks in the clinical development programme) in the FKB327 002/003 clinical studies. More than 230 patients have been treated with FKB327 for ≥ 66 weeks, but patients with UC, were not evaluated and nor was episodic treatment.

Population in need of further characterisation:

The safety of Hulio® in patients with UC, is not expected to differ from the known safety profile in patients with RA. Collection of data in patients with these indications exposed to Hulio® and the impact of remission-withdrawal-retreatment or episodic treatment will be through collection and evaluation of spontaneous reports in the post-marketing setting (routine pharmacovigilance).

Part II: Module SVIII - Summary of the safety concerns

Table 10 SVIII: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain- Barré syndrome [GBS], and optic neuritis [ON]) • BCG disease following live BCG vaccination in infants within utero exposure to Hulio®
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD) • Episodic treatment in ulcerative colitis (UC)

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including AE collection and reporting, PSURs and signal detection will be carried out.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires: None

Other forms of routine pharmacovigilance activities for safety concerns: Not applicable.

III.2 Additional pharmacovigilance activities

Extension study summary

Study short name and title:

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).

Rationale and study objectives:

Primary:

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

Secondary:

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

Study design:

The first part of this ongoing extension study is an open label, randomised, comparative, multi- centre, 2 arm extension Phase 3 study in patients with RA who are taking a stable dose of MTX and who have continued from the preceding Study FKB327 002. The second part of the study is an open label, single arm extension in which all patients will receive FKB327 treatment from Week 30 to Week 76 (Period II), followed by a 4 week Follow up period. For each patient, the study is expected to last 80 weeks (on study treatment for up to 76 weeks with a further post treatment Follow up period of 4 weeks).

Study population:

Consenting patients with RA who had completed all 24 weeks of study procedures (including dosing) according to protocol FKB327-002, with a minimum of 9 doses of study drug received, were continuing with stable concomitant MTX and folate, and in the investigator's opinion, had shown a clinical response to treatment during Study FKB327-002.

Milestones:

Protocol finalised: Q1 2015

Study Start: Q3 2015

Study finish: Q1 2018

Final report submitted: 31 October 2018

Post-authorisation safety study (PASS) summary

Study short name and title:

Safety surveillance of Hulio® (FKB327) (adalimumab) using the rheumatoid arthritis RABBIT registry in Germany: long-term, prospective, observational study.

Rational and study objectives:

This observational post-authorisation safety study aims to characterise the safety profile of the adalimumab biosimilar formulation Hulio®, and to describe the effectiveness and response to the treatment in RA patients in a real-life environment, using already existing data from the German Biologics Registry (RABBIT). In particular, this registry will address the long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune hepatitis, and CHF/MI.

Study design:

This study is an observational prospective cohort study, utilising existing data collected in the RABBIT registry. Data from eligible patients included in the RABBIT registry will be described for up to 5 years from the Hulio® initiation date.

Study population:

Patients diagnosed with RA, with at least one prescription of Hulio® within the RABBIT registry. Patients must fulfil the following inclusion criteria:

- Participation in the RABBIT registry
- RA diagnosis
- Prescribed Hulio®
- Patients with at least one follow-up time point, after being prescribed Hulio®.

Milestones:

Protocol finalized: Q2 2019

Study start: Q3 2019

Study finish: Q4 2035

Final report available: Q4 2036

III.3 Summary Table of additional Pharmacovigilance activities

Table 11: Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities, which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
FKB327-003 study: 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 qppv(ARABESC-OLE). Completed	To compare the safety of long-term treatment with FKB327 and Humira® in patients with RA, and also to evaluate safety, and changes in efficacy, in patients who were switched from FKB327 in the preceding FKB327-002 double blind study to Humira® in the FKB327-003 OLE study and then switched back to FKB327 in the second part of the FKB327-003 OLE study.	Long-term safety in RA.	Protocol finalized	Q1 2015
			Study start	Q3 2015
			Study finish	Q1 2018
			Final report submitted	31 October 2018
German Biologics Register Rheumatoid Arthritis (**RABBIT**): A longitudinal observational study of patients with	To evaluate the long-term safety and confirm the assumption that Hulio® therapy in patients with RA is associated with Similar risks compared	Long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune	Protocol finalized	Q2 2019
			Study start	Q3 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
rheumatoid arthritis treated with biologic and other new advanced targeted therapies (GER). Planned	to patients with similar disease activity receiving established anti-TNF medications.	hepatitis, and CHF/MI.	Study finish	Q4 2035
			Final report available	Q4 2036

