EU Risk Management Plan for Flixabi (Infliximab)

RMP version to be assessed as part of this application:

RMP Version number: 14.0

Data lock point for this RMP:Jan 29, 2024

Date of final sign off: Feb 15, 2024

Rationale for submitting an updated RMP: To update the due dates of the milestones of additional PV activities

Summary of significant changes in this RMP:

Update in the end date and final report due date of the additional pharmacovilance activities ARTIS, BSRBR-RA and RABBIT-RA

Other RMP versions under evaluation: Version number 13.0

Details of the currently approved RMP:

Version number: 12.1

Approved with procedure: EMEA/H/C/004020/IB/0075

Date of approval (opinion date): Nov 30, 2023

QPPV name: John Hart

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

6-MP	6-mercaptopurine
AASLD	American Association for Study of the Liver Diseases
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
aRR	Adjusted relative risk
ARTIS	Antirheumatic Therapies In Sweden
AS	Ankylosing spondylitis
ATI	Antibody(ies) to infliximab
AUC_{last}	Area under the curve from the time of dosing to the last measurable concentration
AZA	Azathioprine
BCC	Basal cell carcinoma
BCG	Bacillus Calmette-Guérin
BIOBADASER	Spanish Registry of Adverse Events of Biological Therapies
BSRBR-RA	British Society for Rheumatology Biologics Register Rheumatoid Arthritis
C1q	Complement 1q
CD	Crohn's disease
CDC	Complement-dependent cytotoxicity
CEDUR	Chronisch Entzündliche Darmerkrankungen, ein Unabhängiges Register (nationwide German IBD registry)
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences

C_{max}	Maximum observed concentration
CNS	Central nervous system
CREDIT	Czech Register of IBD Patients on Biological Therapy
CRP	C-reactive protein
DDD	Defined daily dose
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
dsDNA	Double stranded DNA
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
Fc	Fragment crystallisable
FDA	Food and Drug Administration
FRET	Fluorescence resonance energy transfer
FVC	Forced vital capacity
GVHD	Graft-versus-host disease
HBc	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Health care professional
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HLGT	High-level group term
HLT	High-level term
HR	Hazard ratio
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
IFN	Interferon
Ig	Immunoglobulin
IP	Intraperitoneal or Investigational product, according to context
IRR	Incidence rate ratio

IV	Intravenous
JIA	Juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple sclerosis
MTX	Methotrexate
NAb	Neutralising antibody
NF-κB	Nuclear factor kappa B
NHL	Non-Hodgkin's lymphoma
NMSC	Non-melanoma skin cancer
NYHA	New York Heart Association
O/E	Observed-to-expected
OR	Odds ratio
PK	Pharmacokinetic(s)
PsA	Psoriatic arthritis
PSC	Primary sclerosing cholangitis
PT	Preferred term
PUVA	Psoralen combined with ultraviolet A
PV	Pharmacovigilance
pyd	Person years duration
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RABBIT	Rheumatoid Arthritis Observation of Biologic Therapy
RMP	Risk management plan
RR	Rate ratio
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardised incidence ratio
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
TB	Tuberculosis
Tg	Transgenic

Th	T helper cell
TNF-α	Tumour necrosis factor-alpha
UC	Ulcerative colitis
UK	United Kingdom
US	United States of America
UV	Ultraviolet
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Infliximab
Pharmacotherapeutic group(s) (ATC Code)	L04AB02
Marketing Authorisation Holder	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Flixabi (company code: SB2)
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: Not applicable
	Summary of mode of action Flixabi is a proposed biosimilar to Remicade(infliximab). Infliximab is a chimeric human-murine immunoglobulin (Ig) G1 monoclonal antibody produced in murine hybridoma cells by recombinant deoxyribonucleic acid (DNA) technology. It binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor-α (TNF-α) but not to lymphotoxin-α. TNF-α has a number of effects including mediation of inflammatory responses, modulation of the immune system, and induction of apoptosis. Infliximab has been shown to inhibit the functional activity of TNF-α in a wide variety of *in vitro* bioassays. *In vivo*, infliximab rapidly forms stable complexes with human TNF-α, a process that parallels the loss of TNF-α bioactivity. Elevated concentrations of TNF-α have been found in the joints of rheumatoid arthritis (RA) patients and correlate with elevated disease activity. In RA, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction, and tissue degradation. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis (PsA), short-term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin. Infliximab treatment of Crohn's disease (CD) patients was associated with the following effects: a substantial reduction of the commonly elevated serum inflammatory marker, C-reactive protein (CRP); a reduction in the number of cells capable of expressing TNF-α and interferon (IFN)-γ in the intestinal mucosa; reduced infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites; and evidence of mucosal healing in the intestinal mucosa.
	Important information about its composition Flixabi is a chimeric human-murine Ig G1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	Current: Rheumatoid arthritis, Adult Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Paediatric ulcerative colitis, Ankylosing spondylitis, Psoriatic arthritis, Psoriasis
	Proposed: N/A
Dosage in the EEA	Current: *Adults (≥ 18 years)* Rheumatoid arthritis 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Flixabi must be given concomitantly with methotrexate. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment. Moderately to severely active Crohn's disease 5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with Flixabi should be given. Available data do not support further Flixabi treatment, in patients not responding within 6 weeks of the initial infusion. In responding patients, the alternative strategies for continued treatment are: • Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or, • Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. Fistulising, active Crohn's disease 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with Flixabi should be given. In responding patients, the alternative strategies for continued treatment are: • Maintenance: Additional infusions of 5 mg/kg every 8 weeks, or • Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks.

	Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking. Ulcerative colitis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data suggest that the clinical response is usually achieved within 14 weeks of treatment (i.e., 3 doses). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. Ankylosing spondylitis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e., after 2 doses), no additional treatment with Flixabi should be given. Psoriatic arthritis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Psoriasis 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e., after 4 doses), no additional treatment with Flixabi should be given. Re-administration for Crohn's disease and rheumatoid arthritis If the signs and symptoms of disease recur, Flixabi can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients. Re-administration for ulcerative colitis The safety and efficacy of re-administration, other than every 8 weeks, has not been established. Re-administration for ankylosing spondylitis The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established. Re-administration for psoriatic arthritis The safety and efficacy of re-administration, other than every 8 weeks, has not been established.

	Re-administration for psoriasis Limited experience from re-treatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen. Limited experience from re-treatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment. Re-administration across indications In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended. In this situation, Flixabi should be re-initiated as a single dose followed by the maintenance dose recommendations described above. *Paediatric population* Crohn's disease (6 to 17 years) 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval. The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. Currently available pharmacokinetic data are described but no recommendation on a posology can be made in children younger than 6 years. Ulcerative colitis (6 to 17 years) 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment. The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years. Currently available pharmacokinetic data are described but no recommendation on a posology can be made in children younger than 6 years.

	Method of administration Flixabi should be administered intravenously over a 2-hour period. All patients administered Flixabi are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone, and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously. *Shortened infusions across adult indications* In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of Flixabi (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses > 6 mg/kg have not been studied.
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current: 100 mg powder for concentrate for solution for infusion. The powder is white.
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

This module is not required for a biosimilar in accordance with Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Table V.5., Requirements for initial marketing authorisation applications.[1]

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

As agreed with the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), a toxicity study was not performed as there was no relevant animal model available to evaluate the toxicity of infliximab. As detailed in Table SII.1., reproductive toxicity, developmental toxicity, genotoxicity, carcinogenicity, or safety pharmacology studies were not conducted as these routine toxicological studies are not required for biosimilar products (in line with Committee for Medicinal Products for Human Use [CHMP] guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1).[2]

Table SII.1: Summary of key safety findings from non-clinical studies and their relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Reproductive/developmental toxicity: No reproductive studies were performed with Flixabi in line with the EU guidance on biosimilar products (CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1), which indicates that routine toxicological studies, such as reproduction toxicology, are not required.	Flixabi has been developed as a biosimilar to Remicade. Consequently, the reproductive/developmental toxicity package developed for Remicade should be considered. The SmPC for Remicade includes the following in relation to non-clinical reproductive/developmental toxicity: "In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNF-α, there was no indication of maternal toxicity, embryotoxicity or teratogenicity… In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females." The EMA provided an update to the Remicade product information (January 2011). This stated the following: "Further to the review of information received from ongoing post-marketing data monitoring sources, including data from a pregnancy registry that assessed the potential for an increased incidence of infection, preterm birth, low birth weight, and very low birth weight in infants exposed to infliximab *in utero*, the product information was updated with information on transplacental transfer of infliximab and the detection of infliximab up to 6 months post-partum in the serum of infants."

Key safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity/carcinogenicity: No genotoxicity/carcinogenicity studies were performed with Flixabi in line with the EU guidance on biosimilar products (CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1).	Flixabi has been developed as a biosimilar to Remicade. Consequently, the genotoxicity/carcinogenicity package developed for Remicade should be considered when considering this type of toxicity. According to the SmPC for Remicade, long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNF-α demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.
Hepatotoxicity/nephrotoxicity: No studies of hepatotoxicity or nephrotoxicity were performed with Flixabi.	According to the SmPC, Remicade has not been studied in these patient populations; therefore, no dose recommendations can be made.
Cardiotoxicity: No cardiotoxicity studies were conducted in support of the safety profile of Flixabi.	No effects on the cardiovascular system have been noted in non-clinical studies for the reference product, Remicade. Since Flixabi is being developed as a biosimilar, the safety profile of Remicade can be considered with respect to cardiotoxicity. As per the SmPC for Remicade[3] and the proposed SmPC for Flixabi[4], infliximab is contraindicated in patients with moderate or severe heart failure (New York Heart Association [NYHA] class III/IV). The SmPCs also include the following warning in relation to heart failure: "Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and Remicade must not be continued in patients who develop new or worsening symptoms of heart failure."
Drug interactions: Due to the specificity of infliximab and the extensive clinical experience with the reference product Remicade, non-clinical drug interaction studies were not performed.	According to the SmPC for Remicade, no interaction studies have been performed with Remicade.

