EU Risk Management Plan

Active substance(s) (INN or common name):	**Adalimumab**
Name of Marketing Authorization Holder or Applicant:	**Fresenius Kabi Deutschland GmbH** **Else-Kröner-Straße 1, 61352 Bad Homburg v.d.Höhe** **Germany**
RMP version to be assessed as part of this application:	
RMP version number:	7.0
Data lock point for this RMP:	27 Mar. 2025
Date of final sign off:	08 Aug. 2025
Rationale for submitting an updated RMP:	Consolidated RMP between 6.3 (approved by HAs) and 6.4 (with additional editing needed) – to be provided to EMA in the context of the Procedure EMEA/H/C/004475/II/0024/G (New formulation/Process C), with the responses to the 2nd Request for Supplementary Information. To align the RMP with the current approved RMP of the reference product Humira.
Summary of significant changes in this RMP:	The RMP has been aligned with the current Humira RMP v16.2. Please refer to Annex 8 for summary of changes.
Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

Signatures

Title:	Deputy Qualified Person responsible for PharmacoVigilance in European Economic Area (Deputy EU-QPPV)
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Deputy QPPV signature	

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List of Abbreviations

ACE	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
AIH	Autoimmune hepatitis
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransaminase
AMI	Acute myocardial infarction
ARAMIS	American Rheumatism Association Medical Information System
AS	Ankylosing spondylitis
AST	Aspartate aminotransaminase
AZA	Azathioprine
BCG	Bacillus Calmette–Guérin
BMI	Body mass index
BSA	Body surface area
bw	Body weight
CCDS	Company Core Data Sheet
CD	Crohn's disease
CDAI	Crohn's disease Activity Index
CHF	Congestive heart failure
CHMP	European Medicines Agency Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CMQ	Company MedDRA query
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	Cerebrovascular accident
DB	Double-blind
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DM	Diabetes Mellitus

DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
EC	European Commission
ECG	Electrocardiogram
EM	Erythema multiforme
EMA	European Medicines Agency
eow	Every other week
EPAR	European Public Assessment Report
EU	European Union
5-ASA	5-aminosalicylic acid
GBS	Guillain-Barre syndrome
GPRD	General Practice Research Database
HbC	Hemoglobin c
HBs ab	Hepatitis B surface antigen
HCP	Healthcare Professional
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HL	Hodgkin's lymphoma
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPV	Human papilloma virus
HR	Hazards ratio
HS	Hidradenitis suppurativa
HSTCL	Hepatosplenic T-cell lymphoma
HTLV-1	Human T-cell lymphoma/leukemia virus type I
IBD	Inflammatory bowel disease
Ig	Immunoglobulin
IHD	Ischemic heart disease
IL	Interleukin
ILAR	International League of Associations for Rheumatology
ILD	Interstitial lung disease
IRR	Incidence rate ratio

ITT	Intent-to-treat
IV	Intravenous
JCV	John Cunningham virus
JIA	Juvenile idiopathic arthritis
mAb	Monoclonal antibody
MDI	Major depression inventory
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MN	Minnesota
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTX	Methotrexate
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphoma
NHP	Non-human primate
NMSC	Non-melanoma skin cancer
Non-PsA	Non-psoriatic arthritis
Nr-axSpA	Non-radiographic axial SpA
NSAID	Non-steroidal anti-inflammatory drug
OL	Open-label
ON	Optic neuritis
OR	Odds ratio
pedCD	Pediatric Crohn's disease
pedERA	Pediatric enthesitis-related arthritis
pedPs	Pediatric psoriasis
pedUV	Paediatric Uveitis
PFS	Pre-filled synringe
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
Ps	Psoriasis

PsA	Psoriatic arthritis
PSC	Primary sclerosing cholangitis
PsO	Plaque psoriasis
PSPs	Patient support programs
PT	Preferred term
PUVA	Psoralen + UVA treatment
PVD	Peripheral vascular disease
PYs	Patient-years
QPPV	Qualified person for pharmacovigilance
RA	Rheumatoid arthritis
RABBIT	Rheumatoid Arthritis - Beobachtung der Biologika Therapie
ReA	Reactive arthritis
REMS	Risk evaluation and mitigation strategy
RPLS	Reversible posterior leukoencephalopathy syndrome
RR	Risk Ratio
RMP RR	Reference Medicinal Product risk ratio
RMP/RP	Reference medicinal product/Reference product
6-MP	6-mercaptopurine
SAE	Serious adverse event
SC	Subcutaneous
SEC	Squamous cell carcinoma
SIR	Standardized incidence ratio
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SMR	Standardized mortality rate
SpA	Spondyloarthritis
TB	Tuberculosis
TBD	To be decided
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor

UC	Ulcerative colitis
UK	United Kingdom
US	United States [of America]
uSpA	Undifferentiated spondyloarthritis
UV	Ultraviolet
UVB	Ultraviolet B
VKH	Vogt-Koyanagi-Harada syndrome
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AB04
Marketing Authorization Applicant	Fresenius Kabi Deutschland GmbH
Medicinal products to which this RMP refers	Adalimumab (Product code: MSB11022)
Invented name(s) in the European Economic Area (EEA)	Idacio
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class**: Tumor Necrosis Factor alpha (TNF-α) inhibitors
	Summary of mode of action: Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody (mAb) containing human peptide sequences that binds to human tumor necrosis factor (TNF) and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.
	Important information about its composition: Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	Refer to product information
Indication(s) in the EEA	Current (if applicable): Adults 1. Rheumatoid Arthritis (RA) 2. Psoriatic Arthritis (PsA) 3. Axial Spondyloarthritis (Axial SpA) 4. Crohn's Disease (CD) 5. Psoriasis (Ps) 6. Ulcerative Colitis (UC) 7. Hidradenitis Suppurativa (HS) 8. Uveitis Pediatrics 1. Polyarticular Juvenile Idiopathic Arthritis (pJIA) 2. Paediatric Enthesitis-Related Arthritis (pedERA) 3. Pediatric Crohn's Disease (pedCD) 4. Pediatric Psoriasis (pedPs) 5. Adolescent Hidradenitis Suppurativa (HS)

	6. Paediatric Uveitis (pedUV) 7. Paediatric ulcerative colitis (pedUC)
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): **ADULTS** **Rheumatoid Arthritis (RA)** The recommended dose of Idacio for adult patients with RA is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate (MTX) should be continued during treatment with Idacio. In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg Idacio every week or 80 mg every other week. **Ankylosing spondylitis (AS), axial spondyloarthritis (Axial SpA) without radiographic evidence of AS, and psoriatic arthritis (PsA).** The recommended dose of for patients with AS, axial SpA without radiographic evidence of AS and for patients with PsA is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. **Crohn's Disease (CD)** The recommended induction dose regimen of Idacio for adult patients with moderately to severely active CD is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen of 160 mg at Week 0 (dose can be administered as four injections in one day or two injections per day for 2 consecutive days), 80 mg at Week 2, can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some patients who experience decrease in their response may benefit from an increase in dose frequency to 40 mg every week. **Psoriasis** The recommended dose of Idacio for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting 1 week after the initial dose. **Ulcerative Colitis (UC)** The recommended Idacio induction dose regimen for adult patients with moderate to severe UC is 160 mg at Week 0 (dose can be administered as four injections in 1 day or as two injections per day for 2 consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Idacio every week.

Hidradenitis Suppurativa

The recommended Idacio dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with Idacio if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions, on a daily basis, during treatment with Idacio.

Should treatment be interrupted, Idacio 40 mg every week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated.

Uveitis

The recommended dose of Idacio for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose. Concomitant corticosteroids may be tapered in accordance with clinical practice starting 2 weeks after initiating treatment with Idacio.

PEDIATRICS

Polyarticular Juvenile Idiopathic Arthritis (pJIA) from 2 years of age

Juvenile Idiopathic Arthritis 2 to 12 years body surface area (BSA) dosing:

The recommended dose of Idacio for patients with polyarticular JlA from 2 years of age is based on body weight. Idacio is administered every other week via SC injection.

Idacio Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

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

There is no dosage form of Idacio that allows weight-based dosing for paediatric patients below 30 kg.

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

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

Enthesitis-Related Arthritis

The recommended dose of Idacio for patients with enthesitis-related arthritis 6 years of age is based on body weight

Idacio is administered every other week via subcutaneous injection.

Idacio Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥30 kg	40 mg every other week

There is no dosage form of Idacio that allows weight-based dosing for paediatric patients below 30 kg.

Idacio has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Pediatric Crohn's Disease

Idacio Dose for Paediatric Patients with Crohn's disease

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

Idacio is only available as 40 mg pre-filled syringe and 40 mg pre-filled pen. Thus, it is not possible to administer Idacio to patients that require less than a full 40 mg dose.

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

- ≥40 kg: 40 mg every week or 80 mg every other week

Continued therapy should be carefully considered in a subject not responding by Week 12.

There is no relevant use of adalimumab in children aged below 6 years for this indication.

Pediatric Psoriasis

The recommended Idacio dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight. Idacio is administered via SC injection.

Idacio Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting 1 week after the initial dose

There is no dosage form of Idacio that allows weight-based dosing for paediatric patients below 30 kg.

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

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

The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of adalimumab in children aged less than 4 years for this indication.

Adolescent Hidradenitis Suppurativa (from 12 years of age, weighing at least 30 kg)

The proposed Idacio dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Idacio 40 mg every other week, an increase in dosing frequency to 40 mg every week or 80 mg every other week may be considered.

Antibiotics may be continued during treatment with Idacio if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Idacio.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Idacio may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated.

There is no relevant use of adalimumab in children aged less than 12 years in this indication.

There is no dosage form of Idacio that allows weight-based dosing for paediatric patients below 30 kg.

Paediatric Uveitis (pedUV)

Idacio is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

The recommended dose of Idacio for paediatric patients with uveitis from 2 years of age is based on body weight. Idacio is administered via SC injection. In paediatric uveitis, there is no experience in the treatment with Idacio without concomitant treatment with MTX.

Idacio Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
<30 Kg	-
≥30 Kg	40 mg every other week in combination with MTX

There is no dosage form of Idacio that allows weight-based dosing for paediatric patients below 30 kg.

<table>
<tr><td></td><td>
When Idacio therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥30 kg may be administered 1 week prior to the start of maintenance therapy. No clinical data are available on the use of a Idacio loading dose in children < 6 years of age.
There is no relevant use of adalimumab in children aged less than 2 years in this indication.
It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

<u>Paediatric ulcerative colitis</u>
The recommended dose of Idacio for patients from 6 to 17 years of age with ulcerative colitis is based on body weight. Idacio is administered via subcutaneous injection.

Idacio Dose for Paediatric Patients with Ulcerative Colitis
<table>
<tr><th>Patent Weight</th><th>Induction Dose</th><th>Maintenance Dose Starting at week 4*</th></tr>
<tr><td><40 kg</td><td>• 80 mg at Week 0 (given as two 40 mg injections in one day) and
• 40 mg at Week 2 (given as one 40 mg injection)</td><td>40 mg every other week</td></tr>
<tr><td>≥40 kg</td><td>• 160 mg at Week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and
• 80 mg at Week 2 (given as two 40 mg injections in one day)</td><td>80 mg every other week</td></tr>
</table>
* Paediatric patients who turn 18 years of age while on Idacio should continue their prescribed maintenance dose.
Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.
There is no relevant use of adalimumab in children aged less than 6 years in this indication.
</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>
Current (if applicable):
Clear solution for injection in pre-filled syringe (PFS)
• 40 mg solution for injection in pre-filled syringe
Clear solution for injection in pre-filled pen
• 40 mg solution for injection in pre-filled pen
</td></tr>
<tr><td>
Proposed:
Not Applicable.
</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Part II: Safety Specification

Part II: Module SI Epidemiology of the Indication(s) and Target Population(s)

Not applicable

Part II: Module SII Non-Clinical Part of the Safety Specification

Idacio is a biosimilar to Humira® and has the same target antigen binding epitope and binding affinity as Humira. Idacio has been shown to have the same in vitro and in vivo mechanism of action as Humira and the components of the mechanism of action have also been shown to have the same activity in vitro, and in vivo in disease mouse models of RA and UC . In summary, Idacio has demonstrated analytical similarity in terms of structural, physico-chemical and biological activity in vitro and in vivo.