Part IV: Plans for post-authorisation efficacy studies

FKB327 (Hulio®) has been developed as a biosimilar of adalimumab. The reference product is Humira®. The marketing authorisation application for FKB327 is intended to cover all indications that are authorised for the reference product. The FKB327 marketing authorisation application is based on clinical studies conducted only in the indication of RA, consistent with CHMP guidelines on the clinical development of biosimilar medicinal products ("Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)"). As similarity between FKB327 and Humira® was demonstrated by both in vitro and in vivo studies, the clinical development programme for FKB327 comprised a Phase 1 PK study in healthy subjects comparing FKB327 with EU-approved and US-licensed Humira® and two Phase 3 studies, a double-blinded study and an OLE study, in RA patients. Thus, it can be assumed that FKB327 should be as effective as Humira® in populations with indications that are authorised for Humira® but that have not been studied in clinical trials with FKB327.

With this consideration above, no post-authorisation efficacy studies are planned for Hulio®

Part V: Risk Minimisation Measures

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 12 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk 1: **Serious infections**	Routine risk communication: • Contraindicated in patients with active tuberculosis or other severe infections such as sepsis, and opportunistic infections, in SmPC section 4.3 • Listed as adverse reactions in SmPC section 4.8 • Description of serious infections observed in adalimumab clinical trials provided in SmPC section 4.8. • Contraindicated for the patient with active tuberculosis or other severe infections in PL section 2. • Listed as side effects in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning not to initiate treatment with Hulio® in patients with active infections until infections are controlled, to closely monitor patients for infections before, during and after treatment with Hulio®, and to discontinue Hulio® if a patient develops a new serious infection or sepsis, in SmPC section 4.4 • Warning for the patient not to use if they have a severe infection, and that they will be monitored closely for infections before and during treatment with Hulio®, and for up to 4 months after treatment has finished, in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Identified Risk 2: **Tuberculosis (TB)**	Routine risk communication: • Listed as an adverse reaction in SmPC sections 4.3, 4.4 and 4.8 • Listed as a side effect in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning not to initiate treatment with Hulio® in patients with TB until is controlled, to closely monitor patients for TB before, during and after treatment with Hulio®, and to

	discontinue Hulio® if a patient develops TB, in SmPC section 4.4 • Warning for the patient not to use if they have TB, and that they will be monitored closely for TB before and during treatment with Hulio®, and for up to 4 months after treatment has finished, in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Identified Risk 3: **Malignancies**	Routine risk communication: • Warning that development of malignancies in patients (including children) treated with a TNF antagonist cannot be excluded in the SmPC section 4.4 • Considered listed as an adverse reaction in SmPC section 4.8 • Description of malignancies observed in adalimumab clinical trials provided in SmPC section 4.8 • Warning for the patient that Hulio® can increase the risk of getting cancer in PL section 2 • Listed as a side effect in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be examined for the presence of nonmelanoma skin cancer prior to and during treatment with Adalimumab is included in the SmPC section 4.4. Patients who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course is included in the SmPC section 4.4 (see also risk of adenocarcinoma of the colon in UC) Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Identified Risk 4: **Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis [ON])**	Routine risk communication: • Warning that TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease in SmPC section 4.4 • Listed as an adverse reaction in SmPC section 4.8