Safety pharmacology

Safety pharmacology studies were not performed in line with the EU guidance on biosimilar products (CHMP guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1). Since Flixabi has been developed as a biosimilar to Remicade, the safety pharmacology package developed for Remicade should be considered when considering this type of toxicity.

A series of *in vitro* studies including binding and cell-based assays, followed by *in vivo* efficacy and pharmacokinetic (PK) studies in transgenic (Tg) 197 mice were performed to demonstrate similarity between Flixabi and the reference product, Remicade. The results of all non-clinical studies showed that the in vivo behaviour of Flixabi and Remicade was similar.

Binding assays on TNF-α, complement 1q (C1q) and fragment crystallisable region (Fc) receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, and FcRn), a potency assay using the 293-nuclear factor kappa B (NF-κB)-Luc cell line and cell-based assays including apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC) assays were performed as they are closely related to the mechanism of action of infliximab. Infliximab neutralises both soluble and transmembrane forms of TNF-α, which subsequently inhibits binding of TNF-α with its receptors. In addition, infliximab can lyse cells involved in the inflammatory process. For Fc-related functions of infliximab, the Fc region of infliximab binds to two distinct classes of Fc receptors: a family of Fcγ receptors found primarily on leukocytes and FcRn. The FcRn receptor is expressed primarily on endothelial cells and is involved in recycling of immunoglobulin (Ig) G. C1q initiates complement activation via the classical pathway. As the similarity range for the binding assays and cell-based assays, the mean ± tolerance interval values of reference product batches were adopted. The results showed that there were no significant differences between Flixabi and Remicade in terms of binding activities and inhibition of the TNF-α signalling pathway. The key findings from these studies are summarised in Table SII. 2.

Table SII. 2: Summary of comparative *in vitro* non-clinical pharmacology studies

Study type	Key findings
TNF-α binding assay	The relative binding activity of Flixabi and Remicade to TNF-α ligand was measured by fluorescence resonance energy transfer (FRET). Based on the tolerance interval (± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 85% to 111% (n=27). Results of the FRET assay showed that the TNF-α binding activity of Flixabi was similar to that of Remicade.
FcγRIa binding assay	The relative binding activities of Flixabi and Remicade to FcγRIa were measured through the FRET assay. Based on the tolerance interval (± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 82% to 118% (n=26). Results showed that the FcγRIa binding activity of Flixabi was similar to that of Remicade.
FcγRIIa binding assay	The relative binding activities of Flixabi and Remicade to FcγRIIa were measured through the Alphascreen® based competitive binding assay. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 75% to 127% (n=27). Results showed that the FcγRIIa binding activity of Flixabi was similar to that of Remicade.
FcγRIIb binding assay	The relative binding activities of Flixabi and Remicade to FcγRIIb were measured through the Alphascreen® based competitive binding assay. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 79% to 115% (n=24). The FcγRIIb binding activity of Flixabi was slightly higher than that of Remicade, but it was not considered significant. Six out of ten of the Flixabi batches showed slightly higher binding activities, which were out of the similarity range. However, the magnitude of differences was within assay variability, and there were no signals that the differences were translated into Fc-related cell bioassays such as ADCC activities, which were within the similarity range.

Study type	Key findings
FcγRIIIa binding assay	The relative binding activities of Flixabi and Remicade to FcγRIIIa were measured through the Alphascreen® based competitive binding assay. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 70% to 126% (n=25). The FcγRIIIa binding activity of Flixabi was slightly higher than that of Remicade, but it was not considered significant. Results of the binding assay showed that the binding activity of Flixabi related to the bioassay standard was slightly higher than the similarity range. However, this difference will not possess a physiological effect as the ADCC activity was within the similarity range.
FcRn binding assay	The relative binding activities of Flixabi and Remicade to FcRn were measured through the Alphascreen® based competitive binding assay. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 82% to 117% (n=23). One out of ten of the Flixabi batches showed slightly higher binding activities, which were out of the similarity range. However, the magnitude of differences was within assay variability.
C1q binding assay	The relative binding activities of Flixabi and Remicade to C1q were measured through an enzyme-linked immunosorbent assay (ELISA). Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 75% to 115% (n=21). Results showed that the C1q binding activity of Flixabi was similar to that of Remicade.
Potency assay (TNF-α neutralization assay by NF-κB reporter gene)	The inhibitory activity of infliximab on the TNF-α signalling pathway was measured through the neutralisation assay using a 293-NF-κB-Luc cell line. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 84% to 116% (n=30). Results showed that the inhibitory activity of Flixabi on the signalling pathway was similar to that of Remicade.
Apoptosis	The apoptosis activity of infliximab was measured using a Caspase-Glo® 3/7 kit. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 81% to 119% (n=27). Results showed that the apoptosis activity of Flixabi was similar to that of Remicade.
ADCC	ADCC of Flixabi and Remicade was measured through a cell-based assay. In this assay, 3T3mTNF-α cells overexpressing human membrane TNF-α were used as the target cells and NK92-CD16 cells overexpressing CD16 were used as the effector cells. Protease leaked from target cells was measured by luminescence with a luminogenic peptide substrate (alanyl-alanylphenylalanylaminoluciferin, AAF-Glo™ substrate). Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 51% to 150% (n=20). Results showed that the ADCC activity of Flixabi was similar to that of Remicade.
CDC	CDC of Flixabi and Remicade were measured by a colourimetric assay. In this assay, Flixabi and EU Remicade are pre-incubated with Jurkat cells over expressing human transmembrane TNF-α and human serum which provides a complement source to mediate CDC. Based on the tolerance interval (mean ± *k*SD using two-tiered tolerance limit) of Remicade, the similarity range was set as 78% to 120% (n=26). Results showed that the CDC activity of Flixabi was similar to that of Remicade.

Three *in vivo* studies have been performed to assess the PK and efficacy of Flixabi in comparison to Remicade. PK studies in a Tg197 transgenic mouse model of arthritis were performed to evaluate the PK similarity of Flixabi and either European Union (EU) sourced Remicade (EU Remicade) or United states of America (US) sourced Remicade (US

Remicade) following single or repeated dose administration of 1, 3, or 10 mg/kg by intraperitoneal (IP) injection. Immunogenicity of Flixabi was evaluated as part of the repeated dose PK study in the Tg197 transgenic mouse model. In addition, the efficacy of Flixabi was compared to that of EU Remicade and US Remicade in a Tg197 transgenic mouse model of arthritis at 1, 3, or 10 mg/kg by IP injection.
Furthermore, a PK study was performed in Sprague-Dawley rats with a single dose of Flixabi, EU Remicade, or US Remicade at 1, 3, or 10 mg/kg.

The key findings from these studies are summarised in Table SII. 3 below.

Table SII. 3: Summary of comparative *in vivo* pharmacokinetic and pharmacodynamic studies

Study title	Key findings
In vivo single dose PK study in Tg197 transgenic mouse model of arthritis (BMC320A)	Following single dose administration of 1, 3, or 10 mg/kg Flixabi and EU or US Remicade by IP injection to Tg197 transgenic mice, similar PK profiles in terms of maximum observed concentration (C_{max}) and area under the curve from the time of dosing to the last measurable concentration (AUC_{last}) were observed. These results indicated that there were no significant differences in exposure between Flixabi and Remicade.
In vivo repeated dose PK study in Tg197 transgenic mouse model of arthritis (BMC320B)	Following repeated dose administration (twice per week for 7 weeks) of 10 mg/kg Flixabi and EU or US Remicade by IP injection to Tg197 transgenic mice, similar PK profiles in terms of C_{max} and AUC_{last} were observed. These results indicated that there were no significant differences in exposure between Flixabi and Remicade after repeated treatment at a dose level of 10 mg/kg. The similarity of PK profiles between Flixabi and Remicade in 1 and 3 mg/kg group could not be adequately evaluated due to anti-drug antibody (ADA) development and missing values. In the immunogenicity assessment performed as part of this study, the incidence of anti-infliximab antibody formation was similar between Flixabi and Remicade.
In vivo efficacy study in Tg197 transgenic mouse model of arthritis (BMC319)	Following repeated dose administration (twice per week for 7 weeks) of 1, 3, or 10 mg/kg Flixabi and EU or US Remicade by IP injection to Tg197 transgenic mice, both Flixabi and Remicade suppressed the development of arthritis in a similar manner, as evaluated by changes in arthritic and histopathology scores. All test article groups showed inhibition of *in vivo* arthritis score and histopathology scores in a dose-dependent manner with 1, 3 and 10 mg/kg, and there were no significant differences in *in vivo* arthritis score and histopathology scores between Flixabi and Remicade. Therefore, the effects of Flixabi on arthritis inhibition in the Tg197 mouse model of arthritis were similar to those of Remicade.
In vivo single dose PK study in Sprague-Dawley rats (13-RK-349N)	Following single dose administration of 1, 3, and 10 mg/kg Flixabi, EU Remicade, and US Remicade via IV injection to male Spargue-Dawley rats, the resulting serum concentration-time profiles were similar between Flixabi and Remicade treated groups when same dose levels were compared. Moreover, there were no significant differences in C_{max} and AUC_{last} between Flixabi and Remicade treated groups. In conclusion, the PK profiles of Flixabi administered via IV were similar to those of EU Remicade and US Remicade.

Results from non-clinical *in vitro* studies have shown no significant differences between Flixabi and Remicade in terms of binding activities and inhibition of the TNF-α signalling pathway. In addition, *in vivo* studies in a Tg mouse model of arthritis have shown a similar PK profile and similar efficacy with Flixabi and Remicade. An *in vivo* single dose PK study in Sprague-Dawley rats has also shown a similar PK profile with Flixabi and Remicade.
No safety findings were identified in the non-clinical studies with Flixabi.