Guidelines outlining the required biosimilar antibody therapeutic studies indicate that the developmental and reproductive toxicity, genotoxicity, carcinogenicity and drug interaction studies are not warranted when the proposed biosimilar product has been demonstrated to be highly similar to the reference medicinal product Humira, through extensive structural and functional characterization and animal toxicity studies (CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev 1]). As Idacio is a biosimilar, the relevant evidence supporting Humira should apply equally. Nevertheless, due to regional regulatory requirements (US), the Applicant has conducted a comparative PK/Toxicology study in Cynomolgus monkeys. This study in cynomolgus monkeys confirmed the similarity between the toxicity profiles of Idacio and Humira.

Non-Clinical Safety Findings that are Included as Safety Concerns

There are no non-clinical safety findings that have not been adequately addressed in the subsequently approved adult and pediatric indications.

Part II: Module SIII Clinical Trial Exposure

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing human peptide sequences that bind to human TNF and neutralize the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (CRP and erythrocyte sedimentation rate) and serum cytokines rapidly decrease.

In accordance with regulatory guidelines for a biosimilar development, following the demonstration of physicochemical and functional similarity of Idacio and the reference medicinal product/reference product (RMP/RP), the applicant conducted a pharmacokinetic (PK) study in healthy subjects to support a claim for biosimilarity via a 3-way demonstration of bioequivalence between Idacio, the United States-Reference Medicinal Product, and European Union-Reference Medicinal Product, as per EMA (EMA, 2014) and international regulatory guidelines (FDA, 2015; WHO, 2009) on the development of biosimilar drugs. This study was followed by a clinical efficacy and safety trial in a sensitive patient population i.e. plaque psoriasis (PsO). The latter was selected as the lead indication, due to the relatively high treatment effect observed in clinical trials with Humira® for this indication and being a sensitive population for the comparative immunogenicity assessment thus, facilitating the detection of potential differences between Idacio and the EU-Reference Medicinal Product. Further advantages of plaque psoriasis are 1) fewer co-morbidities that in RA for example (as another common indication) and 2) due to the younger average patient age and the fewer co-morbidities compared to patients with RA less use of concomitant medications which may confound the safety read-out.

According to the Guideline on similar biological medicinal products (EMA, 2014) comparable safety and efficacy of a biosimilar to its reference product has to be demonstrated or otherwise justified in accordance with the data requirements laid down in Directive 2001/83/EC. Further, if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification. In accordance with this guidance extrapolation of the clinical results in psoriasis to the other approved indications for Humira® will be sought to support approval of Idacio in these other indications.

Idacio has the same pharmaceutical form and the same dosage strength as Humira. Data from 3 studies provide clinical evidence supporting the similarity of Idacio to the reference medicinal product Humira. These studies include 2 single dose 3-way PK similarity study in healthy volunteers and a double blind randomized active comparator study in adult subjects with plaque psoriasis.

The clinical trials were conducted in accordance with Good Clinical Practices.

Study EMR200588-001 was a randomized double-blind single dose study that compared the pharmacokinetics (PK), safety, and immunogenicity of MSB11022 with US-licensed Humira and EU-approved Humira in 237 healthy subjects. Of these 78 healthy subjects were exposed to

MSB11022. Results confirm the 3-way PK equivalence of MSB11022 and the EU Reference medicinal product and US-reference product. The safety and immunogenicity data supported the assertion of clinical similarity between MSB11022 and both the US-licensed Humira and the EU-approved Humira.

Study EMR200588-002 was a double-blind trial in subjects with moderate to severe, chronic plaque psoriasis. The primary objective of the study was to assess the similarity in efficacy between MSB11022 and the EU-Reference Medicinal Product, both administered SC. The study assessed the safety, tolerability, immunogenicity, and population PK of MSB11022. The safety population in pivotal study EMR200588-002 consisted of 441 subjects who were exposed to at least 1 dose (full or partial) of MSB11022 or Humira. Of these, 322 subjects were exposed to MSB11022, including 101 subjects who transitioned from Humira to MSB11022 in the Extended Treatment Period (after week 16 to week 52) and 220 subjects were exposed to Humira. A primary endpoint assessment was completed at Week 16 and the data are presented in the Week 54 CSR. Results from this trial demonstrated that the safety and immunogenicity profile of MSB11022 was similar to that of Humira.

Study FKS022-002 was a randomized, double-blind, parallel group, single dose study to compare the pharmacokinetics, safety, tolerability and immunogenicity of MSB11022 (acetate formulation) versus US-licensed Humira and versus Idacio (citrate formulation) in Healthy Subjects. A total of 459 subjects were randomized (1:1:1) to 1 of the 3 treatment groups and 452 received a single dose of study drug ((MSB11022-acetate: 150 subjects; US-Humira: 152 subjects; Idacio: 150 subjects). The results of this study demonstrated that MSB11022-acetate had an equivalent PK profile to that of US-Humira and Idacio, and Idacio had equivalent PK profiles to that of US-Humira.

Studies that are not part of the marketing application

There are three other studies that investigated a different pharmaceutical formulation

1. Study EMR200588-003 was a study to investigate the bioequivalence of an acetate versus a citrate-based formulation of MSB11022.

2. Study MS200588-0004 was a randomized, double-blind 2 arm parallel group multi-dose study in subjects with moderately to severely active RA up to Week 52.

3. Study FKS022-001 was a phase I, randomized, open-label, parallel group study to determine the pharmacokinetics, safety, and tolerability of MSB11022 following a single subcutaneous injection by an auto-injector or by a pre-filled syringe in healthy subjects.

Summaries of MSB11022 exposure have been presented in Table 1, Table 2 and Table 3 below:

Clinical trial exposure data from completed studies are provided below:

Table 1 Estimated Cumulative Exposure by clinical trials and by treatment groups

Estimated Cumulative Exposure by clinical trials and by treatment groups			
Safety Analysis Set			
Study Identifier	Treatment Group	Number of Subjects	Subject Years
EMR0200588-001	MSB11022 Citrate	78	0.21
	US Humira	80	0.22
	EU Humira	79	0.22
EMR0200588-002	MSB11022 Citrate	221	203.65
	EU Humira#/MSB11022* Exposed to Humira	101	29.26
	EU Humira#/MSB11022* Exposed to MSB11022	101	66.04
	EU Humira	119	96.51
EMR0200588-003	MSB11022 Acetate	88	0.245
	MSB11022 Citrate	90	0.25
MS200588_0004	MSB11022 Acetate	143	129.12
	EU Humira	145	126.82
FKS022-001	MSB11022 Acetate– Autoinjector	106	-
	MSB11022 Acetate– Pre-filled syringe	107	-
FKS022-002	MSB11022-acetate	150	-
	US-Humira	152	-
	Idacio	150	-

*EU Humira#/MSB11022 = Humira® to MSB11022 transition treatment group in Study EMR0200588-002

Table 2 Cumulative Subject Exposure by Age and Gender

Cumulative Subject Exposure by Age and Gender				
Safety Analysis Set				
Age group (Years)	**Study Identifier**	**Male (N, %)**	**Female (N, %)**	**Total N**
18 – 56 years	EMR200588-001	77 (98.7)	1 (1.3)	78
19 - 74 years	EMR0200588-002	219 (68.0)	103 (32.0)	322
18 - 55 years	EMR0200588-003	105 (59.0)	73 (41.0)	178
25 - 84 years	MS200588_0004	35 (24.5)	108 (75.5)	143
18 - 55 years	FKS022-001	142 (66.7)	71 (33.3)	213
18 - 55 years	FKS022-022	231 (51.1)	221(48.9)	452
Total	EMR200588-001	77 (98.7)	1 (1.3)	78
	EMR0200588-002	219 (68.0)	103 (32.0)	322

Cumulative Subject Exposure by Age and Gender				
Safety Analysis Set				
Age group (Years)	**Study Identifier**	**Male (N, %)**	**Female (N, %)**	**Total N**
	EMR0200588-003	105 (59.0)	73 (41.0)	178
	MS200588_0004	35 (24.5)	108 (75.5)	143
	FKS022-001	142 (66.7)	71 (33.3)	213
	FKS022-001	231 (51.1)	221(48.9)	452
	Total	809	577	1386

Table 3 Cumulative Subject Exposure by Racial Group

Cumulative Subject Exposure by Racial Group		
Safety Analysis Set		
Race	**Study Identifier**	**Number of Subjects**
White	EMR200588-001	51
	EMR0200588-002	295
	EMR0200588-003	173
	MS200588_0004	142
	FKS022-001	161
	FKS022-002	451
	Total	1273
Black or African American	EMR200588-001	10
	EMR0200588-002	2
	EMR0200588-003	1
	FKS022-001	31
	Total	44
Asian	EMR200588-001	10
	EMR0200588-002	11
	MS200588_0004	2
	FKS022-001	3
	Total	26
American Indian or Alaska Native	EMR0200588-002	13
	FKS022-001	8
	Total	21
Not collected at this site	EMR0200588-002	1
	Total	1
Native Hawaiian or other Pacific Islander	FKS022-001	4
	Total	4
Multiple	FKS022-001	6
	Total	6
Other	EMR200588-001	7
	EMR0200588-003	4
	EMR0200588-004	1
	FKS022-002	1
	Total	13
Total	EMR200588-001	78
	EMR0200588-002	322
	EMR0200588-003	178
	MS200588_0004	143

Cumulative Subject Exposure by Racial Group		
Safety Analysis Set		
Race	**Study Identifier**	**Number of Subjects**
	FKS022-001	213
	FKS022-002	452
	Total	1386

The totality of the evidence available from the analytical similarity assessment program, PK, and clinical studies demonstrate that Idacio is similar to the medicinal product Humira sourced from both EU and the US that was used as a reference.

These studies demonstrated that Idacio and Humira were comparable and the safety profile was consistent with that known for the reference product Humira.

Studies which are not part of the marketing authorizing application are described below:

Study EMR200588-003 was a double-blind 2 arm parallel group single dose bioequivalence study in healthy volunteers, comparing the pharmacokinetics of MSB11022 in acetate-based formulation to MSB11022 in a citrate-based formulation. A total of 178 subjects received a single 40 mg dose of MSB11022-acetate or MSB11022-citrate and were included in the analyses. The analysis of the results showed that MSB11022-acetate (Test) and MSB11022-citrate (Reference), were completely contained within the prespecified bioequivalence margin.

Study MS200588_0004 was a randomized, double-blind 2 arm parallel group multi-dose study in subjects with moderately to severely active RA up to Week 52. The primary objective of this study was to evaluate the safety, immunogenicity and efficacy of MSB11022-acetate compared to Humira® in patients, both administered SC. The study also assessed the safety, tolerability, immunogenicity, and population PK of MSB11022. The study included 288 subjects. The results of the study showed that the efficacy, immunogenicity and safety of MSB11022 and EU approved Humira was comparable.