	• Listed as a side effect in PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning to exercise caution in considering the use of Hulio® in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop, in SmPC section 4.4 • Guidance to perform neurologic evaluation in patients with non- infectious intermediate uveitis prior to and during treatment in SmPC section 4.4 • Warning for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs, in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Identified Risk 5: **BCG disease following live BCG vaccination in infants, within utero exposure to Hulio®**	Routine risk communication: • SmPC section 4.4: Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. • SmPC section 4.6: Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. • PL section 4: Hulio alters immune response. Administration of live vaccines (e.g., BCG vaccine used against tuberculosis) to your infant exposed to Hulio in-utero is not recommended for 5 months following your last Hulio injection during pregnancy. Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients on adalimumab may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy is included in SmPC section 4.4 Patients on adalimumab may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG) to infants exposed to adalimumab in utero is not recommended for 5 months following the

	mother's last adalimumab injection during pregnancy is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Potential Risk 1: **Progressive multifocal leukoencephalopathy (PML)**	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Potential Risk 2: **Reversible posterior leukoencephalopathy syndrome (RPLS)**	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Important Potential Risk 3: **Adenocarcinoma of Colon in ulcerative colitis (UC) patients**	Routine risk communication: • Warning that risk for developing dysplasia or colon cancer is unknown in SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Instruction to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Missing information 1: **Long-term safety information in the treatment of children**	Routine risk communication: • None

aged from 6 years to less than 18 years with Crohn's disease (CD)	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine
Missing information 2: **Episodic treatment in UC**	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only medicine

V.2. Additional Risk Minimisation Measures

Patient (including pediatric) Reminder Card

Objectives:

Important risks covered by the additional risk minimisation measures:

- Infections
- Tuberculosis [TB]
- Malignancies
- Nervous system problems
- Vaccinations

The objective of the additional risk minimisation measures is to educate patients (or caregivers) and prescribers about select important safety information associated with the use of Hulio® such as serious infections, TB, malignancies, vaccinations and demyelinating disorders. In particular the Patient Reminder Card is designed to ensure that information regarding the patient's current therapy and the important risks for Hulio® is held by the patient at all times and is shown to the relevant HCP as appropriate.

In addition, these measures instruct patients to record details of any tests or treatment for TB.

Rationale for the additional risk minimisation activity:

Hulio® is a biosimilar medicinal product to Humira®. As a biosimilar, Hulio® has the same risks and hence needs to follow the same risk minimisation measures as the reference product.

Details of the additional risk minimisation measures are included in Annex 6 - Details of proposed additional risk minimisation activities (if applicable). .

Target audience and planned distribution path:

Appropriate method of distribution of educational material and target group will be

agreed with national competent authorities.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The Applicant will monitor effectiveness and compliance with the Patient Reminder Card by using routine pharmacovigilance, signal detection and medical review. The incidence of adverse reactions will be compared with those described in the SmPC. If there is an increased incidence of adverse reactions or if the reports are different in seriousness, severity or outcome to that described in the SmPC further labelling changes or risk minimisation will be considered. Assessment will be conducted during routine signal detection and the preparation of scheduled PSURs.

The results of such effectiveness measurement and impact of the additional risk minimisation measures remain to be determined.

Removal of additional risk minimisation activities

None.

V.3. Summary table of pharmacovigilance and risk minimisation activities by safety concern

Table 13 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk 1: **Serious infections**	Routine risk minimisation measures: SmPC section 4.3, where patients with severe infections are contraindicated SmPC section 4.4, where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections and to discontinue Hulio® if a patient develops a new serious infection or sepsis SmPC section 4.8, where a description of serious infections observed in adalimumab clinical trials is provided SmPC section 4.8 listed as adverse reactions PL section 2, where patients with active tuberculosis or other severe infections are contraindicated	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: German Biologics Register (RABBIT)