As Flixabi is being developed as a biosimilar product to the reference product Remicade, the safety profile of Remicade can be considered with respect to the safety and toxicity of Flixabi, and no additional non-clinical data are considered to be needed. In addition, many of the routine toxicological studies are not required for biosimilar products in line with the CHMP guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1).[2]

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety data are available from one Phase I clinical study with healthy volunteers and one Phase III clinical study for up to 78 weeks treatment with Flixabi or Remicade as summarised below:

- Study SB2-G11-NHV, a randomised, single-blind, three-arm, parallel group, single-dose study to compare the PK, safety, tolerability, and immunogenicity of 3 formulations of infliximab (Flixabi, EU Remicade, and US Remicade) in healthy adult subjects.
- Study SB2-G31-RA, a randomised, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, PK, and immunogenicity of Flixabi compared to Remicade in adult patients with moderate to severe RA despite methotrexate (MTX) therapy. Patients were enrolled in the study for up to 54 weeks after randomisation. The study also included an additional 24-week, randomised, double-blind, transition-extension period designed to investigate the safety, tolerability, immunogenicity, and efficacy of Flixabi in patients with RA who transitioned from the EU Remicade arm, compared with patients who maintained Remicade treatment after Week 54. In addition, the long-term safety, tolerability, immunogenicity, and efficacy of Flixabi in patients with RA who continued from the Flixabi arm after Week 54, compared with the Remicade arm were investigated. The transition-extension period, which was conducted from Week 54 to Week 78, has been completed.

Exposure data are presented separately for the healthy volunteer study (SB2-G11-NHV) because subjects received a single dose of Flixabi only. For this reason, exposure data are not tabulated for study SB2-G11-NHV, but are summarised in the paragraph below.

In study SB2-G11-NHV, 159 subjects were assigned in a 1:1:1 ratio to either Flixabi (n=53), EU Remicade (n=53), or US Remicade (n=53). All randomised subjects received a single dose of 5 mg/kg infliximab in the form of Flixabi, EU Remicade, or US Remicade, and were followed up until 10 weeks for PK assessment and safety monitoring. The majority of subjects exposed to Flixabi were male (n=49) and all except 2 subjects were white. The age of subjects exposed to Flixabi ranged from 19 to 55 years.

Exposure data in patients are available from a single Phase III clinical study in patients with RA. In the study SB2-G31-RA, patients with moderate to severe RA who had had an inadequate response to MTX and who had been on a stable dose of MTX for at least 4 weeks before screening were randomised in a 1:1 ratio to receive either Flixabi 3 mg/kg (n=290) or EU Remicade 3 mg/kg (n=293). Flixabi or Remicade was administered via a 2-hour IV infusion at Weeks 0, 2, 6, and then every 8 weeks until Week 46. From Week 30, the dose level was allowed to increase step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks if the patient's RA symptoms were not well controlled by the existing dose. Flixabi or EU Remicade was co-administered with oral or parenteral MTX (10-25 mg/week) and folic acid (5-10 mg/week). Patients who meet pre-defined criteria will continue in the randomised, double-blind, transition-extension period, which consists of an additional 24 weeks of treatment. In the transition-extension period, patients receiving Remicade were randomised again in a 1:1 ratio to either continue on Remicade or be transitioned to Flixabi at Week 54, up to Week 70. Patients receiving Flixabi continued to receive extended Flixabi treatment up to Week 70. Patients

received 3 to 7.5 mg/kg of either Flixabi or Remicade every 8 weeks via IV infusion for 2 hours. The dose level could be increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks, if the patient's RA symptoms were not well controlled from the existing dose. The transition-extension period study has been completed and all of the study data of up to 78 weeks is included in this version of the RMP.

Exposure to Flixabi in the randomised, double-blind, Phase III study is presented by duration of exposure in Table SIII. 1, by age group and gender in Table SIII. 2, and by ethnic or racial origin in Table SIII. 3. Exposure is not presented by special populations (e.g., pregnant women, lactating women, renal impairment, hepatic impairment, cardiac impairment, and immunocompromised) because these populations have been excluded from the clinical studies.

Table SIII. 1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	**Patients**	**Person time**
Up to 3 months	384	92.6
3-6 months	361	68.8
6-9 months	246	60.2
9-12 months	231	54.0
12-15 months	201	47.8
15-18 months	186	18.8
Total person time		342.3

Table SIII. 2: Age group and gender

Age group	**Patients**		**Person time**	
	M	**F**	**M**	**F**
≥ 18 to < 65 years	62	269	58.5	237.3
≥ 65 to < 75 years	14	38	12.5	32.6
≥ 75 years	0	1	-	1.4
Total person time			71.0	271.3

Table SIII. 3: Ethnic origin

Ethnic origin	Patients	Person time
White	339	305.1
Asian	43	35.4
Other	2	1.8
Total	384	342.3

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

The clinical development programme for Flixabi as a proposed biosimilar to Remicade (infliximab) comprised of Phase I and Phase III clinical studies. The first study was a randomised, single-blind, three-arm, single-dose study to compare the PK, safety, tolerability, and immunogenicity of Flixabi, EU Remicade, and US Remicade in healthy adult subjects (study SB2-G11-NHV). The second was a Phase III, randomised, double-blind, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of Flixabi compared to Remicade over 54 weeks in patients with moderate to severe RA despite MTX therapy (study SB2-G31-RA). The study included a randomised, double-blind, transition-extension period consisting of an additional 24 weeks designed to evaluate the safety, tolerability, immunogenicity, and efficacy of Flixabi in patients with RA who transitioned from the Remicade arm, compared with patients who maintained Remicade treatment after Week 54. In addition, the long-term safety, tolerability, immunogenicity, and efficacy of Flixabi in patients with RA who continued from the Flixabi arm after Week 54, compared with the Remicade arm, were also investigated.

In the healthy volunteer Phase I study, inclusion and exclusion criteria were designed to ensure that the study population were healthy and homogenous to clarify any risks associated with the study and enable appropriate comparison of the PK, safety, tolerability, and immunogenicity of Flixabi and Remicade. Healthy male or female (non-child bearing potential) subjects aged 18-55 years with all screening results within the normal range (or outside the normal range but not clinically significant) were included in the study. The following conditions or disorders that could increase the risks of the study or confound evaluations were excluded:

- History and/or current presence of clinically significant atopic allergy, hypersensitivity, or allergic reactions, including known or suspected clinically relevant drug hypersensitivity to any components of the test and reference investigational product (IP) formulation or comparable drugs
- Active or latent tuberculosis (TB) or history of TB
- History of invasive systemic fungal infections or other relevant opportunistic infections, including local fungal infections or a history of herpes zoster
- Any systemic or local infection, a known risk for developing sepsis and/or known active inflammatory process within 6 months prior to the first administration of IP
- Serious infection within 6 months prior to the first administration of IP
- History of and/or current cardiac disease
- History of and/or current significant gastrointestinal, renal, hepatic, cardiovascular, haematological, metabolic, or pulmonary disease classed as significant by the investigator

- History of cancer including lymphoma, leukaemia, and skin cancer
- Impaired liver function
- History of immunodeficiency including a positive test for human immunodeficiency virus (HIV)
- Any clinically significant illness within 4 weeks prior to screening
- A serious mental disease

Other exclusion criteria included previous treatment with infliximab, receipt of live vaccine(s) within 30 days prior to screening or requiring live vaccine(s) between screening and the final study visit, alcoholic beverage intake of more than 28 units per week, evidence of drug abuse as indicated by a positive urinary drug screening at screening and/or baseline, intake of medication with a half-life > 24 hours within 1 month or 10 half-lives of the medication prior to the first administration of IP, donation of > 100 mL blood within 4 weeks before the first administration of IP, participation in another study with an investigational drug within 1 month prior to first treatment, receipt of a biological or immunosuppressive agent within 3 months of screening, subjects who were not likely to complete the study, anyone directly involved in the conduct of the study (or a relative thereof), vulnerable subjects, or pregnant and nursing women.

The Phase III clinical study included male or female patients aged 18-75 years who had been diagnosed (at least 6 months before screening) as having moderate to severe active RA despite MTX therapy and who had been treated with MTX for at least 6 months before randomisation and were on a stable dose of MTX (10-25 mg/week) for at least 4 weeks prior to screening. Female patients were only eligible for inclusion if they were not pregnant or nursing at screening and were not planning to become pregnant during the study.

In general, exclusion criteria included any major illness/condition or any serious disorder that would increase the risks associated with the study or confound the evaluation of the effect of Flixabi treatment. These included the following conditions/disorders:

- Bone marrow hypoplasia
- Significant systemic RA involvement
- Other inflammatory or rheumatic diseases
- History of any malignancy within the 5 years before screening
- History of lymphoproliferative disease including lymphoma
- History of congestive heart failure (CHF) (NYHA Class III/IV) or unstable angina
- Uncontrolled diabetes mellitus or uncontrolled hypertension
- History of organ transplantation
- Physical incapacitation
- History of demyelinating disorders
- Any conditions significantly affecting the nervous system which may have interfered

with the investigator's assessment on disease activity scores including joint counts.

- History of serious infection or treatment with antibiotics for an infection within 8 weeks (IV) or 2 weeks (oral) of randomisation
- A history of chronic or recurrent infection
- A history of infected joint prosthesis which had not been removed or replaced
- Positive serological test for hepatitis B or C or a known history of HIV infection
- Active TB, recent exposure to TB, or evidence of latent TB

Subjects with latent TB could be enrolled in the study if the patient underwent TB prophylaxis according to country-specific guidelines for at least 1 month and continued the remaining course thereafter.

Other exclusion criteria included known hypersensitivity to human Ig proteins or other components of Flixabi or Remicade, previous treatment with any biological agents including TNF-inhibitors, treatment with prohibited concomitant medications within specified timeframes (including live/live-attenuated vaccine within 8 weeks before randomisation), haematological abnormalities or abnormal renal or hepatic function, and any substance abuse (alcohol or drug) problem within the 3 years before screening.