Study FKS022-001 was a phase I, randomized, open-label, parallelgroup study to determine the pharmacokinetics, safety, and tolerability of MSB11022 (acetate formulation) following a single subcutaneous injection by an auto-injector (AI) or by a pre-filled syringe (PFS) in healthy subjects. A total of 213 subjects were received a single dose of MSB11022 (106 subjects in the AI treatment arm and 107 subjects in the PFS treatment arm). The results of the study showed that the pharmacokinetics, safety, and tolerability of MSB11022 injected via AI and PFS were comparable.

Part II: Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Several exclusion criteria were applied to the clinical studies to avoid exposure of particularly vulnerable subjects and to allow clear interpretation of study results. These criteria, which are outlined below, are not contraindications for therapy in the approved indications. Some of these criteria are mentioned in the summary of product characteristics for Idacio as situations in which caution should be applied when using the product.

Criterion 1: Chronic recurring infections and history of invasive infection (e.g., listeriosis and histoplasmosis)
Reason for exclusion: Criterion to avoid a potential safety bias in the study at Baseline.
Is it considered to be included as missing information? No.
Rationale: Comprehensive wording concerning infections (including chronic infections) is currently in section 4.4 "Special warnings and precautions for use" of the Summary of Product Characteristics (SmPC).

Criterion 2: Prior exposure to natalizumab (Tysabri®) or efalizumab (Raptiva®)
Reason for exclusion: Standard criterion due to limited information on the concomitant or sequential use of these two biologics with other immunosuppressant drugs. This criterion limits any potential bias on the safety results concerning infections in a study.
Is it considered to be included as missing information? No.
Rationale: The current SmPC, section 4.4 "Special warnings and precautions for use" recommends not to administer other biologics concurrently with Idacio due to the increased risk of infections.

Criterion 3: History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease or subject with intermediate uveitis or panuveitis who has signs of intermediate uveitis (e.g., presence or history of snowbanking or snowballs) and symptoms and/or Magnetic Resonance Imaging (MRI) findings suggestive of a demyelinating disease, such as multiple sclerosis.
Reason for exclusion: Adalimumab use in patients with a history of or symptoms and/or diagnostic findings suggestive of demyelinating disease is not recommended due to the known association of anti-TNF agents with demyelinating disorders.
Is it considered to be included as missing information? No.
Rationale: Demyelination is currently addressed in section 4.4 "Special warnings and precautions for use" of the SmPC. Further information for the uveitis specific patient population is also included in section 4.4.

Criterion 4: History of HIV or HIV positive test
Reason for exclusion: Use in patients with HIV, which results in an immunocompromised state, is not recommended.
Is it considered to be included as missing information? Yes.
Rationale: NA

Criterion 5: Hepatitis B: HBs antigen positive (+) or detected sensitivity on the Hepatitis B virus (HBV) DNA PCR qualitative test for HBc Ab/HBs ab positive subjects
Reason for exclusion: Reactivation of hepatitis B has occurred in patients receiving TNF-antagonists.

Is it considered to be included as missing information? No.
Rationale: Reactivation of hepatitis B is currently addressed in section 4.4 "Special warnings and precautions for use" of the SmPC.

Criterion 6: Evidence of dysplasia or history of malignancy (including lymphoma and leukaemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix
Reason for exclusion: Patients with a history of malignancy, though treated, may have an elevated risk of recurrence. These patients have not been studied on adalimumab and, therefore, there is no information for guidance.
Is it considered to be included as missing information? No.
Rationale: Comprehensive wording concerning malignancy is currently in section 4.4 "Special warnings and precautions for use" of the SmPC.

Criterion 7: Women who are pregnant, nursing, or who plan to become pregnant
Reason for exclusion: Pregnant women are rarely enrolled in a clinical trial unless a product is specifically indicated for a pregnancy-related indication.
Is it considered to be included as missing information? No.
Rationale: In accordance with the reference product, Humira.

Criterion 8: History of clinically significant drug or alcohol abuse in the last 12 months
Reason for exclusion: Criterion to avoid a potential safety bias in the study at Baseline.
Is it considered to be included as missing information? Yes.
Rationale: NA

Criterion 9: Known hypersensitivity to adalimumab or its excipients
Reason for exclusion: Patients with known hypersensitivity to adalimumab or excipients should not use.
Is it considered to be included as missing information? No.
Rationale: Use in this population is contraindicated in the label.

Criterion 10: Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections
Reason for exclusion: To avoid any possible impact by adalimumab, in relationship with its immunosuppressant effect, on the treatment of a current or recent infection.
Is it considered to be included as missing information? No.
Rationale: Use in this population is contraindicated in the label.

Criterion 11: History of moderate to severe congestive heart failure (New York Heart Association Class III or IV)
Reason for exclusion: Therapy with adalimumab for patients with Class III or IV heart failure is not recommended based on studies performed in patients with CHF and other TNF inhibitors, which showed an increase in the risk for worsening of CHF.
Is it considered to be included as missing information? No.
Rationale: Use in this population is contraindicated in the label.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program for Idacio includes 3 studies, 2 enrolling healthy volunteers and one efficacy and safety studies in patients with plaque psoriasis.

The results from the completed clinical studies with Idacio available to date demonstrate that the safety and immunogenicity profile of Idacio is similar to that of Humira®. Due to the small size of the safety database, lack of precision for estimated differences in AE / ADR are to be expected reflecting heterogeneity of the enrolled individuals and the properties of the underlying sampling distribution. The probability to detect uncommon or rare adverse events in this setting will also be limited. In addition, risks associated with prolonged latency until the onset of the adverse event (e.g., in case of a slow disease dynamic, effects requiring a prolonged treatment duration, or effects that depend on the slow accumulation of the medicinal product) are probably under-represented in the current data set.

Given the role of the clinical evidence in a biosimilar development program these limitations are not considered critical. It is the entirety of the evidence in support of a proposed biosimilar, i.e., the physico-chemical characterization and performance in the functional assays plus the abbreviated clinical program that in aggregate provide the justification for the assertion that Idacio and Humira® are comparable versions of adalimumab. The remaining residual uncertainty at this point is very small despite the noted limitations of the clinical data set.

Under the premise that Idacio and Humira® are comparable versions of adalimumab, the accumulated safety data on Humira® is considered to equally inform of the safety profile of Idacio. The most current estimate of total patient exposure to Humira® in AbbVie conducted clinical trials is 48,262.4 PYs. Additionally, 65,813.2 PYs exposure to Humira® have accumulated in AbbVie conducted registries. The estimated cumulative postmarketing patient exposure since the International Birth Date (31 December 2002) through 31 December 2021 is 9,827,466 PYs. This volume of patient exposure spanning 17 years should allow the identification of rare events that appear in less than 1:10,000. In addition, there is evidence that the experience can provide:

- identification of adverse reactions that may be due to prolonged exposure to adalimumab;
- identification of adverse reactions with long latency; and
- identification of adverse reactions due to cumulative effects, if any.

New patient populations are constantly being added through approval of new indications and new age groups. Although there is 20 years of postmarketing observation of patients taking adalimumab, safety data continues to be monitored for the appearance of new reactions.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 4 Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure
Pregnant or Breastfeeding Women	No studies with Idacio have been conducted in breastfeeding women. **Data from reference medicinal product Humira**: A total of 590 pregnant women were exposed to adalimumab in the OTIS pregnancy registry (257 pregnant women with RA or CD treated with adalimumab during the first trimester [main prospective cohort study] and 333 pregnant women treated with adalimumab who did not meet the main prospective cohort study enrollment criteria [exposure series cohort]).
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Patients with hepatic and renal impairment have not been directly studied in Idacio or Humira clinical trials.
Other • Children • Elderly Patients • Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population • Ps, UC, and JIA patients receiving episodic treatment	Idacio has not been studied in all indications applied for. The biosimilar guidance explicitly states that the robust originator data are the cornerstone for extrapolation to other indications. **Data from reference medicinal product Humira**: Clinical and postmarketing experience in the paediatric age groups for approved indications of pJIA (aged 2 years and above), pedCD (aged 6 to 17 years), and pedERA (aged 6 years and above) has been obtained in these relatively small patient populations. There is minimal representation of patients younger than the age groups represented in Humira clinical trials since the prevalence of these disorders is extremely low or nonexistent in these age groups. As a result, the European Medicines Agency (EMA) Paediatric Committee has agreed to grant waivers for the following patient populations. • Children aged less than 12 years for HS • Children aged less than 6 years for CD • Children aged less than 4 years for UC and Ps • Children aged less than 2 years for pJIA, PsA, and noninfectious uveitis • Children aged less than 6 years for pedERA. There is significant clinical trial and postmarketing experience in the elderly age group from the pivotal RP clinical trials. The majority of these patients have RA.

	Comorbid conditions including cardiac disorders, diabetes, and the use of multiple concomitant medications have been explored in clinical trials and postmarketing surveillance for evidence of safety signals. As a result, the warning that serious infections are more common in patients > 65 years of age was added to the label. Humira, the originator adalimumab, has been studied in patients of a defined disease severity for the approved indications and is not approved for other forms of severity of the disease. For instance, the most severe form of CD has not been studied in clinical trials. Less severe forms of these indications are not approved for Idacio therapy and should be amenable to standard of care treatment. Patients in the Ps, UC, and MA indications receiving episodic treatment have not been well characterized.
Patients of relevant different Ethnic Origin	Due to the limited size of clinical studies the sub population analysis on different racial origin with respect to safety did not show differences. However, Adalimumab has been studied in subject populations that included men and women of a variety of racial backgrounds and eithnicities in clinical studies. conducted by the originator.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms that affect metabolism, degradation or pharmacological effects of TNF inhibitors including adalimumab.

Part II: Module SV Post-Authorization Experience

On 02 Apr 2019, the European Commission first approved Idacio (adalimumab biosimilar) for all indications approved for the reference product Humira at that time

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Patient treatment years were calculated by dividing the estimated number of syringes (syringes and pens) distributed by Fresenius Kabi's with average number of syringes used by a patient each year. The estimates of the number of syringes that would be used by a patient on a full year of adalimumab therapy [average annual dose] were derived from the data presented in the RMP of reference product Humira. An estimated average annual dose of 28 syringes was used in the calculation of patient treatment years.

SV.1.2 Exposure

Estimated worldwide cumulative post-marketing patient exposure from the date of approval (Apr 2019) to Mar. 2025 was approx. 242,094 patient treatment years. This estimate is based on sales data and is derived as the number of syringes/pens of IDACIO sold worldwide divided by the estimated average number of syringes/pens used by a patient each year. The estimates for number of syringes/pens that would be used by a patient on a full year of adalimumab therapy [average annual dose] corresponds to that proposed by the reference product Humira. Cumulatively, 6,778,628 units of Idacio were sold worldwide. An estimated average annual dose of 28 syringes was used in the calculation of patient treatment years. Exposure by country in patient treatment years is summarized in Table 5 below.