	PL section 2, where a warning is given for the patient not to use if they have a severe infection, and they will be monitored closely for infections PL section 4 listed as side effects Legal status (prescription-only medicine) Additional risk minimisation measures: Patient Reminder Card	
Important Identified Risk 2: **Tuberculosis (TB)**	Routine risk minimisation measures: SmPC section 4.3 where patients with active tuberculosis is contraindicated. SmPC section 4.4, where a warning is given not to initiate treatment in patients, to closely monitor patients for TB, and to discontinue Hulio® if a patient develops TB or sepsis SmPC section 4.8, where a description of TB observed in adalimumab clinical trials is provided SmPC section 4.8 listed as adverse reactions PL section 2, where patients with active tuberculosis is contraindicated PL section 2 where a warning is given for the patient not to use if they have a TB, and that they will be monitored closely for TB PL section 4 listed as side effects Legal status (prescription-only medicine) Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: German Biologics Register (RABBIT)

	Patient Reminder Card	
Important Identified Risk 3: **Malignancies**	Routine risk minimisation measures: SmPC section 4.4, where a warning is given about the possible development of malignancies in patients (including children) treated with a TNF antagonist SmPC section 4.8, where a description of malignancies observed in adalimumab clinical trials is provided SmPC section 4.8 listed as an adverse reaction. PL section 2, where a warning is given that Hulio® can increase the risk of getting cancer PL section 4 is listed as a side effect Legal status (prescription-only medicine) Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: German Biologics Register (RABBIT)
Important Identified Risk 4: **Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS], and optic neuritis [ON])**	Routine risk minimisation measures: SmPC section 4.4, where a warning is given that TNF-antagonists, including adalimumab, have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease SmPC section 4.4, where a warning is given to exercise caution in considering the use of Hulio® in patients with pre-existing or recent-onset central	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	or the peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop. SmPC section 4.4, where guidance is given to perform Neurologic evaluation in patients with non-infectious intermediate uveitis prior to and during treatment. SmPC section 4.8 listed as an adverse reaction PL section 2 where a warning is given for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs PL section 4 listed as a side effect Legal status (prescription-only medicine) Additional risk minimisation measures: Patient Reminder Card	
Important Identified Risk 5: **BCG disease following live BCG vaccination in infants within utero exposure to Hulio®**	Routine risk minimisation measures: SmPC section 4.4: Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. SmPC section 4.6: Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	these infants may be at increased risk for infection. PL section 4: Hulio alters immune response. Administration of live vaccines (e.g., BCG vaccine used against tuberculosis) to your infant exposed to Hulio in-utero is not recommended for 5 months following your last Hulio injection during pregnancy. Additional risk minimisation measures: Patient Reminder Card	
Important Potential Risk 1: **Progressive multifocal leukoencephalopathy (PML)**	Routine risk minimisation measures: Legal status (prescription only medicine) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risk 2: **Reversible Posterior leukoencephalopathy syndrome (RPLS)**	Routine risk minimisation measures: Legal status (prescription only medicine) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential Risk 3: **Adenocarcinoma of colon in ulcerative colitis (UC) patients**	Routine risk minimisation measures: SmPC section 4.4 where a warning is given that the risk for developing dysplasia or colon cancer in UC patients is unknown	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

	SmPC section 4.4 where instruction is given to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma Legal status (prescription only medicine) Additional risk minimisation measures: None	None
Missing information 1: **Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)**	Routine risk minimisation measures: *Legal status (prescription-only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing information 2: **Episodic treatment in UC**	Routine risk minimisation measures: *Legal status (prescription-only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Part VI: Summary of the risk management plan

Summary of risk management plan for Hulio® (adalimumab)

This is a summary of the risk management plan (RMP) for Hulio®. The RMP details important risks of Hulio®, how these risks can be minimised, and how more information will be obtained about Hulio®'s risks and uncertainties (missing information).

Hulio®'s summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Hulio® should be used.

This summary of the RMP for Hulio® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hulio®'s RMP.

I. The medicine and what it is used for

Hulio® is authorised for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis, psoriatic arthritis, plaque psoriasis in adults and children, hidradenitis suppurativa, Crohn's disease in adults and children, ulcerative colitis, and non-infectious uveitis in adults and children (see SmPC for the full indication). It contains adalimumab as the active substance, and it is given by subcutaneous injection.