For the transition-extension period, the main exclusion criteria are any significant medical conditions, such as an occurrence of a serious adverse event (SAE) or intolerance of Flixabi or Remicade during the randomised, double-blind period, which may render the patient unsuitable to participate in the study at the discretion of the investigator, and treatment or planned treatment with prohibited medications including live/live-attenuated vaccine or biological agents other than Flixabi or Remicade.

During the study periods, 'importance' of individual exclusion criterion was not discussed. Also, whether or not each criterion is subject for 'missing information' was not assessed. Instead, as a biosimilar of Remicade, missing information of Flixabi is aligned with that of reference product, based on the EMA guide on similar biological medicinal products.

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 rare/very rare adverse reactions, adverse reactions with a prolonged exposure/long latency, dose-related reactions, and the reactions occur in other claimed indications (adult/paediatric CD, adult/paediatric UC, adult AS, adult PsA, and adult psoriasis).

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

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Children</td><td>Not included in the clinical development program</td></tr>
<tr><td>Elderly

The pivotal Phase III study to evaluate the efficacy, safety, PK, and immunogenicity of Flixabi compared to Remicade in patients with RA included patients up to 75 years of age. No difference in response to Flixabi in the elderly population has been identified.</td><td>
<table>
<tr><th rowspan="2">Age group</th><th colspan="2">Patients</th><th colspan="2">Person Time</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>≥ 65 to < 75 years</td><td>14</td><td>38</td><td>12.5</td><td>32.6</td></tr>
<tr><td>≥ 75 years</td><td>0</td><td>1</td><td>-</td><td>1.4</td></tr>
<tr><td>Total</td><td>14</td><td>39</td><td>12.5</td><td>34.0</td></tr>
</table>
</td></tr>
<tr><td>Pregnant women

Although prohibited by protocol, exposure to infliximab during pregnancy occurred. There was 1 subject from the Remicade treatment group who had a positive pregnancy test at Week 38. Following confirmation of the pregnancy, this subject withdrew from the study. The pregnant subject was exposed to Remicade from Jan 24 to Aug 20, 2014 and the date of last menstrual period was Jul 24, 2014. The subject delivered a 2.7 kg male baby via vaginal delivery (Apgar score 8 at 1 minute, 9 at 5 minutes) on April 16, 2015, and both the subject and the baby were reported to be in good condition.</td><td>1</td></tr>
<tr><td>Breastfeeding women</td><td>Not included in the clinical development program</td></tr>
<tr><td>Patients with relevant comorbidities:
• Patients with hepatic impairment
• Patients with renal impairment
• Patients with cardiovascular impairment (including NYHA class III or IV CHF)
• Patients with other relevant co-morbidity (including history of organ transplantation)
• Immunocompromised patients
• Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Not included in the clinical development program</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin

Most subjects enrolled in the two clinical studies (SB2-G11-NHV and SB2-G31-RA) were Caucasian in origin (all but 4 subjects in study SB2-G11-NHV and 86.6% of the Flixabi-treated patients in study SB2-G31-RA) but these studies also enrolled subjects of other racial or ethnic origins. There are no known obvious safety or tolerability differences with regard to race and/or ethnic origin in infliximab.</td><td>
<table>
<tr><th>Ethnic origin</th><th>Patients</th><th>Person time</th></tr>
<tr><td>White</td><td>339</td><td>305.1</td></tr>
<tr><td>Asian</td><td>43</td><td>35.4</td></tr>
<tr><td>Other</td><td>2</td><td>1.8</td></tr>
<tr><td>Total</td><td>384</td><td>342.3</td></tr>
</table>
</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
</table>

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Exposure has been estimated based on international sales data, based on the below presented assumptions:

- Flixabi is available as powder for concentrate for solution for infusion. One vial contains 100 mg of infliximab.
- Flixabi is sold per unit. Each unit is 1 vial/pack.
- The Defined Daily Dose (DDD) for infliximab is 3.75 mg.
- The number of patient-days can be estimated as total number of units sold × 100 mg (dose per vial)/3.75 mg (DDD), and the patient-years is calculated as patient-days/365.25.

SV.1.2 Exposure

Cumulatively from the International Birth Date (IBD) on December 04, 2015 through Jul 31, 2023, the patient exposure was about 588,306 patient-years of treatment for Flixabi.

Table SV.1 Exposure Table by Region

Country	Trade Name	Number of Units Sold	Total Number of Patient-Years
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Country	Trade Name	Number of Units Sold	Total Number of Patient-Years
[redacted]			

[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential of misuse for illegal purposes is low.

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

Not applicable as the risks are aligned with those of the reference product.

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

Based on the EMA guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both Flixabi and the reference product, Remicade.

Important identified risks	Important potential risks	Missing information
• Serious infection/sepsis • Demyelinating disorders • BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi • Malignancy	• Colon carcinoma/dysplasia (in paediatric UC)	None

In addition to the above, “immunogenicity” has been included as an important potential risk of Flixabi as per the request from the EMA, although immunogenicity profile was considered comparable between the treatment groups from SB2-G31-RA study.

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

There were no new safety concerns found from the last version to the data lock point.

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

Based on the EMA guide on similar biological medicinal products, the RMP should take into account identified and potential risks associated with the use of the reference product. Therefore, this section will contain all the important identified risks and important potential risks described in the RMP for the reference product, Remicade, and from the scientific literature.

The SB2-G31-RA study was conducted in patients with moderate to severe RA and it has been concluded that the Flixabi safety profile was comparable with that of Remicade.

Although immunogenicity profile was considered comparable between the treatment groups, "immunogenicity" has been included as an important potential risk as per the request from the EMA. In addition, "BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi" was also included as an important identified risk, following the EMA recommendation.

The reference product, Remicade, has been used in clinical practice for more than 10 years and the risk profile is well known.

For each risk presented in this section, the clinical trial safety database was searched for specified events using Standardised Medical Query (SMQ)/High level group terms (HLGTs), PTs, High level terms (HLTs), and search stems for that risk based on Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. (Refer to Annex 7 for the specific adverse event terms and/or stems used for risks analysis.)

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

SVII.3.1.1 Important identified risk

Serious infection/sepsis

Potential mechanisms:

Serious infection/sepsis
TNF-α mediates inflammation and modulates cellular immune responses. Experimental data show that TNF-α is essential for the clearing of intracellular infections.[4]
TNF plays significant roles in the regulation of the immune system, including systemic inflammation, host defence, and organogenesis. Reduction of TNF levels by infliximab may result in the inhibition of such beneficial TNF response to pathogenic organisms. Sepsis, an infection-induced immune response, is characterized by both a pro-inflammatory cytokines such as TNF and IL-1 and an anti-inflammatory cytokines such as IL-10 and TGF-beta. In abdominal sepsis (i.e., cecal ligation and puncture) in gene targeted mice, the injection of TNF has shown to exert a protective effect against a bacterial superinfection. Thus, TNF inhibitors such as infliximab may suppress the beneficial effects of TNF and increase the potential for bacterial infection.[14]

HBV reactivation
TNF-α is known to play a role in host immune response to HBV and HBV replication, thus making anti-TNF-α drugs possible promoters of HBV reactivation.[3]

Opportunistic infections
TNF-α plays an important role in the maintenance of lymphoid microarchitecture, and also generates optimal cellular, humoral, and phagocytic responses, particularly for intracellular pathogens. Host defense against pathogens is severely impaired in the absence of TNF.[14]
TNF-α prominently mediates inflammation and modulates cellular immune responses.

Experimental data show that TNF-α is essential for the clearing of intracellular infections.[4] The inhibition of TNF by infliximab may suppress the advantageous activities of TNF and lead to the increase of the potential for opportunistic infections.

TB
TNF blocking facilitates the progression from latent to active TB by interfering with different steps in the immune response against *mycobacterium tuberculosis*.[7] Animal studies have also shown that TNF-α plays a key role in the formation and maintenance of granulomas, which is an important part of TB infection resolution in the host.[13]

Evidence source(s) and strength of evidence:

Study SB2-G31-RA; SmPCs for Flixabi and Remicade, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

Serious infection/sepsis

- Frequency with 95% CI:

  Frequency in the Flixabi clinical study (SB2-G31-RA)

  There were 14 events of serious infections in 14 patients treated with Flixabi (subject incidence: 3.646%; 95% CI: 2.007, 6.041%), corresponding to an exposure adjusted event rate of 4.090 events per 100 patient-years (95% CI: 2.236, 6.863). There were 8 events of serious infections in 8 patients treated with Remicade (subject incidence: 2.730%; 95% CI: 1.186%, 5.309%), corresponding to an exposure adjusted event rate of 2.889 events per 100 patient-years (95% CI: 1.247, 5.693).

  Table SVII.3.1.1.5 Subject incidence and exposure-adjusted rate of serious infections including sepsis (excluding opportunistic infections and TB)

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	14 (3.646)	2.007, 6.041	342.277	14	4.090	2.236, 6.863
Remicade	293	8 (2.730)	1.186, 5.309	276.91	8	2.889	1.247, 5.693

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcome:

  All 14 events of the Flixabi treatment group were reported to be serious (4.090 events per 100 patient-years; 95% CI: 22.236, 6.863). Also, in the Remicade treatment

group, all 8 events were reported to be serious (2.889 events per 100 patient-years; 95% CI: 1.247, 5.693)

Table SVII.3.1.1.6 Subject incidence and exposure-adjusted rate of serious infections including sepsis (excluding opportunistic infections and TB) that were SAEs

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	14 (3.646)	2.007, 6.041	342.277	14	4.090	2.236, 6.863
Remicade	293	8 (2.730)	1.186, 5.309	276.910	8	2.889	1.247, 5.693

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Severity:

  In the Flixabi treatment group, 7 events of serious infections were reported to be severe in severity (2.045 events per 100 patient-years; 95% CI: 0.822, 4.214). In the Remicade treatment group, 4 events of serious infections were reported to be severe in severity (1.445 events per 100 patient-years; 95% CI: 0.394, 3.699).