Table 5 IDACIO Post-Marketing (Non-Study) Exposure - Number of Patient Treatment Years by Country and Year

Country	Patient Treatment Years approx. (Cumulative until Mar. 2025)
Albania	233
Andorra	147
Argentina	258
Australia	467
Austria	3,990

Country	Patient Treatment Years approx. (Cumulative until Mar. 2025)
Belgium	1,098
Bosnia-Herz.	36
Brazil	79,355
Canada	10,448
Chile	3,403
Colombia	2,043
Croatia	884
Czech Republic	1,994
Dominican Rep.	65
Ecuador	3
Egypt	561
Estonia	261
Finland	575
France	13,589
French Guiana	1
Germany	10,519
Greece	5,413
Guadeloupe	62
Hong Kong	33
Hungary	335
Iraq	192
Ireland	1,041

Country	Patient Treatment Years approx. (Cumulative until Mar. 2025)
Israel	1,167
Italy	12,942
Latvia	58
Lithuania	1,642
Malaysia	3
Martinique	21
Mayotte	2
Netherlands	2,464
Paraguay	165
Poland	3,423
Portugal	3,585
Region Africa	797
Réunion	454
Romania	82
Saudi Arabia	245
Serbia	241
Singapore	137
Slovakia	1,173
Slovenia	261
Spain	25,259
Sweden	5,732
Switzerland	72

Country	Patient Treatment Years approx. (Cumulative until Mar. 2025)
Taiwan	197
United Kingdom	40,918
United States	4,074
TOTAL approx.	**242,094**

Part II: Module SVI Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

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

Part II: Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The list of safety concerns considered in the initially submitted RMP (version 4.0; Date of approval: 03-Oct-2019) is as detailed below:

Important Identified risks:
- Serious infections
- Tuberculosis (TB)
- Malignancies
- Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS], and optic neuritis [ON])
- BCG disease following live BCG vaccination in infants with in utero exposure to Idacio

Important Potential risks:
- Progressive multifocal leukoencephalopathy (PML)
- Reversible posterior leukoencephalopathy syndrome (RPLS)
- Adenocarcinoma of colon in UC patients

Mising information:
- Patients with immune-compromised conditions
- Episodic treatment in Ps, UC, and JIA
- Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD
- Long-term safety data in the treatment of children with uveitis

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
- Reactivation of Hepatitis B
- Vasculitis
- Amyotrophic lateral sclerosis
- Pulmonary embolism
- Sarcoidosis

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

- Congestive Heart Failure
- Myocardial infarction
- Cerebrovascular Accident
- Interstitial lung disease
- Cutaneous vasculitis
- Stevens-Johnson syndrome
- Erythema multiforme
- Worsening and new onset of Psoriasis
- Haematologic reactions
- Intestinal perforation
- Intestinal stricture in Crohn's Disease
- Liver failure
- Autoimmune Hepatitis
- Immune reactions (including Lupus-like Reactions and Allergic reactions)
- Medication errors and maladministration
- Off label use
- Infections in infants exposed to adalumumab in utero (see also new identified risk of BCG disease following live BCG vaccination in infants with in utero exposure to Idacio under SVII.1.2)

Known risks that do not impact the risk-benefit profile:

- Lichenoid skin reactions

Other reasons for considering the risks not important:

- Other malignancies: this risk is covered under the identified risk of malignancies.
- Medication error with paediatric vial: In accordance with the RMP for reference product Humira®.
- Opportunistic infections: this risk is covered under the identified risk of serious infections.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks

Identified risk 1: Serious infections

Reason for Inclusion: As anti-TNFs may alter T-cell mediated immunity some impact on host defence against infections might be expected.

Identified risk 2: Tuberculosis

Reason for Inclusion: As anti-TNFs may alter T-cell mediated immunity some impact on host defence against infections including TB might be expected.

Identified risk 3: Malignancies

Reason for Inclusion: As anti-TNFs may alter T-cell mediated immunity there may be influence on the occurrence of malignancy, but the mechanism is unknown.

Identified risk 4: Demyelinating Disorders- including MS, GBS, and ON

Reason for Inclusion: The mechanisms by which anti-TNFs may induce demyelination remain to be clearly established.

Identified risk 5: BCG disease following live BCG vaccination in infants with in utero exposure to Idacio

Reason for Inclusion: This identified risk has been considered important as requested by the EMA for Humira, the reference adalimumab for Idacio.

Important Potential Risks

Potential risk 1: Progressive multifocal leukoencephalopathy

Reason for Inclusion: PML is a rare disorder that damages the material (myelin) that covers and protects nerves in the brain. The potential mechanism for PML is reactivation of polyomavirus JC in the brain that is believed to be started by severe immunosuppression as in HIV infection. There is no known association of PML with the use of adalimumab or other TNF inhibitors, however, because PML is rare and often fatal its appearance in patients on biologic medications including adalimumab is under observation.

Potential risk 2: Reversible posterior leukoencephalopathy syndrome

Reason for Inclusion: RPLS is a syndrome characterized by headache, confusion, seizures and visual loss. This syndrome appears in patients who become severely immunosuppressed by drugs like those used for anti-rejection. Stopping the drug(s) makes the condition reverse. There is no known association of this event with adalimumab use; however, rare RPLS postmarketing reports in patients using adalimumab have been received and although most have other causes, the reports are under observation for a possible association.

Potential risk 3: Adenocarcinoma of colon in UC patients

Reason for Inclusion: There is a known increased risk of adenocarcinoma of colon in UC patients that increases with amount of bowel inflammation as well as the length of time a patient has the disease. Since early detection can limit the bad outcomes from adenocarcinoma of colon, patients with UC, regardless of the therapy used, should receive routine adenocarcinoma of colon screening (colonoscopy) more frequently than that recommended for the general population according to current practice guidelines. Since there may be an increased risk of cancer in patients receiving adalimumab, it is not known if this therapy increases the risk of adenocarcinoma of colon even more in UC patients, thus, the reports of this cancer are under observation in this patient group.

Missing information

Missing Information 1: Episodic treatment in Ps, UC and JIA

Reason for Inclusion: The population requires more characterization.

Data to be Collected Post-Authorization: Routine pharmacovigilance surveillance is being performed.

Missing Information 2: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Reason for Inclusion: The population requires more characterization.

Data to be Collected Post-Authorization: Routine pharmacovigilance surveillance is being performed.

Missing Information 3: Long-term safety information in the treatment of children with uveitis

Reason for Inclusion: The population requires more characterization.

Data to be Collected Post-Authorization: Routine pharmacovigilance surveillance is being performed.

Missing information 4: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Reason for Inclusion: Safety profile in this population requires more characterization.

Data to be Collected Post-Authorization: Routine pharmacovigilance surveillance is being performed.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Removed Missing Information:
Information 3: Long-term safety information in the treatment of children with uveitis

Reason for Removal: To align the list of safety concerns with the reference product Humira.

Reclassified Missing Information:
Information 2: Episodic treatment in Ps, UC and JIA reclassified to Episodic treatment in UC.

Reason for Reclassification: To align the list of safety concerns with the reference product Humira.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and important potential risks

The overall benefit risk profile of Idacio is thought to correspond to that of Humira®, the reference adalimumab. All the established potential and identified risks are listed in the Humira® Risk Management Plan 16.2 and are considered equally applicable to Idacio.

Table 6 Presentation of Important Identified Risks

Important Identified risk 1: Serious infections

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Serious infections has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the pivotal adult study EMR200588-002 in psoriasis patients, through Week 54, the overall subject incidence of adverse events in the SOC "Infections and Infestations" was 50.7% in the MSB11022 arm, 37.8% in the Humira® arm, and 48.5% in the Humira®/MSB11022 switch arm. There were 7 serious adverse events (SAEs) of infection: respiratory tract infection viral, peritonsillar abscess and sinusitis in the MSB11022 arm, arthritis bacterial and

pneumonia in the Humira® arm, and appendicitis and staphylococcal abscess in the Humira®/MSB11022 switch arm. The most commonly reported AEs of infection were nasopharyngitis (18.6%, 16.0% and 16.8%), pharyngitis (5.4%, 1.7%, and 3.0%) and upper respiratory tract infection (5.4%, 5.0% and 5.0%).

According to the Idacio SmPC, respiratory tract infections have been reported to occur very commonly (≥ 1/10).

Severity and nature of risk

Risk severity ranges from mild infectious processes to sepsis and death.

Background incidence/prevalence/mortality

RA:
The incidence of infections per 100 person-years in Olmsted County, Minnesota (MN) residents ages ≥ 18 years of age was 19.64 among those with RA and 12.87 among those without RA (RR = 1.53 [95% CI: 1.41 - 1.65]). The incidence of infections requiring hospitalization was also greater in for RA patients than non-RA patients, 9.57 per 100 person years versus 5.09 per 100 person years (RR = 1.88 [95% CI: 1.71 - 2.07]) (Doran 2002a).

In the North American Rheumatism Association, Medical Information System (ARAMIS) database, the rate of serious infection requiring hospitalization among individuals with RA equaled 3.1 per 100 person-years. The rate among RA patients receiving no treatment equaled 1.1 per 100 person years, while the rate among those receiving DMARDs equaled 2.9 (RR = 2.7 [95% CI: not reported]) (Singh 1999).

Among 609 RA patients in Olmsted County, MN, 64% had at least one infection and 48% had at least one infection requiring hospitalization (mean 12.7 years per patient follow-up time) (Doran 2002b). Infection was a common cause of death in an Olmsted County, MN RA cohort with 15.2% of death certificates listing infection as the primary cause of death (Doran 2002c).

The SMR for non-pulmonary infection was 6.2 in a cohort of 898 RA patients from the North American ARAMIS database whose cause of death was known; the SMR for pneumonia was 5.3 (Wolfe 1994).

Ps
In Ps patients not treated with biologics, the incidence rates of serious infections ranged from approximately 0.3 to 2.1 per 100 person-years (Reich 2015, Kimball 2014, Gottlieb 2014, Kalb 2015, Wakkee 2011).

Among Swedish inpatients hospitalized with psoriasis, the mortality rate due to infective disease was increased compared to the general population (unadjusted SMR = 2.25 [95% CI: 1.5 — 3.3]). This risk decreased and was no longer significant when the analysis was restricted to psoriasis patients hospitalized for psoriasis only (Boffetta 2001).

UC:
Multiple studies have suggested that H. pylori infection is less prevalent in patients with IBD than in controls. This finding has been associated with 5-ASA (Piodi 2003) and sulfasalazine therapy (el-Omar 1994). Incidence of serious infection in paediatric patients (<18 years) with ulcerative colitis not exposed to TNF-a inhibitors was approximately 6.5 events per 100 person years (Wintzell 2019).

Risk Factors and Risk Groups

Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those with advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).

While taking Idacio, your risk for infection might increase, particularly if you are over 65 years of age, taking immunosuppressive treatment (e.g., 6-MP, AZA), a heavy smoker, or have a history of decreased lung function. Infections may be serious and, in rare cases, life threatening.

Preventability:

Having a high degree of suspicion with prompt treatment of signs or symptoms of infection, even in the absence of fever.

Using the minimum amount of immunosuppressive drugs to accomplish and sustain remission.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Important Identified risk 2: Tuberculosis (TB)

Potential mechanisms: Adalimumab may alter T-cell mediated immunity through modulation of TNF-a.

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Tuberculosis has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with MSB11022 to date, there was 1 report of tuberculosis (TB) in the MSB11022 arm.

Only clinically active TB infections are presented (TB test positivity alone, or latent TB, are not included).

In controlled trials, the rate of TB in subjects treated with adalimumab was 0.1E/100 PYs. It ranged from 0/100 PYs in the pedUC, JIA, PSA, AS, CD, Ps, pedPs, HS, and peripheral SpA indications and 3.0/100 PYs in the uveitis indication.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 354 deaths with associated fatal AEs occurred among 47,911 (0.7%) subjects. Of the 354 deaths with associated fatal AEs, 2 were due at least in part to TB.