Further information about the evaluation of Hulio®'s benefits can be found in Hulio®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/hulio

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Hulio®, together with measures to minimise such risks and the proposed studies for learning more about Hulio®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Hulio® is not yet available, it is listed

under 'missing information' below.

In the case of Hulio®, these routine measures are supplemented with additional risk minimisation measures mentioned under relevant risks below.

II.A List of important risks and missing information

Important risks of Hulio® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered to patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hulio®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.).

Table 14 Part VI: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS], and optic neuritis [ON]) • BCG disease following live BCG vaccination in infants within utero exposure to Hulio®
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD) • Episodic treatment in UC

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk 1: Serious infections	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). In the clinical studies conducted with Hulio® to date, the most common treatment- related infections included bronchitis, nasopharyngitis

	and urinary tract infection, although the overall number of patients experiencing any serious infection was small (20 subjects [3.0%] receiving Hulio®). Serious infections have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh JA et al, 2015)[7]. Other risks associated with serious infections include very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 where patients with severe infections are contraindicated SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided SmPC section 4.8 listed as adverse reactions PL section 2, where patients with active tuberculosis or other severe infections are contraindicated PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for infections PL section 4 listed as side effects Legal status (prescription only medicine) Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10). TESAEs that occurred in more than 1 patient were: disseminated TB (2 patients, 1 [0.2%] in each treatment group) and latent TB (2 patients [0.3%], both with FKB327). No case of pulmonary TB was reported on FKB327 compared to 2 cases [0.4%] on Humira®. Tuberculosis has been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Standard-dose and high-dose biological drugs (with or without traditional disease-modifying anti-rheumatic drugs [DMARDs]) have been shown to be associated with a statistically significant increase in serious infections in methotrexate-naïve rheumatoid arthritis patients compared with traditional DMARDs; the absolute risk increase of serious infections with biologic therapy was identified as 6 per 1000 for standard-dose biologic and 17 per 1000 for high-dose biologic therapy (Singh JA et al, 2015)[7]. Other risks associated with serious infections include very young people and elderly people; concomitant immunosuppressive therapies, including steroids, chemotherapy drugs or radiation; history of previous serious or recurrent infections; compromised circulation (e.g. longstanding diabetes); compromised skin integrity (e.g. large burns or severe trauma); and splenectomy or dysfunctional spleen.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 where patients with active tuberculosis are contraindicated SmPC section 4.4 where a warning is given not to initiate treatment in patients with active infections, to closely monitor patients for infections, and to discontinue Hulio® if a patient develops a new serious infection or sepsis SmPC section 4.8 where a description of serious infections observed in adalimumab clinical trials is provided SmPC section 4.8 listed as adverse reactions PL section 2 where patients with active tuberculosis are contraindicated