Table SVII.3.1.1.7 Subject incidence and exposure-adjusted rate of serious infections including sepsis (excluding opportunistic infections and TB) that were severe

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	7 (1.823)	0.736, 3.720	342.277	7	2.045	0.822, 4.214
Remicade	293	4 (1.365)	0.373, 3.458	276.910	4	1.445	0.394, 3.699

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient: Serious infections can influence the patient's quality of life and overall health. Some of these infections might lead to hospitalisation, long-lasting antimicrobial therapy, and sometimes even result in death.

HBV reactivation

- Frequency with 95% CI: Frequency in the Flixabi clinical study (SB2-G31-RA) – Not applicable in the Flixabi study. Subjects with a positive serological test for hepatitis B or hepatitis C were to be excluded from the Flixabi study.

- Seriousness/outcome: Not applicable in the Flixabi study

- Severity: Not applicable in the Flixabi study

- Impact on individual patient: HBV reactivation may affect a patient's physical functioning and lifespan and have a severe effect on the patient's quality of life. The need

to take antiviral therapy, including IFN-α injections and related ADRs may also negatively affect patient's quality of life.

Opportunistic infections

- Frequency with 95% CI:

  Frequency in the Flixabi clinical study (SB2-G31-RA)

  There were 8 events of opportunistic infections (3 events of oral herpes, 3 events of herpes zoster and 2 events of herpes virus infection) in 7 patients treated with Flixabi (subject incidence: 1.823%; 95% CI: 0.736%, 3.720%), corresponding to an exposure adjusted event rate of 2.337 events per 100 patient-years (95% CI: 1.009, 4.605). There were 9 events of opportunistic infections (6 events of oral herpes, 2 events of herpes zoster, and 1 event of atypical mycobacterial pneumonia) in 6 patients treated with Remicade (subject incidence: 2.048%; 95% CI: 0.755%, 4.404%). This corresponded to an exposure adjusted event rate of 3.250 events per 100 patient-years (95% CI: 1.486, 6.170).

Table SVII.3.1.1.4 Subject incidence and exposure-adjusted rate of opportunistic infections

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	7 (1.823)	0.736, 3.720	342.277	8	2.337	1.009, 4.605
Remicade	293	6 (2.048)	0.755, 4.404	276.910	9	3.250	1.486, 6.170

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcome:

  There were no serious events of opportunistic infections reported in the Flixabi or Remicade treatment groups (SB2-G31-RA).
  The outcome of all 8 events of opportunistic infections reported in the Flixabi treatment group was resolved. In the Remicade treatment group, the outcome of 8 events was resolved and 1 event (atypical mycobacterial pneumonia) was unknown.

- Severity: There were no severe events of opportunistic infections reported in the Flixabi or Remicade treatment groups (SB2-G31-RA).

TB

- Frequency with 95% CI:

  Frequency in the Flixabi clinical study (SB2-G31-RA)

  There were 41 events of TB (40 events of latent TB and 1 event of tuberculous pleurisy) in 32 patients treated with Flixabi (subject incidence: 8.333%; 95% CI:

5.770%, 11.561%), corresponding to an exposure adjusted event rate of 11.979 events per 100 patient-years (95% CI: 8.596, 16.250). There were 25 events of TB (24 events of latent TB and 1 event of pulmonary TB) in 23 patients treated with Remicade (subject incidence: 7.850%; 95% CI: 5.041%, 11.546%). This corresponded to an exposure adjusted event rate of 9.028 events per 100 patient-years (95% CI: 5.843, 13.327).

Table SVII.3.1.1.8 Subject incidence and exposure-adjusted rate of TB

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	32 (8.333)	5.770, 11.561	342.277	41	11.979	8.596, 16.250
Remicade	293	23 (7.850)	5.041, 11.546	276.910	25	9.028	5.843, 13.327

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcome:

The event of tuberculous pleurisy in the Flixabi treatment group was reported to be serious (0.292 events per 100 patient-years; 95% CI: 0.007, 1.628).

Table SVII.3.1.1.9 Subject incidence and exposure-adjusted rate of TB that were SAEs

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	1 (0.260)	0.007, 1.442	342.277	1	0.292	0.007, 1.628
Remicade	293	N/A	N/A	N/A	N/A	N/A	N/A

[a] Subject incidence = N1/N × 100.
[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the 41 events of TB in the Flixabi treatment group, 26 events were resolved, 6 events were resolving, 6 events were not resolved, and 3 events were unknown. Of the 25 events of TB in the Remicade treatment group, 11 events were resolved, 5 events were resolving, 6 events were not resolved, and 3 events were unknown.

- Severity:

The event of tuberculous pleurisy in the Flixabi treatment group was reported to be severe in severity (0.292 events per 100 patient-years; 95% CI: 0.007, 1.628).

Table SVII.3.1.1.10 Subject incidence and exposure-adjusted rate of TB that were severe

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI

Flixabi	384	1 (0.260)	0.007, 1.442	342.277	1	0.292	0.007, 1.628
Remicade	293	N/A	N/A	N/A	N/A	N/A	N/A

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Risk factors and risk groups:

Serious infection/sepsis

Combined use of immunosuppressants is associated with an increased risk of serious infections.[6] The risk factors include age > 65 years, concomitant use of abatacept, and MTX.[3,4]

HBV reactivation

Immune suppression, including in patients receiving chemotherapy and immunosuppressive therapy, is seen as a high risk factor in hepatitis B surface antigen (HBsAg)-positive patients.[9] Prophylaxis with entecavir or tenofovir for 6 to 12 months after the end of immunosuppressive therapy is deemed mandatory in these patients. Additionally, screening and vaccination is recommended in serologically negative cases for patients with IBD to prevent HBV reactivation.[10]

In a recent study, HBsAg together with detectable HBV DNA, rituximab administration or treatment with steroids were shown to be independent risk factors leading to HBV reactivation.[11]

HBV reactivation risk in HBsAg negative patients was assessed at the level of 3-10% in a study of 244 lymphoma patients by Hui et al. Mainly this was attributed to the concomitant administration of rituximab and steroid drugs.[12]

Opportunistic infections

The risk factors include age > 65 years and concomitant use of abatacept, and MTX. Patients suffering from chronic infections or who have a history of recurrent infections, or patients who have travelled or lived in endemic areas for histoplasmosis, blastomycosis, etc., might constitute a risk group for opportunistic infections.

TB

Particular immune compromised groups, such as HIV patients and patients receiving immunosuppressive therapy, are at higher risk for TB infection, as well as TB reactivation.[15] The risk factors include age > 65 years, concomitant use of abatacept, and MTX.[3]

Preventability:

Serious infection/sepsis

Severe infections such as sepsis and abscesses are marked contraindications for Flixabi and infliximab.[4] There are no current guidelines for prevention of infection in patients receiving biologics.[8] Patients are advised to avoid exposure to potential risk factors for infection as appropriate.[4] warning message is added to the Flixabi SmPC with advice for patients to avoid exposure to potential risk factors for infection as appropriate.

Suppression of TNF-α may mask symptoms of infection such as fever. Early recognition of

atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.[3,4]

HBV reactivation
According to the recent guidelines, patients planned to undergo immunosuppressive therapy should be screened for HBsAg and anti-hepatitis B core antigen (HBc), and HBV DNA load should be measured in patients prior to initiation of treatment (in HbsAg-positive and HBsAg-negative patients with positive anti-HBc antibodies). Antiviral therapy, regardless of the HBV DNA level, for the duration of treatment and for 12 months after cessation of treatment should be initiated in HbsAg-positive patients and in HBsAg-negative patients who are anti-HBc positive with detectable serum HBV DNA. HBsAg-negative, anti-HBc positive patients undergoing immunosuppressive therapy with undetectable serum HBV DNA and regardless of anti-HBs status should be followed carefully by means of ALT and HBV DNA testing. Treatment will be initiated in case of HBV reactivation confirmation prior to ALT elevation. The check-up frequency ranges from 1 to 3 months, depending on the type of immunosuppressive therapy and comorbidities.[9] HBV testing prior to initiation of treatment with Flixabi is included in the Flixabi SmPC. Consultation with a physician experienced in the treatment of Hepatitis B in HBV-positive patients is also recommended. HBV carriers requiring treatment with Flixabi are to be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.[4]

Opportunistic infections
Opportunistic infections are marked contraindications for Flixabi and infliximab.[4] There are no current known guidelines for prevention of infection in patients receiving biologics.[8] Patients are advised to avoid exposure to potential risk factors for infection as appropriate.[3,4] A warning message is added to the Flixabi SmPC with advice for patients to avoid exposure to potential risk factors for infection as appropriate.
Suppression of TNF-α may mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.[3,4]

TB
Infliximab is contraindicated in active TB. As per the Flixabi SmPC, patients are to be carefully evaluated for presence of TB infection prior to start of therapy with Flixabi. Consultation with a physician experienced in treating TB is required prior to therapy initiation in patients with latent or inactive TB.[4]
Guidelines for TB prevention in patients receiving biologic treatment, including TNF-α blockers, published by different professional organisations include activities for patient screening prior to therapy initiation, as well as recommendations on treatment and follow-up for patients with latent TB.[15]

<u>Impact on the risk-benefit balance of the product:</u>

Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures of the reference product are well-established, and Flixabi is well-aligned with the risk management/mitigation plan as a biosimilar.

Public health impact:

The masked clinical signs of infection and characteristic of opportunistic infection in immunocompromised patients have additional impact on early diagnostics and treatment of these infections. The potential development of bacterial infections, including serious ones and sepsis, could lead to extensive use of antibiotics in the patient population and development of resistant bacterial cultures. The potential public health impact of HBV reactivation and TB is not known.