Severity and nature of risk

Risk severity ranges from mild infectious processes to sepsis and death.

Background incidence/prevalence/mortality

In the USA, TB incidence was significantly higher among RA patients on traditional DMARD and corticosteroid therapies compared to RA patients not treated with these therapies (RR = 1.2 [95% CI: 1.0 - 1.5] and RR = 1.7 [95% CI: 1.3 -2.2], respectively) (Brassard 2006).

In Sweden, the incidence of hospitalization due to TB among RA inpatients was two-times higher than the incidence among referent inpatients (RR = 2.0 [95% CI: 1.2 -3.4]) (Askling 2005).

In South Korea, the rate of TB among RA patients not taking TNF-α inhibitors equalled 257 per 100,000 person-years, representing an 8-fold increase in TB risk compared to general population (RR = 8.9 [95% CI: 4.6 - 17.2]) (Seong 2007).

Risk Factors and Risk Groups

Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992)

Preventability:

All patients must be screened for latent TB before initiating adalimumab.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

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

Important Identified risk 3: Malignancies

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Malignancies has been classified as an identified risk for Idacio in accordance with the reference product.

Data from adalimumab trials as described below.

Rare cases of certain types of cancer in children and adults have been reported in patients taking TNF blockers.

Patients who have severe, long standing rheumatoid arthritis are at higher than average risk of getting lymphoma or leukaemia. The risk is independent of adalimumab usage.

If you take adalimumab, the risk of getting lymphoma, leukaemia, or other cancers may increase.

No reports of HSTCL were received from any clinical trial, open label (OL) or controlled.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with MSB11022 to date, there were no reports of lymphoma, HSTCL, leukemia, NMSC, melanoma, MCC or other malignancies.

In controlled trials, the rate of malignancy in subjects treated with adalimumab was 1.2/100PY. It ranged between 0/100 PYs in the pedUC, JIA, PSA, AS, CD, pedPs, nr-axSpA, and peripheral SpA indications and 2.4/100 PYs in the uveitis indication

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 354 deaths with associated fatal AEs occurred among 47,911 (0.7%) subjects. Of the 354 deaths with associated fatal AEs, 88 (0.2% of subjects) were at least in part to malignancy.

Severity and nature of risk

The risk for lymphoma, leukaemia, and HSTCL includes death. The risk for NMSC includes disfigurement, and possibly death in rare cases of metastatic squamous cell skin cancer. The risk for melanoma includes disfigurement, death, and metastatic disease. The risk for MCC includes metastatic disease and death

Background incidence/prevalence/mortality

Lymphoma

RA

The incidence of Non-Hodgkin's lymphoma (NHL) in a cohort of 789 Spanish RA patients was 13 per 10,000 PYs (95% CI: 4 -41) and was greater than seen in the general population (SIR 5.24 [95% CI: 1.1 - 15.7]) (Abasolo 2008).

Compared to malignancy rates in the general population, the RR for NHL and Hodgkin's lymphoma (HL) were 2.4 (95% CI: 1.9 -2.9) and 3.4 (95% CI: 1.8 - 5.6), respectively, among 20,699 Denmark RA inpatients followed 1 to 15 years after initial hospitalization (Mellemkjaer 1996).

The SIR of NHL and HL developing 1 to 4 years after initial RA hospitalization in a study of 42,262 Swedish RA inpatients was 2.42 (95% CI: 1.94 - 2.98) and 2.76 (95% CI: 1.25 -5.26), respectively (Hemminki 2008b).

The SIR for NHL was 2.39 (95% CI: 1.61 - 3.41) for males and 2.04 (95% CI: 1.60 - 2.58) for females among 124,143 Scottish RA inpatients, excluding events occurring; 3 months after initial hospitalization. The reported SIR in this study for HL was 5.49 (95% CI: 2.36 - 10.8) for males and 3.04 (95% CI: 1.39 - 5.78) for females (Thomas 2000b).

In Sweden, the SIR for lymphoma was 1.98 (95% CI: 1.5 -2.6), the SIR for NHL was 1.88 (95% CI: 1.3 -2.6), and the SIR of HL was 2.34 (95% CI: 1.2 -4.1) among 11,683 RA patients with inpatient records between 1965 and 1983 and followed-up through 1984 (Gridley 1993).

A case-control study of 378 Swedish inpatients with RA and 378 matched controls found the risk of lymphoma was increased in those with medium (OR = 7.7 [4.8 - 12.3]) and high RA inflammatory activity (OR = 71.3 [24.1 - 211.4]) in comparison with those with mild inflammation (Baecklund 2006).

A study using inpatient records for patients with RA from California hospitals linked to the California Cancer Registry reported the standardized incidence ratio (SIR) for Hodgkin's lymphoma for males was 2.76 (95% CI: 1.32 - 5.08) and 1.62 (95% CI: 0.91 -2.68) for females.

For Non-Hodgkin's lymphoma, the SIR for males was 2.07 (95% CI: 1.71 - 2.48) and 1.37 (95% CI: 1.19 - 1.57) for females. The study included 84,475 patients with a diagnosis of RA recorded on a hospital discharge record between 1991 and 2002 and excluded events occurring ≤ 6 months after initial hospitalization (Parikh-Patel 2009).

Among 459 RA patients treated with MTX and receiving care at rheumatology clinics in Melbourne, Australia, the SIR for NHL was 5.1 (95% CI: 2.2 - 10.0) and the SIR for HL was 8.9 (95% CI: 0.2 -49.8). MTX treatment began prior to June 1986 for all patients and follow-up spanned 1983 to 1998 (Buchbinder 2008). The period prevalence (March 1999 through June 2005) of HL in a cohort of 221 male Spanish RA patients was 0.45% (95% CI: 0.011 - 2.5) (Abasolo 2008). The period prevalence (March 1999 through June 2005) of NHL in a cohort of 568 females Spanish RA patients was 0.17% (95% CI: 0.004 - 0.98) (Abasolo 2008). The pooled analyses of four National Data Bank for Rheumatic Diseases sites estimated the SMR of NHL to be 2.04 (no 95% CI reported) (Wolfe 2003b).

PsA
In the study by Gross et al the incidence of lymphoma in PsA patients (0.04 per 100 patient –years) and found a rate similar to RA patients (Gross et al 2014). Similar rates of lymphoma (IR:44 per 100,000 person-years (were also seen among Swedish PsA patients that visited outpatient rheumatology or internal medicine departments (Hellgren et al, 2014)

Psoriasis
The prevalence of lymphoma in several populations ranges from 0.12% to 1.1% higher rates are seen in those older than 65 years (Carretero et al 2015). Results from a large UK population based cohort study showed that the attributable risk of lymphoma related to psoriasis was 7.9 per 100,000 patient years (Gelfand et al 2006)

AS
A Swedish population-based case control study of hospitalized patients with AS found no increased risk of lymphoma (OR 1.0 (95% CI: 0.6 - 1.7) (Askling 2006).

CD
Authors of a meta-analysis estimated the incidence of lymphoma in CD to be 1.77 per 10,000 PY (95% CI: 0.75 - 2.78) based on 7 studies involving 15,579 CD patients. The pooled RR of lymphoma from 8 studies with 36,576 patients was 1.42 (95% CI: 1.16 -1.73) compared to the general population (von Roon 2007).

The adjusted incidence of lymphoma was 47.2 per 100,000 PY in a population-based cohort of 2,857 CD patients in Manitoba, Canada. In this study, the incidence rate ratio (IRR) of lymphoma for CD patients compared to individuals without IBD was 2.40 (95% CI: 1.17 -4.97) (Bernstein 2001b).

UK database: The SIR of NHL among 21,788 Swedish CD patients hospitalized with a CD diagnosis between 1964 and 2004 was 4.01 (95% CI: 2.59 - 5.92) 1 to 4 years after hospitalization (Hemminki 2009).

The adjusted RR of NHL and HL occurring at least 1 year after initial hospitalization for CD in 5,127 English inpatients was 1.01(95% CI: 0.61 - 18.7) and 0.69 (0.2 - 3.91), respectively (Goldacre 2008).

A study of 2,645 Danish patients starting 1 year subsequent to hospitalization with CD between 1977 and 1989 and followed until the end of 1993 reported the SIR of NHL as 1.5 (95% CI: 0.4 - 3.7) (Mellemkjaer 2000).

The standard morbidity ratio for lymphoma was 1.35 (95% CI: 0.37 - 3.45) in a population of 1,251 CD patients diagnosed in Stockholm from 1955 - 1984 and followed until 1989 (Persson 1994).

The incidence of lymphoma equaled 0.42 per 1,000 person-years (0.33 - 0.54) among patients identified in the UK GPRD database with a first diagnosis of psoriasis during the period 1994 through 2004. The incidence of lymphoma among patients without psoriasis equaled 0.24 per 1,000 person-years (95% CI: 0.17 -0.33). The IRR was 1.76 (95% CI: 1.19 - 2.58) (Brauchli 2009b).

UC
The age-adjusted incidence of lymphoma was 29.8 per 100,000 PY in a population-based cohort of 2,672 UC patients in Manitoba, Canada (Bernstein 200lb). In this study, the IRR of lymphoma for UC patients compared to individuals without IBD was 1.03 (95% CI: 0.47 -2.24) (Bernstein 2001b).

Compared to patients hospitalized for other conditions, the adjusted RR of NHL and HL occurring at least 1 year after to initial hospitalization for UC in 6,990 English inpatients was 1.19 (95% CI: 0.64 -2.01) and 1.60 (95% CI: 0.33 - 4.78) (Goldacre 2008). A case-control study conducted using Swedish and Danish registry data found no increased risk of Hodgkin's lymphoma in ulcerative colitis patients compared to matched controls without UC (OR: 0.8, 95% CI: 0.3 - 2.5) (Landgren 2006). A study conducted in Florence, Italy yielded results inconsistent with those presented above. UC cases identified in Florence, Italy from 1978 - 1992 and followed through 1997 experienced much higher rates of Hodgkin's disease (SIR: 9.3, 95% CI: 2.5 - 23.82) but not Non-Hodgkin's lymphoma (SIR: 1.8 95% CI: 0.20 - 6.5) than would be expected (Palli 2000).

In Sweden, the SIR for non-Hodgkin's lymphoma occurring at least 1year after the first hospitalization with a UC diagnosis was 1.34 (95% CI: 1.03 -1.71) among 27,656 patients between 1964 -2004 (Hemminki 2008a).

The SMR for NHL was 2.27 (95% CI: 0.03 - 12.6) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 (Palli 1998).

A study conducted in 1160 UC cases diagnosed in Copenhagen from 1962 - 1987 found no increase in risk of lymphoma (standardized morbidity ratio = 0.51 [95% CI: 0.06 - 1.82]) (Winther 2004).

Hepatosplenic T-Cell Lymphoma

The frequency of this aggressive form of lymphoma is exceedingly rare. Accurate incidence rates are not available. For adalimumab-indicated populations, the background prevalence of HSTCL is not well described.

Leukemia

RA

The incidence rate of leukemia per 10,000 PYs as shown in a cohort of 789 Spanish RA patients was 17.0 (95% CI: 7.0 - 50.0) for the time period 1999 to 2005. The SIR was 8.8 (95% CI: 2.4 -22.6) (Abasolo 2008).