	PL section 2 where a warning is given for the patient not to use if they have a severe infection, and that they will be monitored closely for TB PL section 4 listed as side effects Legal status (prescription only medicine) Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *German Biologics Register (RABBIT)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 3: Malignancies	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, malignancies have been reported to occur commonly (≥ 1/100 to < 1/10) to uncommonly (≥ 1/1,000 to < 1/100). One case (0.2%) of basal cell carcinoma (BCC) was reported in the clinical studies conducted with FKB327, with one case (0.2%) of squamous cell carcinoma (SCC) reported in the Humira® treatment group. There have been one case (0.2%) breast cancer and one case (0.2%) cervix carcinoma in the FKB327 treatment group but none in Humira treatment group in the clinical studies conducted with Hulio® to date. There have been no treatment-related cases of hepatosplenic T-cell lymphoma, leukaemia, melanoma, Merkel cell carcinoma in the clinical studies conducted with Hulio® to date. One treatment-related case of lymphoma in the FKB327 treatment group was reported as a post-study event. Malignancies have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors groups and risk	Patients with RA have a 10 % increase in overall malignancy risk compared with the general population. Furthermore, the SIR estimates for patients with RA continued to show an increased risk of lymphoma and lung cancer as previously observed. Overall, SIR estimates for colorectal and breast cancers continued to show a decrease in risk, whereas cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk among patients with RA compared with the general population.
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.4 where a warning is given about malignancies in patients treated with a TNF antagonist SmPC section 4.8 where a description of malignancies observed in adalimumab clinical trials is provided SmPC section 4.8 listed several malignancies PL section 2 where a warning is given that Hulio® can increase the risk of getting cancer PL section 4 listed as a side effect Legal status (prescription only medicine) Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: German Biologics Register (RABBIT) See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS], and optic neuritis [ON])	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. According to the Humira® SmPC, demyelinating disorders have been reported to occur rarely (≥ 1/10,000 to < 1/1,000). There have been no treatment-related cases coded as a recognised demyelinating disorder, although one (0.2%) treatment-related adverse event of hypoaesthesia was reported in the clinical studies conducted with Hulio®. Demyelinating disorders have been classed as an identified risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors associated with an increased risk for MS are a combination of genetic susceptibility (HLA-DR15 haplotype) and environmental exposures (including latitude, vitamin D deficiency, season of birth, Epstein Barr virus infection, and smoking behaviour) (O'Gorman et al, 2012) [20]. These factors appear to act synergistically and the risk of MS is increased in individuals exposed to more than one factor (Disanto et al 2012) [21]. Being Caucasian and female increases risk, as does having a family relative with MS [34] Risk factors for GBS include male sex, prior infection (e.g. Campylobacter jejuni, Epstein Barr virus, cytomegalovirus, mycoplasma, HIV, and more recently Zika virus [Blázquez &

	Saiz 2016] [23]), vaccines, malignancies (e.g. lymphomas, especially Hodgkin's disease) (Ansar &Valadi 2015)[22]. Risk factors for optic neuritis include female sex, race (more frequent in white Caucasians, genetic mutations (as per MS), bacterial/viral infections, sarcoidosis/lupus and some drugs (e.g. quinine and some antibiotics) [26]
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 where a warning is given that TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disease SmPC section 4.4 where a warning is given to exercise caution in considering the use of Hulio® in patients with pre-existing or recent- onset central or peripheral nervous system demyelinating disorders, and to consider discontinuation if these disorders develop SmPC section 4.4 where guidance is given to perform neurologic evaluation in patients with non-infectious intermediate uveitis prior to and during treatment SmPC section 4.8 listed as an adverse reaction PL section 2 where a warning is given for the patient to talk to their doctor if experiencing symptoms such as weakness, numbness or tingling of the limbs. Legal status (prescription only medicine) Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important identified risk 5: BCG disease following live BCG vaccination in infants within utero exposure to Hulio®	
Evidence for linking the risk to the medicine	Data from reference product trials, registries and database. Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation Guidelines prior to initiating adalimumab therapy. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5

	months following the mother's last adalimumab injection during pregnancy.
Risk factors and risk groups	Infants who are exposed to adalimumab intrauterine.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4: Administration of live vaccines (e.g., BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. SmPC section 4.6: Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. PL section 4: Hulio alters immune response. Administration of live vaccines (e.g., BCG vaccine used to prevent tuberculosis) to your infant exposed to Hulio in-utero is not recommended for 5 months following your last Hulio injection during pregnancy. Legal status (prescription-only medicine) Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important potential risk 1: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of PML in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of PML in the clinical studies conducted with Hulio® to date. PML has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	PML primarily affects individuals with chronically and severely suppressed immune systems and is associated primarily with HIV patients, haematological malignancies, or relapsing–remitting multiple sclerosis patients treated with natalizumab. PML is also associated with other conditions such as organ transplantation, solid malignancies, sarcoidosis, autoimmune disorders (e.g. lupus, RA), and congenital immune deficiencies; these populations individually contribute a relatively small number

	of cases and together account for less than 10% of all reported PML cases (Pavlovic et al, 2015) [27].
Risk minimisation measures	Routine risk minimisation measures: None Legal status (prescription-only medicine) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important potential risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)	
Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. There have been no reports of RPLS in all clinical trials with adalimumab. Similarly, there have been no treatment-related cases of RPLS in the clinical studies conducted with Hulio® to date. RPLS has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Suspected aetiologias in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee et al, 2008) [30].
Risk minimisation measures	Routine risk minimisation measures: None Legal status (prescription-only medicine) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Important potential risk 3: Adenocarcinoma of colon in ulcerative colitis (UC) patients