Demyelinating disorders

Potential mechanisms: TNF blockade augments the number of peripheral T cells which in turn enhances auto-immune responses by changing the function of antigen presenting cells, potentiating signalling of T-cell receptor and/or reducing the apoptosis of autoreactive T-cells. Consequently, these T-cells lead to maturation of B-cells to those secreting autoantibodies to neuronal specific antigens. This sequence of events leads to development of drug-induced neuropathies. [16]

Evidence source(s) and strength of evidence: Study SB2-G31-RA; Flixabi SmPC, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI:

  Frequency in the Flixabi clinical study (SB2-G31-RA)

  There were 1 event of demyelinating disorder in 1 patient treated with Flixabi (subject incidence: 0.260%; 95% CI: 0.007%, 1.442%), corresponding to an exposure adjusted event rate of 0.292 events per 100 patient-years (95% CI: 0.007, 1.628). There were no events of demyelinating disorders treated with Remicade.

Table SVII.3.1.1.14 Subject incidence and exposure-adjusted rate of demyelinating disorders

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	1 (0.260)	0.007, 1.442	342.277	1	0.292	0.007, 1.628
Remicade	293	N/A	N/A	N/A	N/A	N/A	N/A

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Seriousness/outcome:

None of the demyelinating disorders in the Flixabi study (SB2-G31-RA) were reported to be serious. The outcome of 1 event (demyelination) in the Flixabi treatment group was unknown.

- Severity: There were no severe events of demyelinating disorders in either the Flixabi or Remicade treatment groups.

- Impact on individual patient: Central and peripheral demyelinating disorders can impact significantly on a patient's quality of life due to the severe nature of the symptoms of MS, Guillain-Barré syndrome, etc. These disorders may lead to patient disability as well as increased morbidity and mortality.

Risk factors and risk groups: Patients with pre-existing MS or Guillain-Barré syndrome belong to the high-risk group. Additionally, first-degree relatives of patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36, evidence strongly suggesting that TNF inhibitors should not be used in first-degree relatives of patients with MS. [17]

Preventability: According to the Flixabi SmPC, in patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be considered carefully prior to initiating treatment with infliximab. Discontinuation of Flixabi should be considered if these disorders develop.[4]
In the guidelines for management of psoriasis and PsA 2008 by the American Academy of Dermatology Inc., it is reported that there is an association between anti-TNF therapy and demyelinating diseases such as MS.[17] Use of TNF inhibitors should be avoided in patients with MS or other demyelinating diseases.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The potential public health impact is unknown.

BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi

Potential mechanisms: Due to its inhibition of TNF-α, infliximab administered during pregnancy could affect normal immune responses in the newborn. Infliximab crosses the placenta and has been detected in the serum of infants up to 6 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal.[3,4]

Evidence source(s) and strength of evidence: SmPCs for Flixabi and Remicade Section 4.4 'Special warnings and precautions for use' and Section 4.6 "Fertility, pregnancy and lactation"; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory

requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Frequency in the Flixabi clinical study (SB2-G31-RA) – There were no reports of BCG breakthrough infection and agranulocytosis in either the Flixabi or Remicade treatment groups.

- Seriousness/outcome: There were no reports of BCG breakthrough infection and agranulocytosis in either the Flixabi or Remicade treatment groups.

- Severity: There were no reports of BCG breakthrough infection and agranulocytosis in either the Flixabi or Remicade treatment groups.

- Impact on individual patient: Both the infant and the family's quality of life may be significantly impacted.

Risk factors and risk groups: Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth. Cases of agranulocytosis have also been reported (see section 4.8).[3,4]

Preventability: Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Flixabi treatment.
When using TNF inhibitors, it is prudent to discontinue treatment around the third trimester when transfer across the placenta is greatest, and to restart postpartum.[18]
A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab.[3,4] If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. (see section 4.6).

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: Information on the public health impact is not available.

Malignancy

Potential mechanisms:

Malignancy
The exact mechanism is unknown, but TNF-α plays an important role in the immune response. Therefore, it might be proposed that suppression of TNF-α with a TNF-α blocking

agent such as infliximab might contribute to a reduced immune response increasing the risk of malignancy development

Lymphoma
The exact mechanism is unknown, but TNF-α plays an important role in the immune response. Therefore, it might be proposed that suppression of TNF-α with a TNF-α blocking agent such as infliximab might contribute to a reduced immune response increasing the risk of developing malignancies such as lymphoma. In addition, as TNF-α induces apoptosis and plays a role in tumour suppression, anti-TNF-α monoclonal antibodies were considered to increase the risk of cancer.[19]

HSTCL
Literature evidence suggests that HSTCL is associated with immunodeficiency. The two mechanisms involved in increased incidence of cancers in immunosuppressed patients include: (i) decreased immunosurveillance due to inhibition of TNF signalling, where the risk is higher during T-cell immunosuppression and the latency period is short for the associated malignancies and (ii) exposure to the immunosuppressant such as AZA/6-MP therapies, which can cause cellular damage or chromosomal abnormalities.[20]

Paediatric malignancy
TNF-α exhibits a crucial role in the body's immune response. Among paediatric patients, the immune system is not completely developed. Hence, suppression of TNF-α in the body may have a greater impact for developing malignancies in children.
The permeability of tumour blood vessels increases in the presence of TNF (low dose). This increases the tissue concentration of chemotherapeutic agents and enhances the cytotoxicity of natural killer and CD8+ T-cells, thereby destroying immunogenic tumour cells.[21]
Administration of infliximab may cause neutralisation of TNF and allow certain tumour cells to survive.

Leukaemia
The exact mechanism is unknown. TNF-α plays a vital role in generating immune responses. Inhibition of TNF-α activity by blocking agents such as infliximab might contribute to a reduced immune response, which may allow some tumour cells to survive and hence, increase the possibility of developing haematological malignancies including leukaemia.

Evidence source(s) and strength of evidence:

Study SB2-G31-RA; SmPCs for Flixabi and Remicade, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications.
Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI:

Frequency in the Flixabi clinical study (SB2-G31-RA)

There were 7 events of malignancy (excluding lymphoma, HSTCL, leukaemia, skin cancer including melanoma and Merkel cell carcinoma, and cervical cancer) in 7 patients treated with Flixabi (subject incidence: 1.823%; 95% CI: 0.736%, 3.720%): breast cancer, brain neoplasm, prostate cancer, eye naevus, lip and/or oral cavity cancer, thyroid neoplasm and gastrointestinal submucosal tumour. Among these events, brain neoplasm was reported based on brain MRI and CT findings and was not a confirmed diagnosis, implying that the possibility of malignancy is considered low. Gastrointestinal submucosal tumour is also considered unlikely to be a malignancy according to its clinical features. The events corresponded to an exposure adjusted event rate of 2.045 events per 100 patient-years (95% CI: 0.822, 4.214). There was 1 event (papillary thyroid cancer) of malignancy in 1 patient treated with Remicade (subject incidence: 0.341%; 95% CI: 0.009%, 1.887%). This corresponded to an exposure adjusted event rate of 0.361 events per 100 patient-years (95% CI: 0.009, 2.012).

Table SVII.3.1.2.1 Subject incidence and exposure-adjusted rate of malignancy

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	7 (1.823)	0.736, 3.720	342.277	7	2.045	0.822, 4.214
Remicade	293	1 (0.341)	0.009, 1.887	276.910	1	0.361	0.009, 2.012

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

There were no reports of lymphoma, HSTCL, leukaemia, melanoma, Merkel cell carcinoma, or cervical cancer in either the Flixabi or Remicade treatment groups.

- Seriousness/outcome:

Of the 7 events of the Flixabi treatment group, 4 events (breast cancer, brain neoplasm, lip and/or oral cavity cancer and prostate cancer) were reported to be serious (1.169 events per 100 patient-years; 95% CI: 0.318, 2.992). None of the events in the Remicade treatment group were reported to be serious.

Table SVII.3.1.2.2 Subject incidence and exposure-adjusted rate of malignancy that were SAEs

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	4 (1.042)	0.285, 2.645	342.277	4	1.169	0.318, 2.992
Remicade	293	N/A	N/A	N/A	N/A	N/A	N/A

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

Of the 7 malignancies in the Flixabi treatment group, 2 events (breast cancer and lip and/or oral cavity cancer) were resolved, 1 event (thyroid neoplasm) was resolving, 3 events (prostate cancer, eye naevus and gastrointestinal submucosal tumour) were not recovered and 1 event (brain neoplasm) was unknown.

- Severity:

The 2 events (brain neoplasm and prostate cancer) of the Flixabi treatment group were reported to be severe in severity (0.584 events per 100 patient-years; 95% CI: 0.071, 2.111). The 1 event (papillary thyroid cancer) of the Remicade group was reported to be severe in severity (0.361 events per 100 patient-years; 95% CI: 0.009, 2.012).

Table SVII.3.1.2.3 Subject incidence and exposure-adjusted rate of malignancy that were severe

Drug	Total subjects N	No. of subjects with event N1 (%)[a]	95% CI of event rate	Exposure (patient-years) E	No. of events n	Exp-adj event rate[b]	Exp-adj rate 95% CI
Flixabi	384	2 (0.521)	0.063, 1.869	342.277	2	0.584	0.071, 2.111
Remicade	293	1 (0.341)	0.009, 1.887	276.910	1	0.361	0.009, 2.012

[a] Subject incidence = N1/N × 100.

[b] Exposure-adjusted (Exp-adj) event rate per 100 patient-years = n/E × 100.

- Impact on individual patient: Malignancy can affect a patient's physical functioning and lifespan and have a severe effect on the patient's quality of life. The diagnosis of malignancy may lead to fear about the effects of malignancy and can also cause psychological distress. Factors such as tolerance to treatment and degree of social and emotional support might impact the patient's quality of life.