In Sweden, the SIR for leukemia was 1.23 (95% CI: 0.8 - 1.8) among 11,683 patients with a diagnosis of RA on inpatient hospital records from 1965 through 1983 and followed through 1984. The period at risk excluded the 60 days after the first admission date (Gridley 1993).

The SIR of leukemia developing 1 to 4 years after initial RA hospitalization in a study of Swedish RA patients first hospitalized with a diagnosis of RA ranged from 1.65 (95% CI: 1.08 -2.42) for the period 1990 - 1999 to 2.03 (95% CI: 1.05 -3.56) for the period 2000 -2004 respectively (Hemminki 2008b). The SIR for acute myeloid leukemia ranged from 2.51 (95% CI: 1.14 - 4.8) to 6.9 (95% CI: 2.95 - 13.66), respectively (Hemminki 2008b).

CD

Authors of a meta-analysis of 4 studies involving 5,901 patients with CD reported the incidence of leukemia per 10,000 PYs as 0.82 (95% CI: 0.11 -2.25) (von Roon 2007). Utilizing 6 studies involving 27,272 patients with CD, the authors reported the RR of leukemia as 1.15 (95% CI: 0.69 - 1.92) compared to the general population (von Roon 2007).

The SIR of leukemia among 21,788 Swedish CD patients hospitalized with a diagnosis of CD recorded on the discharge between 1964 and 2004 was 1.35 (95% CI: 0.54 -2.80) 1 to 4 years after initial hospitalization (Hemminki 2009).

A study of 5,127 hospitalized English CD patients reported an adjusted RR of lymphoid leukemia compared to a non-IBD reference cohort occurring at least 1 year after initial hospitalization of 0.97 (95% CI: 0.12 -3.53) (Goldacre 2008). The adjusted RR of myeloid leukemia was 2.0 (95% CI: 0.73 -4.41) (Goldacre 2008).

A follow-up study of 2,645 Danish patients starting 1 year subsequent to hospitalization with CD between 1977 - 1989 reported the SIR of leukemia as 1.2 (95% CI: 0.2 - 3.4) (Mellemkjaer 2000).

The standard morbidity ratio for leukemia was 0.70 (95% CI: 0.02 - 3.93) in a population of 1,251 CD patients in Stockholm County with inpatient hospital records from 1955 - 1984 and followed until 1989 (Persson 1994).

The age-adjusted incidence rate of leukemia/multiple myeloma per 100,000 PYs as shown in a population-based cohort of 2,857 CD patients in Manitoba, Canada was 18.0 (95% CI not reported) from 1984 - 1997 (Bernstein 200lb). The IRR of leukemia/multiple myeloma in CD patients compared to non-IBD residents of Manitoba by age, sex, and postal area of residence was 0.79 (95% CI: 0.24 -2.54) (Bernstein 200lb).

Ps

The SIR for leukemia cancers among 15,858 Swedish patients with a Ps diagnosis on inpatient hospital records between 1965 and 2004 was 1.47 (95% CI: 0.97 -2.14) 2: 1 year after last Ps hospitalization (Ji 2009).

The SIR for leukemia among 6,910 Danish patients with a Ps diagnosis on inpatient hospital records between 1977 and 1987 and followed-up through 1993 was 0.9 (95% CI: 0.5 - 1.6) (Frentz 1999).

The incidence of leukemia equaled 0.33 per 1,000 person-years (95% CI: 0.25 - 0.43) among patients identified in the UK GPRD database with a first diagnosis of psoriasis during the period 1994 through 2004. The incidence of leukemia among patients without psoriasis equaled 0.17 per 1,000 person-years (95% CI: 0.12 - 0.25). The IRR was 1.89 (1.21 - 2.94) (Brauchli 2009b).

UC

The age-adjusted incidence rate of leukemia/multiple myeloma per 100,000 PYs as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada was 19.6 (95% CI not reported) from 1984 - 1997 (Bernstein 200lb). The IRR of leukemia/multiple myeloma in UC patients compared to non-IBD residents of Manitoba by age, sex, and postal area of residence was 1.02 (95% CI: 0.37 -2.86) (Bernstein 200lb).

A study of 6,990 hospitalized English UC patients reported an adjusted RR of lymphoid leukemia compared to reference cohort occurring at least 1 year after initial hospitalization of 0.31 (95% CI: 0.001 -1.75) from 1963 through March 1999 (Goldacre 2008). The adjusted RR of myeloid leukemia was 2.15 (95% CI: 1.02 -4.03) (Goldacre 2008).

In Sweden, the SIR for leukemia occurring at least 1 year after the first hospitalization with a UC diagnosis equaled 0.98 (95% CI: 0.70 -1.35) among 27,606 patients between 1964 and 2004 (Hemminki 2008a).

The SMR for leukaemia was 1.43 (95% CI: 0.02 - 7.9) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 (Palli 1998).

For adalimumab indicated populations, the background prevalence of leukemia is not well described.

NMSC

RA

The SIR for NMSC was 0.97 (95% CI: 0.77 - 1.20) for males and 1.06 (95% CI: 0.92 - 1.21) for females among 26,623 Scottish RA patients hospitalized between 1981 and 1996, excluding events occurring ≤ 3 months after initial hospitalization (Thomas 2000b).

In Sweden, the SIR for NMSC was 1.17 (95% CI: 0.8 - 1.7) among 11,683 patients with a hospital diagnosis of RA between 1965 and 1983 and followed up through 1984 (Gridley 1993).

Excluding the first year of follow-up, the RR for basal cell carcinoma was 1.3 (95% CI: 1.1 - 1.4) among 20,699 Denmark patients with an RA inpatient diagnosis during 1977 - 1987 and followed up through 1991 compared to that of the general Danish population. The RR for squamous cell carcinoma was 1.4 (95% CI: 1.1 - 1.9) for the same cohort (Mellemkjaer 1996).

The SIR of squamous cell carcinoma after initial RA hospitalization occurring in 2000 -2004 and followed up through 2004 equaled 3.93 (95% CI: 2.78 - 5.4) in Danish RA patients (Hemminki 2008b).

AS

Excluding the first year of follow-up, the SIR for NMSC among 6,621 Swedish patients with an AS inpatient diagnosis during 1965 - 1995 and followed up through 1995 equaled 0.76 (95% CI: 0.33 -1.37) (Feltelius 2003).

CD

The SIR of squamous cell carcinoma among 21,788 Swedish patients with a CD inpatient diagnosis occurring from 1964 -2004 was 2.14 (95% CI: 1.13 - 3.67) for the period 1 to 4 years after hospitalization (Hemminki 2009).

Excluding the first year following first hospitalization for CD, the SIR for NMSC equaled 1.2 (95% CI: 0.7 - 1.8) in a follow-up study of 2,645 Danish CD patients with hospitalization occurring during 1977 - 1989 and followed through December 1993 (Mellemkjaer 2000).

The standard morbidity ratio for NMSC was 1.53 (95% CI: 0.19 - 5.52) in a population of 1,251 CD patients in Stockholm County, Sweden diagnosed during 1955 - 1984 and followed until 1989 (Persson 1994).

Ps

The SIR for squamous cell carcinoma among 5,687 Finnish Ps patients with an inpatient PS diagnosis during 1973 - 1984 and followed up through 1995 was 3.2 (95% CI: 2.3 -4.4) excluding the first 6 months following initial Ps hospitalization. In the same cohort, the SIR for basal cell carcinoma equaled 1.2 (95% CI: 1.0 - 1.5) (Hannuksela-Svahn 2000).

The SIR for NMSC among 6,905 Danish Ps patients with an inpatient Ps diagnosis between 1977 and 1987 and followed up through 1993 was 2.46 (95% CI: 2.13 -2.83) (Frentz 1999).

Excluding the first year of follow-up after initial hospitalization for Ps, the SIR for squamous cell skin cancer among 15,858 Swedish Ps patients hospitalized between 1965 and 2004 and followed-up through 2004 equaled 2.08 (95% CI: 1.67 -2.55) (Ji 2009).

UC
Results from the Danish cancer registry data (1977 - 1989) found a slight increase in NMSC in ulcerative colitis patients compared to the general Danish population (RR = 1.4 [95% CI: 1.0 -1.9]) (Mellemkjaer 1995).

In Sweden, the SIR for squamous cell skin cancer occurring at least 1 year after the first hospitalization with a squamous cell skin cancer diagnosis equaled 1.03 (95% CI: 0.78 - 1.34) among 27,606 patients between 1964 and 2004 (Hemminki 2008a).

RA
The period prevalence (March 1999 through June 2005) of NMSC among male and female Spanish RA patients was 0.90% (0.01 - 3.2) and 0.53% (0.1 - 1.5), respectively (Abasolo 2008).

Background mortality

For adalimumab -indicated populations, the background mortality from NMSC is not well described.

Melanoma

RA
The incidence rate of melanoma per 10.000 PYs as shown in a cohort of 789 Spanish RA patients was 4.0 (95% CI: 1.0 - 31.0) (Abasolo 2008).

Compared to the general Danish population, the relative risk (RR) for melanoma was 1.1 (95% CI: 0.8 - 1.5) among 20,699 Denmark RA patients with inpatient records between 1977 and 1991 and followed 1 - 15 years after initial hospitalization. The first year of follow-up for cancer was excluded from the analysis (Mellemkjaer 1996).

The SIR for melanoma was 0.34 (95% CI: 0.04 - 1.22) for males and 1.21 (95% CI: 0.79 - 1.77) for females among 26,673 Scottish RA patients with inpatient hospital records between 1981 and 1996, excluding events occurring <3 months after initial hospitalization (Thomas 2000b). In Sweden, the SIR for melanoma was 0.93 (95% CI: 0.5 - 1.6) among 11,683 RA patients with inpatient hospital records between 1965 and 1983 and followed-up through 1984. Patients with less than 60-days of follow up prior to death or cancer were excluded (Gridley 1993).

The SIR of melanoma developing 1 -4 years after initial RA hospitalization in a study of Danish RA patients with inpatient hospital records between 2000 and 2004 was 1.83 (95% CI: 1.00 -3.07) (Hemminki 2008b).

A study using inpatient records from California hospitals linked to the California Cancer Registry reported the standardized incidence ratio (SIR) for melanoma was 0.80 (95% CI: 0.63 - 1.00) for males and 0.63 (95% CI: 0.51 - 0.76) for females among 84,475 patients with inpatient records between 1991 and 2002, excluding events occurring < 6 months after initial hospitalization (Parikh-Patel 2009).

Among 459 RA patients treated with MTX and receiving care at rheumatology clinics in Melbourne, Australia, the SIR for melanoma was 3.0 (95% CI: 1.2 - 6.2). MTX treatment began prior to June 1986 for all patients and follow-up spanned 1983 - 1998 (Buchbinder 2008).

The period prevalence (March 1999 through June 2005) of melanoma as shown in a cohort of 568 female Spanish RA patients was 0.17% (95% CI: 0.004 - 0.98) (Abasolo 2008).

CD
The age-adjusted incidence rate of melanoma per 100,000 PYs as shown in a population-based cohort of 2,857 CD patients in Manitoba, Canada was 16.4 (95% CI not reported) for the years 1984 - 1997 (Bernstein 200lb). In this study, the IRR comparing the population-based cohort of CD patients with non-CD residents of Manitoba by age, sex, and postal area of residence for melanoma was 1.06 (95% CI: 0.32 -3.50) (Bernstein 200lb).

The SIR of melanoma among 21,788 Swedish CD patients with inpatient hospital records between 1964 and 2004 was 1.41 (95% CI: 0.75 -2.43 1 - 4 years subsequent to initial CD hospitalization (Hemminki 2009).