Evidence for linking the risk to the medicine	Hulio® is a biosimilar medicine to the reference product Humira®. In all RA trials with adalimumab, the rate of ALS was determined as < 0.1 event per 100 patient-years of exposure. Although there have been no treatment-related cases of adenocarcinoma of the colon in UC patients in the clinical studies conducted with Hulio® (studies were conducted in rheumatoid arthritis patients). However, adenocarcinoma of the colon has been classed as a potential risk for Hulio® in accordance with the reference product.
Risk factors and risk groups	Risk factors for colon cancer include extent and duration of UC, primary sclerosing cholangitis, a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis (Lakatos & Lakatos, 2008) [31]. The standardized incidence rate (SIR) for colorectal cancer was 8.6 (95% CI, 3.8 –19.5) in those of young age and 4.8 (95% CI, 3.9 –5.9) in those with extensive colitis. Men with UC had a greater risk of colorectal cancer (SIR, 2.6; 95% CI, 2.2–3.0) than women (SIR, 1.9; 95% CI, 1.5–2.3) (Jess et al, 2012).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, where a warning is given that the risk for developing dysplasia or colon cancer in UC patients is unknown SmPC section 4.4, where instruction is given to screen UC patients for dysplasia at regular intervals before therapy and throughout their disease course (including use of colonoscopy and biopsies) if they are at increased risk or have a prior history of dysplasia or colon carcinoma Legal status (prescription-only medicine) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None*

Missing information 1: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn's disease (CD)	
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription-only medicine

	Additional risk minimisation measures: None

Missing information 2: Episodic treatment in UC	
Risk minimisation measures	Routine risk communication: None Other routine risk minimisation measures beyond the Product Information: Legal status: prescription-only medicine Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Hulio®.

II.C.2 Other studies in post-authorisation development plan

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).**

Study FKB327-003 has been completed, and final study report submitted 31 October 2018.

Safety surveillance of Hulio® (FKB327) (adalimumab) using the rheumatoid arthritis RABBIT registry in Germany: long-term, prospective, observational study.

Purpose of the study:

This observational post-authorisation safety study aims to characterize the safety profile of the adalimumab biosimilar formulation Hulio®, and to describe the effectiveness and response to the treatment in RA patients in a real-life environment, using already existing data from the German Biologics Registry (RABBIT). In particular, this registry will address the long-term safety in RA with emphasis on TB/other serious infection, malignancies, elevated ALT levels, autoimmune hepatitis, and CHF/MI.

Part VII: Annexes

List of annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures

The proposed key message for educational materials is provided below. Their actual content and communication plan in individual countries will be agreed with national competent authority prior to launch.

Patient educational material:

- The Summary of Product Characteristics
- Patient Reminder card

Patient Reminder card:

- Important safety information that the patient needs to know before and during their treatment with Hulio® (with repeated reference to the Hulio® patient information leaflet)
- A warning message for patients to inform their healthcare professional of any existing health problems before Hulio® treatment begins
- Information that the healthcare professional will screen the patient for signs and symptoms of TB before starting Hulio® treatment
- A warning message for patients to inform their healthcare professional of any unusual symptoms or side effects they experience during Hulio® treatment
- That Hulio® treatment may increase the risk of infections, tuberculosis, cancer, nervous system problems
- Information regarding vaccination
- Contact details of the Hulio® prescriber
- Patient name and details of current therapy (indication, start date, dose)
- Instructions to record details of any tests or treatment for TB

The patient information pack:

- Patient information leaflet