<u>Risk factors and risk groups:</u>

Malignancy
Patients with a history of malignancies. Patients with increased risk of malignancies due to heavy smoking. When considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[3,4]

Lymphoma
There is an increased background risk for lymphoma and leukaemia in RA patients with long standing, highly active, inflammatory disease.[3,4]
Studies by Askling et al.[22] and Baecklund et al.[23] have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease.
In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more

comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma.[24]

HSTCL
The vast majority of HSTCL cases with infliximab use have occurred in patients with CD or UC and most were reported in adolescents or young adult males. Almost all patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) concomitantly with or immediately prior to infliximab. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered, as the risk for development of HSTCL among such patients cannot be excluded.[3,4]

Paediatric malignancy
According to the Remicade and Flixabi SmPCs, children and adolescents exposed to infliximab are the risk groups.[3,4] Underlying autoimmune disease and concomitant use of immunosuppressants could increase the risk of malignancies among patients on infliximab; however, a clear causal relationship could not be established.[25]

Leukaemia
According to the Remicade and Flixabi SmPCs, patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after infliximab treatment. Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.[3,4]

Melanoma
Patients with risk factors for skin cancer. Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[3,4]

Merkel cell carcinoma
Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma.[26]

Cervical cancer
A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age.[3,4]

Preventability: According to Section 4.4 ‘Special warnings and precautions for use’ of the Flixabi SmPC, caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Caution should be exercised when considering treatment of patients with increased risk for malignancy due to heavy smoking.[3,4] Furthermore, for prevention of HSTCL the potential risk of administering infliximab in combination with AZA or 6-MP amongst patients with IBD including CD or UC should be carefully assessed.[3,4]

For prevention of melanoma and Merkel cell carcinoma, periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.[3,4] Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.. All patients treated with anti-TNF should be protected against UV radiation and receive a dermatologic examination before starting therapy and once a year thereafter.[27]

For prevention of cervical cancer, periodic screening for cervical cancer should continue in wo men treated with infliximab, including those over 60 years of age.[3,4]

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the pro duct is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The public health impact is not known.

SVII.3.1.2 Important potential risks

Colon carcinoma/dysplasia (in paediatric ulcerative colitis)

Potential mechanisms: The exact mechanism is unknown, but TNF-α plays an important role in the immune response. Therefore, it might be proposed that suppression of TNF-α with a TNF-α blocking agent such as infliximab might contribute to a reduced immune response increasing the risk of colon carcinoma/dysplasia development.

Evidence source(s) and strength of evidence: SmPCs for Flixabi and Remicade, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Characterisation of the risk:

- Frequency with 95% CI: Flixabi has not been studied in paediatric patients with UC.
- Seriousness/outcome: No data are available.
- Severity: No data are available.
- Impact on individual patient: The diagnosis of colon carcinoma or dysplasia may lead to fear about the effects of malignancy and can also cause psychological distress. Factors such as tolerance to treatment and degree of social and emotional support might impact the patient's quality of life.

Risk factors and risk groups: Patients with a history of malignancies, with long-standing UC or PSC, with a family history of colorectal cancer.

Preventability: All patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or PSC), or 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. This evaluation should include colonoscopy and biopsies per local recommendations.
Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits to the individual patients must be carefully reviewed and consideration should be given to discontinuation of therapy.[3,4]

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The public health impact is not known.

Immunogenicity

Potential mechanisms: There is no identified factor to contribute to the potential immunogenicity difference between Flixabi and the reference product. More information will be collected during the post authorisation period.

Evidence source(s) and strength of evidence: Not applicable as the information follows the regulatory recommendation for Flixabi as a biosimilar. In SB2-G31-RA study, the immunogenicity of Flixabi group showed no statistically-meaningful difference in ADA positivity compared to other groups.

Characterisation of the risk:

- Frequency with 95% CI:

  Frequency in the Flixabi clinical study (SB2-G31-RA)

  For overall ADA that developed from Week 0 up to Week 78, there was no statistically significant difference between treatment groups in the proportion of subjects with ADA positive results against Flixabi between the Flixabi/Flixabi vs. Remicade/Flixabi treatment groups (p-value = 0.601), Flixabi/Flixabi vs. Remicade/Remicade treatment groups (p-value = 0.373) and Remicade/Flixabi vs. Remicade/Remicade treatment groups (p-value = 0.770), with 133 (66.2%) subjects in the Flixabi/Flixabi treatment group, 59 (62.8%) subjects in the Remicade/Flixabi treatment group and 61 (60.4%) subjects in the Remicade/Remicade treatment group reporting an overall ADA positive result from Week 0 up to Week 78.
  For overall ADA that developed during from Week 54 to Week 78, the incidence is 53.6% for Flixabi/Flixabi, 45.7% for Remicade/Flixabi and 50.5% for the Remicade/Remicade treatment group.
  It is noted that the baseline overall ADA result up to Week 54 for the extended safety set for the 3 treatment groups was not the same (60.7% for the Flixabi/Flixabi treatment group, 56.4% for the Remicade/Flixabi treatment group and 53.5% for the Remicade/Remicade treatment group). Therefore, the fact that the ADA incidence for the Remicade/Flixabi treatment group lies between the incidences for the Flixabi/Flixabi treatment group and the Remicade/Remicade treatment group at Week 78 does not mean that the transition led to an increased immunogenicity by Flixabi.

Table SVII.3.1.2.7 Incidence of anti-drug antibodies and neutralising antibodies to infliximab for the transition-extension period (extended safety set)

		Flixabi/Flixabi N=201			Remicade/Flixabi N=94			Remicade/Remicade N=101			Total N=396		
Timepoint	Parameter	n'	n	(%)	n'	n	(%)	n'	n	(%)	n'	n	(%)
Week 78 overall*	ADA	201	133	(66.2)	94	59	(62.8)	101	61	(60.4)	396	253	(63.9)
Week 78 overall**	ADA	194	104	(53.6)	94	43	(45.7)	101	51	(50.5)	389	198	(50.9)

ADA = anti-drug antibody; NAb = neutralising antibody; n': number of subjects with available ADA/NAb results against Flixabi at each timepoint
Percentages were based on n'.
*Overall ADA (or NAb) results were defined as "Positive" for subjects with at least one ADA (or NAb) positive up to Week 78 after Week 0, otherwise results were determined as "Negative".
**Overall ADA (or NAb) results were defined as "Positive" for subjects with at least one ADA (or NAb) positive up to Week 78 after Week 54, otherwise results were determined as "Negative"

For NAb from Week 0 to Week 78, 126 (94.7%) subjects in the Flixabi/Flixabi treatment group, 49 (83.1%) subjects in the Remicade/Flixabi treatment group and 55 (90.2%) subjects in the Remicade/Remicade treatment group tested positive for NAb among the subjects with positive ADA up to Week 78.

- Seriousness/outcome: No data are available.
- Severity: No data are available.
- Impact on individual patient: Clinical impact of potential immunogenicity of Flixabi was considered minimal, but relevant information will be collected continuously.

Risk factors and risk groups: Relevant information will be collected further during the post-authorisation period.

Preventability: Relevant information will be collected further during the post-authorisation period.

Impact on the risk-benefit balance of the product: Impact on the risk-benefit balance of the product is minimal as the effective risk management/mitigation measures are in place.

Public health impact: The potential public health impact is not known.

SVII.3.2 Presentation of the missing information

None

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII. 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infection/sepsis Demyelinating disorders BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi Malignancy
Important potential risks	Colon carcinoma/dysplasia (in paediatric UC) Immunogenicity
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

III.2 Additional pharmacovigilance activities

<BSRBR-RA summary>

Study short name and title: BSRBR-RA - British Society for Rheumatology Biologics Register – Rheumatoid Arthritis

Rationale and study objectives: An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.

Study design: National prospective study

Study population: Patients in the UK with rheumatological disorders treated with biologics and other new advanced targeted therapies

Milestones:

- Protocol submission: 2015 3Q (completed)
- Study start: 2017 1Q (completed)
- Study end: 2025 (planned)
- Final report: 2026

<ARTIS summary>

Study short name and title: ARTIS - Anti-rheumatic Therapies In Sweden

Rationale and study objectives: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with infliximab.

Study design: National prospective, observational, uncontrolled cohort study

Study population: Patients in the Sweden with rheumatological disorders treated with biologics

Milestones:

- Protocol submission: 2015 3Q (completed)

- Study start: 2019 4Q (completed)
- Study end: 2025 (planned)
- Final report: 2026 (planned)

<RABBIT-RA summary>

Study short name and title: RABBIT-RA - Rheumatoid Arthritis Observation of Biologic Therapy – Rheumatoid Arthritis

Rationale and study objectives: A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs

Study design: Prospective, observational cohort study

Study population: Adult patients in Germany with RA

Milestones:

- Protocol submission: 2015 4Q (completed)
- Study start: 2017 1Q (completed)
- Study end: 2025 (planned)
- Final report: 2026 (planned)

<BIOBADASER summary>

Study short name and title: BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies

Rationale and study objectives: 1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence; 2. To identify unexpected adverse events; 3. To identify relevant adverse events that occur following the suspension of the treatment; 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments; 5. To identify risk factors for suffering adverse reactions with these treatments; 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment

Study design: National observational study

Study population: Spanish patients with rheumatic diseases who are treated with biologics

Milestones:

- Protocol submission: 2016 3Q (completed)
- Study start: 2016 4Q (completed)
- Study end: 2025 (planned)

- Final report: 2027 (planned)

III.3 Summary Table of additional Pharmacovigilance activities

Table 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				
N/A				
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				
N/A				
Category 3 - Required additional pharmacovigilance activities				
BSRBR-RA - The British Society for Rheumatology Biologics Register-rheumatoid arthritis Ongoing	An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 3Q (No update in the previously submitted protocol; hence, a new version was not submitted and protocol submission is considered as completed)
			Study start	2017 1Q (completed)
			Study finish	2025 (planned)
			Final report	2026
ARTIS - Anti-rheumatic Therapies In Sweden Ongoing	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with infliximab.	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 3Q (final protocol submitted)
			Study start	2019 4Q (completed)
			Study finish	2025 (planned)
			Final report	2026 (planned)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
RABBIT-RA - Rheumatoid Arthritis Observation of Biologic Therapy Ongoing	A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 4Q (no update in the previously submitted protocol; hence, a new version was not submitted and protocol submission is considered to be completed)
			Study start	2017 1Q (completed)
			Study finish	2025 (planned)
			Final report	2026 (planned)
BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies Ongoing	1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence 2. To identify unexpected adverse events 3. To identify relevant adverse events that occur following the suspension of the treatment 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments 5. To identify risk factors for suffering adverse reactions with these treatments 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2016 3Q (completed)
			Study start	2016 4Q (completed)
			Study finish	2025 (planned)
			Final report	2027 (planned)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	with rheumatic diseases, as well as the reasons for the interruption of the treatment			