A study of 5,127 hospitalized English CD patients reported the adjusted RR of malignant melanoma that occurred at least one year subsequent to initial hospitalization as 0.57 (95% CI: 0.07-2.07) for the period 01 January 1963 to 31 March 1999 (Goldacre 2008).

A follow-up study of 2,645 Danish patients starting 1 year subsequent to hospitalization with CD between 1977 and 1989 reported the SIR of melanoma as 0.8 (95% CI: 0.2 - 2.4) (Mellemkjaer 2000).

The standard morbidity ratio for melanoma was 1.21 (95% CI: 0.25 -3.53) in a population of 1251 CD patients in Stockholm with inpatient hospital records from 1955 - 1984 and followed until 1989 (Persson 1994).

Ps
The SIR for melanoma among 15,858 Swedish Ps patients with inpatient hospital records between 1965 and 2004 was 0.95 (95% CI: 0.66 - 1.32) 2: 1 year after initial Ps hospitalization (Ji 2009).

The SIR for melanoma among 5,687 Finnish Ps patients with inpatient hospital records between 1973 and 1984 and followed up through 1995 was 0.8 (95% CI: 0.3 - 1.6) 2: 6 months following initial Ps hospitalization (Hannuksela-Svahn 2000). The SIR for melanoma among 6,905 Danish Ps patients with inpatient hospital records between 1977 and 1987 and followed-up through 1993 was 1.3 (95% CI: 0.8 -2.1) (Frentz 1999).

The incidence of melanoma among 33,760 psoriasis patients in the UK equaled 0.18 per 1,000 person-years (0.13 - 0.26). The incidence of melanoma among 34,001 patients without psoriasis equaled 0.22 per 1,000 person-years (95% CI: 0.16 -0.31) (Brauchli 2009b).

UC
The age-adjusted incidence rate of melanoma per 100,000 PYs as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada was 16.7 (95% CI not reported) (Bernstein 2001b). In this study, the IRR comparing the population-based cohort of UC patients with non-UC residents of Manitoba by age, sex, and postal area of residence for melanoma was 1.11 (95% CI: 0.40 - 3.13) (Bernstein 2001b).

When compared to non-IBD, the adjusted RR of melanoma among 6,990 English UC patients with inpatient hospital records between 01 January 1963 to 31 March 1999 was 0.81 (95% CI: 0.22 -2.11) at least 1 year subsequent to the initial UC hospitalization (Goldacre 2008).

In Sweden, the SIR for melanoma was 1.01 (95% CI: 0.78 - 1.29) at least 1 year subsequent to initial UC hospitalization among 27,606 UC patients with inpatient hospital records between 1964 and 2004 (Hemminki 2008a).

Background morality:

For adalimumab-indicated populations, the background mortality from melanoma is not well described.

Merkel Cell Carcinoma
Studies estimate the incidence of MCC in the general population is in the range of 1.3 to 4.4 case per 1,000,000, (Reichgelt 2011, Kaae 2010, Hodgson 2005, Gatta 2011) and increases dramatically with age (18.3 to 56.2 per 1,000,000 for those aged 65 -69 years and 85+ years, respectively) (Hodgson 2005). RA and other autoimmune diseases may increase the risk of MCC in elderly patients (Lanoy 2010). Ina case-control study using SEER Medicare-linked data, RA was associated with an increased risk of MCC [OR = 1.39 (1.10 -1.75)] (Lanoy 2010). Psoriasis may increase the risk of MCC [Psoriasis OR = 1.29] while autoimmune gastrointestinal conditions may decrease the risk of MCC [Crohn's disease OR = 0.46; Ulcerative colitis OR = 0.83], but these results failed to meet statistical significance (Lanoy 2010). The study findings are limited to elderly patients (2'. 65 years) and did not adjust for immunosuppressive therapy (Lanoy 2010).

In Europe, the prevalence of MCC is estimated to be 0.86 per 100,000 (Gatta 2011).

In Europe, the 5-year survival of MCC is estimated to be 39.1% (Gatta 2011).

Risk Factors and Risk Groups

Lymphoma
Factors associated with an increased risk of NHL include weakened immune system (e.g., heritable disease, certain drugs used after an organ transplant), infection (e.g., HIV, Epstein-Barr virus, H. pylori, human T-cell lymphoma/leukemia virus type I (HTLV-I), and hepatitis C), and age (over 60 years) (National Cancer Institute 2008).

Factors associated with an increased risk of HL include weakened immune system (e.g., heritable disease, certain drugs used after an organ transplant), viral infection (e.g., HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older) (National Cancer Institute 2008).

A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01 - 13.9) (Beaugerie 2009).

HSTCL

Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks in Section SVII.3 may or may not be applicable to HSTCL which is rare (Kotlyar 2011, Parakkal 2011).

Leukemia

Factors associated with an increased risk of leukemia include radiation, tobacco smoking, benzene exposure, prior chemotherapies (e.g., alkylating agents), genetic diseases including Down syndrome, blood disorders (e.g., myelodysplastic syndrome), HLTV-I, and a family history of leukemia (National Cancer Institute 2014).

Non-Melanoma Skin Cancer

Factors associated with an increased risk of skin cancer include radiation (e.g., sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants, thiopurines (Peyrin-Biroulet 2011)), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic (National Cancer Institute 2011). Additional risk factors that increase squamous cell cancer risk are HPV infection and actinic keratosis (National Cancer Institute 2011).

Melanoma

Factors associated with an increased risk of melanoma include UV radiation (e.g., sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles (National Cancer Institute 2011).

Merkel Cell Carcinoma

Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g., organ transplant, HIV), other cancers (e.g., squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and hematological neoplasias) and UV light exposure (Becker 2010).

Preventability:

For all malignancies, patients are instructed to do the following: Tell your doctor if you develop symptoms including but not limited to fevers, weight loss, swelling of your lymph nodes, fatigue, easy bruising, or bleeding. These may be early signs and symptoms of cancer. Further testing may be needed to determine if this is the case.

Tell any doctor you see that you are taking Idacio. Show your Patient Reminder Card to any healthcare professional that you consult.

Tell your doctor if you are taking AZA or 6-MP in addition to Idacio.

For NMSC, Melanoma, and MCC:

Preventative skin examinations by a physician on an annual basis in patients, sunscreen use and education concerning the risk and prompt detection of lesions.

Patients are instructed to do the following: If new skin lesions appear during or after therapy, or if existing lesions change appearance, tell your doctor.

Skin examinations by a physician should be performed before starting Idacio and on an annual basis while on Idacio, especially if you have a history of extensive immunosuppressive therapy or if you are a psoriasis patient with a history of PUVA treatment.

Physicians should educate their patients about sunscreen use and the importance of prompt detection of lesions.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

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

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity that may in turn influence the appearance of demyelinating disorders, but the mechanism is unknown.

Evidence source(s) and strength of evidence: Idacio is a biosimilar medicine to the reference product Humira®. Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON]) has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with MSB11022 to date, there were no reports of demyelinating disorders.

According to the Idacio SmPC, demyelinating disorders has been reported to occur rarely (≥1/10,000 to < 1/1,000).

Severity and nature of risk

The risk includes serious disability and death.

Background incidence/prevalence/mortality

RA
A cohort study conducted using the GPRD found that the incidence of MS, the most common demyelinating disease, was not increased in RA patients compared to the general population (SIR = 0.73 [95% CI: 0.39 - 1.25]).

Additionally, MS patients were not at increased risk of developing RA (SIR = 0.80 [95% CI: 0.54 - 1.14]) (Somers 2009).

CD
A cohort study conducted using the GPRD found the risk of MS/demyelinating disease/optic neuritis was increased among CD patients compared to those without IBD (RR = 2.12 [95% CI: 0.94 - 4.50]) (Gupta 2005).

A cross-sectional study of health records in Manitoba Canada found the prevalence of MS among CD patients equaled 0.41%. Risk of MS was not significantly elevated compared to non-IBD controls (OR = 1.11 [95% CI: 0.67 - 1.84) (Bernstein 2006).

A cross-sectional analysis of two large administrative medical claim databases (IMS Health and MarketScan) found MS prevalence was increased among patients with CD compared to those without IBD (OR = 1.48 [95% CI: 1.00 - 2.18] in MarketScan and OR = 1.59 [95% CI: 1.17 - 2.16] in IMS Health) (Cohen 2008b).

A cross-sectional study of administrative medical claims (Kaiser Permanente Medical Care Program) found MS prevalence was greater among patients with CD than patients without IBD (OR = 2.4 [95% CI: 1.2 -4.8 (Weng 2007).

A cross-sectional analysis of the GPRD found MS and optic neuritis prevalence was similar between patients with CD and without IBD (OR = 1.35 [95% CI: 0.83 -2.22] and OR = 0.96 [95% CI: 0.39 -2.34], respectively). However, the combined prevalence of MS, optic neuritis and demyelination was greater in CD patients compared to controls (OR = 1.54 [95% CI: 1.03 -2.32]) (Gupta 2005).

UC
A cohort study conducted using the GPRD found the incidence of MS/demyelinating disease/optic neuritis was increased among UC patients compared to patients without IBD (RR = 2.63 [95% CI: 1.29 - 5.15]) (Gupta 2005).

A cross-sectional study of health records in Manitoba Canada found the prevalence of MS among UC patients equaled 0.54%. This prevalence was higher than the prevalence observed in non-IBD controls (OR = 1.90 [95% CI: 1.19 -3.03) (Bernstein 2006).

A cross-sectional analysis was conducted in two large administrative medical claim databases (IMS Health and MarketScan). Among IMS Health enrolees, MS prevalence was increased among patients with UC compared to those without IBD (OR = 1.47 [95% CI: 1.11 - 1.95]). Among MarketScan enrolees, MS prevalence was similar among patients with UC and those without IBD (OR = 1.17 [95% CI: 0.81 - 1.68]) (Cohen 2008b).

A cross-sectional study of administrative medical claims (Kaiser Permanente Medical Care Program) found MS prevalence was greater among patients with UC than patients without IBD (OR = 2.3 [95% CI: 1.6 -3.3) (Weng 2007).

A cross-sectional analysis of the GPRD found MS and optic neuritis prevalence was increased in patients with UC compared to those without IBD (OR = 1.49 [95% CI: 1.03 - 2.16] and OR = 2.72 [95% CI: 1.47 - 5.04], respectively). The combined prevalence of MS, optic neuritis and demyelination was greater in UC patients compared to controls (OR 1.75 [95% CI: 1.28 -2.39]) (Gupta 2005).

Uveitis

A retrospective analysis of a large administrative claims database (MarketScan) found the incidence of demyelinating disease was highest in patients with intermediate uveitis (1.00/100 PYs compared to 0.24/100 PYs for anterior uveitis, 0.44/100 PYs for posterior uveitis, and 0.75/100 PYs for panuveitis uveitis) and MS (0.81/100 PYs compared to 0.12/100 PYs for anterior uveitis, 0.21/100 PYs for posterior uveitis, and 0.34/100 PYs for panuveitis).

In a small study, Zein et al reported that the prevalence of MS in patients with uveitis was 1.3% and that 44% of the 16 MS cases had ON (Zein 2004).

Among 2,617 uveitis patients treated at a single center in Vienna, Austria between 1995 and 2009, the prevalence of MS equaled 1.0%. MS was one of the most common comorbidities associated with intermediate uveitis with a prevalence rate of 4.9% among this group (Barisani-Asenbauer 2012).