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
N/A				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Serious infection/sepsis	Routine risk communication: SmPC section 4.2, 4.3, 4.4, and 4.8 and PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitor for infections before, during and after treatment in SmPC section 4.4 • Recommendations to test for HBV infection before commencing treatment in SmPC section 4.4 • Recommendation to evaluate for active and inactive TB before commencing treatment in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Demyelinating disorders	Routine risk communication: SmPC section 4.2, 4.4 and 4.8 and PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi	Routine risk communication: SmPC section 4.2, 4.4, 4.6, and 4.8 and PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Malignancy	Routine risk communication: SmPC section 4.2, 4.4 and 4.8, and PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for periodic screening for cervical cancer in women in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication

Safety concern	Routine risk minimisation activities
Colon carcinoma/dysplasia (in paediatric UC)	Routine risk communication: SmPC section 4.2 and4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to screen for dysplasia at regular intervals in patients with at increased risk or a prior history of dysplasia/colon carcinoma in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Prescription-only medication
Immunogenicity	Routine risk communication: SmPC section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Prescription-only medication

V.2. Additional Risk Minimisation Measures

<Patient Reminder Card>

Objectives:

To provide adequate information to patients to make them aware of the increased risks of the following:

- HBV during the Flixabi treatment
- Worsening and acquisition of opportunistic infections during the Flixabi treatment
- Worsening and acquisition of serious infections during the Flixabi treatment
- TB during the Flixabi treatment
- BCG breakthrough infection in infants with *in utero* or breast-feeding exposure to Flixabi
- Infection after *in utero* exposure to Flixabi.

Rationale for the additional risk minimisation activity:

This particular additional risk minimisation measure for above safety concerns is aligned with that of reference product and follows the EMA request.

Target audience and planned distribution path:

Patient reminder card is provided to Flixabi prescribing physicians for distribution to patients receiving Flixabi. This card provides important safety information for patients.

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

Not applicable.

<Removal of additional risk minimisation activities>

N/A

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infection/sepsis	<Routine risk minimisation measures> SmPC Sections 4.2, 4.3, 4.4, and 4.8, and PL sections 2 and 4 Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	<Additional risk minimisation measures> Patient Reminder Card	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER
Demyelinating disorders	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4, and 4.8, and PL section 4 Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4, 4.6 and 4.8, and PL section 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER
Malignancy	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4 and 4.8, and PL section 2 and 4 Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER
Colon carcinoma/dysplasia (in paediatric UC)	<Routine risk minimisation measures> SmPC Section 4.2, 4.4 Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> None <Additional pharmacovigilance activities> None
Immunogenicity	<Routine risk minimisation measures> SmPC Section 4.8 Prescription-only medication	<Routine pharmacovigilance activities> None <Additional pharmacovigilance activities> Monitor the related adverse events (refer to the routine PV activity) in the already proposed registry of the RMP for Flixabi: BSRBR-RA, ARTIS, RABBIT, BIOBADASER

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR FLIXABI

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

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

This summary of the RMP for Flixabi 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 Flixabi's RMP.

I. The medicine and what it is used for

Flixabi is authorised for the treatment of rheumatoid arthritis, Crohn’s disease (adult and pediatric), ulcerative colitis (adult and pediatric) , ankylosing spondylitis, psoriatic arthritis, and psoriasis (see SmPC for the full indication). It contains infliximab as the active substance, and it is given by the intravenous route of administration.

Further information about the evaluation of Flixabi’s benefits can be found in Flixabi’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/flixabi

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

Important risks of Flixabi, together with measures to minimise such risks and the proposed studies for learning more about Flixabi'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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Flixabi, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks (see section II.B, below).

In addition to risk minimization measures, information about adverse reactions is collected continuously and regularly analysed, including in Periodic Safety Update Reports (PSURs) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Flixabi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Flixabi. 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);

List of important risks and missing information	
Important identified risks	Serious infection/sepsis Demyelinating disorders Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi Malignancy
Important potential risks	Colon carcinoma/dysplasia (in paediatric ulcerative colitis [UC]) Immunogenicity
Missing information	None

II.B Summary of important risks

II.B.1 Important identified risk

Serious infection/sepsis	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; SmPCs for Flixabi and Remicade, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	*Serious infection/sepsis* Combined use of immunosuppressants is associated with an increased risk of serious infections. The risk factors include age > 65 years,

Serious infection/sepsis	
	concomitant use of abatacept, and MTX. *Hepatitis B virus reactivation* Immune suppression, including in patients receiving chemotherapy and immunosuppressive therapy, is seen as a high risk factor in hepatitis B surface antigen (HBsAg)-positive patients. Prophylaxis with entecavir or tenofovir for 6 to 12 months after the end of immunosuppressive therapy is deemed mandatory in these patients. Additionally, screening and vaccination is recommended in serologically negative cases for patients with IBD to prevent HBV reactivation. In a recent study, HBsAg together with detectable HBV DNA, rituximab administration or treatment with steroids were shown to be independent risk factors leading to HBV reactivation HBV reactivation risk in HBsAg negative patients was assessed at the level of 3-10% in a study of 244 lymphoma patients by Hui et al. Mainly this was attributed to the concomitant administration of rituximab and steroid drugs. *Opportunistic infections* The risk factors include age > 65 years and concomitant use of abatacept, and MTX. Patients suffering from chronic infections or who have a history of recurrent infections, or patients who have travelled or lived in endemic areas for histoplasmosis, blastomycosis, etc., might constitute a risk group for opportunistic infections. *Tuberculosis* Particular immune compromised groups, such as HIV patients and patients receiving immunosuppressive therapy, are at higher risk for TB infection, as well as TB reactivation. The risk factors include age > 65 years, concomitant use of abatacept, and MTX
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.2, 4.3, 4.4, and 4.8, and PL section 2 and 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; Flixabi SmPC, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.

Demyelinating disorders	
Risk factors and risk groups	Patients with pre-existing MS or Guillain-Barré syndrome belong to the high-risk group. Additionally, first-degree relatives of patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36, evidence strongly suggesting that TNF inhibitors should not be used in first-degree relatives of patients with MS.
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4, and 4.8 and PL section 4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade Section 4.4 'Special warnings and precautions for use' and Section 4.6 "Fertility, pregnancy and lactation"; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth. Cases of agranulocytosis have also been reported.
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4, 4.6, and 4.8 and PL section 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card (BCG only)
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

Malignancy	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; SmPCs for Flixabi and Remicade, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	*Malignancy*

Malignancy	
	Patients with a history of malignancies. Patients with increased risk of malignancies due to heavy smoking. When considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. *Lymphoma* There is an increased background risk for lymphoma and leukaemia in RA patients with long standing, highly active, inflammatory disease. Studies by Askling et al.[22] and Baecklund et al. have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease. In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma. *HSTCL* The vast majority of HSTCL cases with infliximab use have occurred in patients with CD or UC and most were reported in adolescents or young adult males. Almost all patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) concomitantly with or immediately prior to infliximab. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered, as the risk for development of HSTCL among such patients cannot be excluded. *Paediatric malignancy* According to the Remicade and Flixabi SmPCs, children and adolescents exposed to infliximab are the risk groups.[3,4] Underlying autoimmune disease and concomitant use of immunosuppressants could increase the risk of malignancies among patients on infliximab; however, a clear causal relationship could not be established. *Leukaemia* According to the Remicade and Flixabi SmPCs, patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after infliximab treatment. Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Malignancy	
	Melanoma Patients with risk factors for skin cancer. Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. *Merkel cell carcinoma* Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma. *Cervical cancer* A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age.
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.2, 4.4 and 4.8, and PL sections 2 and 4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risk

Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Patients with a history of malignancies, with long-standing UC or PSC, with a family history of colorectal cancer.
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.2, and 4.4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> See section II.C of this summary for an overview of the post-authorisation development plan.

Immunogenicity	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Relevant information will be collected further during the post-authorisation period
Risk minimisation measures	<Routine risk minimisation measures> SmPC Section 4.8 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Monitor the related adverse events (refer to the routine PV activity) in the already proposed registry of the RMP for Flixabi: BSRBR-RA, ARTIS, RABBIT, BIOBADASER See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

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 Flixabi.

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

<BSRBR-RA - British Society for Rheumatology Biologics Register – Rheumatoid Arthritis>

Purpose of the study: An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.

<ARTIS - Anti-rheumatic Therapies In Sweden>

Purpose of the study: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with infliximab.

<RABBIT-RA - Rheumatoid Arthritis Observation of Biologic Therapy – Rheumatoid Arthritis>

Purpose of the study: A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs

<BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies>

Purpose of the study: 1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence; 2. To identify unexpected adverse events; 3. To identify relevant adverse events that occur following the suspension of the treatment; 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments; 5. To identify risk factors for suffering adverse reactions with these treatments; 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up forms

None

Annex 6 - Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures

<Patient reminder card>

Samsung Bioepis will adopt an educational approach similar to the activity in place for the reference product. The educational programme consists of a patient reminder card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals(s) (HCPs) treating the patient about on-going treatment with the product.

The patient reminder card shall contain the following key messages:

- A reminder to patients to show the patient reminder card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Flixabi
- A statement that the brand name and batch number should be recorded
- Provision to record the type, date, and result of TB screenings
- That treatment with Flixabi may increase the risks of serious infections/sepsis, opportunistic infections, tuberculosis, hepatitis B reactivation, BCG breakthrough in infants with *in utero* or breast-feeding exposure to infliximab and when to seek attention from an HCP
- Contact details of the prescriber