The prevalence of MS among 1,686 uveitis patients treated at a single center in Germany was reported between 2001 and 2006. MS was diagnosed in 10.3% of patients with intermediate uveitis (Jakob 2009).

A single-center Spanish study including 1,022 uveitis patients treated between 2009 and 2012 reported that the overall prevalence of MS equaled 0.8%. MS had the highest prevalence among patients with intermediate uveitis (7%), while the prevalence among patients with panuveitis equaled 0.6% (Llorenc 2015).

A retrospective cohort study including 1,450 uveitis patients treated between 1985 and 2000 at a single center in the US reported that the prevalence of MS and ON equaled 1.0% and 0.5%, respectively (Smith and Rosenbaum 2004)

No studies/analyses with incidence or prevalence data for demyelinating disorders in pedUV patients are available.

For adalimumab indicated populations, the background mortality from demyelinating disorders is not well described.

Risk Factors and Risk Groups

Factors associated with an increased risk of MS include genetic predisposition (e.g., HLA-DR2 (HLA-DRBl *15), ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors (Ramagopalan 2010).

Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age (Sejvar 2011).

Subjects with intermediate uveitis have a high prevalence of demyelination (Zein 2004, Llorenc 2012, Messenger 2015).

Preventability:

Screening and evaluation by a physician for demyelinating disorders in patients with intermediate uveitis.

Patients are instructed of the following: If you have demyelinating disease such as MS, your doctor will decide if you should receive Idacio.

Show your Patient Reminder Card to any healthcare professional that you consult.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact

Important Identified risk 5: BCG disease following live BCG vaccination in infants with in utero exposure to Idacio

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. BCG disease following live BCG vaccination in infants within utero exposure to Idacio has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

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

Frequency by Incidence

In the clinical studies conducted with Idacio to date, there were no reports of BCG disease.

Risk Factors and Risk Groups

Infants who are exposed to Idacio intrauterine.

Preventability:

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

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. Additional risk minimization tool language is being proposed with this RMP update. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Table 7 Presentation of Important Potential Risks

Important Potential Risk 1: Progressive Multifocal Leukoencephalopathy (PML)

Potential mechanisms:

Reactivation of Polyomavirus JC (often called JC virus).

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Progressive Multifocal Leukoencephalopathy has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with Idacio to date, there were no reports of PML.

Severity and nature of risk

Severe neurological disabilities and death.

Background incidence/prevalence/mortality

RA
Estimates from ARTIS equal 0.3 per 100,000 (0.1 -0.6) person-years in the general population, 1.0 per 100,000 person-years (0.3 -2.5) among RA patients overall, 0.8 (0.2 -2.5) per 100,000 person-years among RA biologic-naive patients, and 2.3 (0.1 -71) per 100,000 person-years among RA biologic-treated patients (Arkema 2012).

PML is a rare demyelinating disease of the CNS caused by JC virus (JCV), a polyomavirus. JCV is widespread and about 50% to 85% of populations in the United States and Europe are antibody positive (Weber 2008).

The mortality of PML in the United States (estimated from analysis of national mortality and AIDS surveillance data) rose from 0.15 cases per million before the AIDS pandemic to 0.61 cases per million during the HIV/AIDS era (Weber 2008, Holman 1991).

Risk Factors and Risk Groups

PML occurs predominantly among severely immunosuppressed patients. A descriptive analysis of PML cases identified through claims found approximately 40% of patients were aged 40 to 49 years and 75% were male (Eng 2006). Currently, over 80% of PML cases are diagnosed in patients with HIV AIDS (Weber 2008). Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukemia (Carson 2009). Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases (Carson 2009, Calabrese 2007, Bartt 2006, Govindappa 2007).

The potential mechanism for PML is reactivation of polyomavirus JC in the brain that is believed to be started by severe immunosuppression as in HIV infection. There is no known association of PML with the use of adalimumab or other TNF inhibitors, however, because PML is rare and often fatal its appearance in patients on biologic medications including adalimumab is under observation.

Preventability:

Reversal of immune deficient state.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Important Potential Risk 2: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Reversible Posterior Leukoencephalopathy Syndrome has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with Idacio to date, there were no reports of RPLS.

Severity and nature of risk

Neurological disabilities, multisystem organ involvement, and sequelae, blindness, death.

Background incidence/prevalence/mortality

For Idacio-indicated populations, the background incidence, prevalence or mortality of RPLS is not well described.

Risk Factors and Risk Groups

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

RPLS is a syndrome characterized by headache, confusion, seizures and visual loss. This syndrome appears in patients who become severely immunosuppressed by drugs like those used for anti-rejection. Stopping the drug(s) makes the condition reverse. There is no known association of this event with adalimumab use; however, rare RPLS reports in patients using adalimumab have been received and although most have other causes, the reports are under observation for a possible association.

Preventability:

Unknown

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

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

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Idacio is a biosimilar medicine to the reference product Humira®. Adenocarcinoma of colon in ulcerative colitis (UC) patients has been classified as an identified risk for Idacio in accordance with the reference product.

Characterization of the Risk:

Frequency by Incidence

In the clinical studies conducted with Idacio to date, there were no reports of adenocarcinoma of colon in ulcerative colitis (UC) patients.

Severity and nature of risk

The risk includes death.

Background incidence/prevalence/mortality

The age-adjusted incidence rate of colon cancer in a population-based cohort of 2,672 UC patients in Manitoba, Canada from 1984 to 1997 was 161.1 per 100,000 PYs (95% CI not reported) (Bernstein 2001b). In this study, the

IRR comparing the population-based cohort of 2,672 UC patients in Manitoba, Canada with a non-UC cohort matched on age, sex, and postal area of residence for colon cancer was 2.75 (95% CI: 1.91 - 3.97) (Bernstein 2001b).

Excluding the first year after initial UC hospitalization, the adjusted RR of colon cancer among 6,990 English patients with an inpatient diagnosis of UC between 01 January 1963 through 31 March 1999 and followed through 31 March 1999 was 2.22 (95% CI: 1.71 - 2.83) when compared to hospitalized patients without IBD (Goldacre 2008).

For adalimumab-indicated populations, the background prevalence of colorectal cancer in the UC population is not well described.

The SMR for colon cancer was 0.75 (95% CI: 0.01 - 4.2) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 (Palli 1998). The SMR for colorectal cancer was 4.4 (95% CI: 3.2 - 0.9) in a study of 2,509 patients diagnosed with UC between 1965 and 1983 in Sweden and followed through 1986 (Ekbom 1992).

The SMR for rectal cancer was 4.35 (95% CI: 0.9 - 12.7) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 (Palli 1998).

Risk Factors and Risk Groups

Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid PSC (Van Assche 2013), diet, and cigarette smoking (National Cancer Institute 2006).

There is a known increased risk of adenocarcinoma of colon in UC patients that increases with degree of bowel inflammation as well as the duration of disease. Since early detection can limit morbidity from adenocarcinoma of colon, patients with UC, regardless of the therapy used, should receive routine screening (colonoscopy) more frequently than that recommended for the general population according to current practice guidelines. Since there may be an increased risk of cancer in patients receiving adalimumab, it is not known if this therapy further increases the risk of adenocarcinoma of colon in UC patients, thus, reports of this cancer are under observation in this patient group.

Preventability:

Not preventable, however early detection can limit morbidity. There is a known increased risk of adenocarcinoma of colon in UC patients. As a result, the routine screening of UC patients for dysplasia prior to and during therapy with adalimumab is more frequent than the recommended screening frequency for the general population according to current practice guidelines. Routine screening is recommended in the product label.

Impact on the Risk-Benefit Balance of the Product:

Appropriate risk minimization measures are in place. With these measures in place, the risk benefit balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

SVII.3.2 Presentation of the Missing Information

Table 8 Presentation of the Missing Information

Missing information 1: Episodic treatment in UC.
The population is in need of further characterization. Routine pharmacovigilance surveillance is being performed.
Missing information 2: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD
The population is in need of further characterization. Routine pharmacovigilance surveillance is being performed.

Missing information 3: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis
The population is in need of further characterization. Routine pharmacovigilance surveillance is being performed.

Part II: Module SVIII Summary of the Safety Concerns

In view of the structural similarity and comparable performance in the functional assays, as well as the exemplary data showing correspondence of their clinical behavior there is ample evidence that Idacio and Humira® are comparable versions of adalimumab. Accordingly, the expected safety profile of Idacio is the same as that of Humira®.

Important identified and potential risks as well as missing information include the following:

Summary of Safety Concerns	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including MS, GBS and optic neuritis) • BCG disease following live BCG vaccination in infants with in utero exposure to Idacio
Important potential risks	• Progressive Multifocal Leukoencephalopathy (PML) • Reversible Posterior Leukoencephalopathy Syndrome (RPLS) • Adenocarcinoma of colon in UC patients
Missing information	• Episodic treatment in UC • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Part III: Pharmacovigilance Plan (including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Fresenius Kabi has established an effective pharmacovigilance system to collect, collate and evaluate individual case safety reports obtained through spontaneous reporting systems, identified from the worldwide scientific literature or received from competent authorities. Individual case safety reports are followed up to ensure that all relevant information is captured. Cumulative safety information is regularly reviewed during signal detection processes.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for malignancies and premalignancies:

Fresenius Kabi has a standardized global process for the use of follow-up questionnaires within the pharmacovigilance system as part of post-marketing surveillance. This process includes contact to the healthcare professional (HCP) or reporter using the questionnaire via phone, fax or send letter/form. The follow-up to consumer will include an attempt to obtain consent to contact the HCP. A minimum number of queries are made depending on the seriousness of the case; medical judgment or local regulations are applied to determine if further attempts (above the minimum) should be made. Data collection will occur using the questionnaire listed in Annex 4.

See Annex 4 of the RMP.

III.2 Additional Pharmacovigilance Activities

III.2.1 Observational registry (RABBIT) Study #1 (Study Identifier: FKS0-000-RAB)

Study short name and title:

Participation in a Medical Society Registry established in one of the major EU markets for patients with Rheumatoid Arthritis following a prospective cohort design and collecting data on Idacio.

Rationale and study objectives:

The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.

Study design:

The candidate Medical Society Registries follow an observational prospective cohort design. As the intent is to join an existing investigational effort. The modalities of patient enrollment data collection and other pertinent details will already be pre-specified in the governing documents for this investigation.

Further details concerning the study design are specified in the protocol of the selected Medical Society Registry.

The pre-selected primary candidate registry for this study is the German biologics register RABBIT ("Rheumatoid Arthritis - Beobachtung der Biologika Therapie").

Study population:

The study population is defined by clinical protocol governing the Medical Society Registry. For inclusion into the Idacio sub-study the following inclusion criteria must be fulfilled:

1. Diagnosed by the qualifying medical condition: rheumatoid arthritis (RA) as diagnosed by a rheumatologist.
2. Existing regimen including Idacio
3. Signed informed consent
4. Age ≥18 years of age

Current Status

Early termination of Idacio participation in the long term observational rheumatoid arthritis registry in Germany (RABBIT) due to lack of patient enrolment.

Justification:

The Marketing Authorization Holder (MAH) proposed to terminate participation of Idacio in the RABBIT observational registry in Germany due to lack of patient enrolment. The MAH had expected a target enrolment of 150 patients in this registry between Q1'2020 and Q1'2025. As of 01 Oct. 2024, however, only 63 patients have been enrolled. The MAH does not expect the registry to reach the target of 150 patients by Q1'2025.

Based on the extensive post-marketing data available for Idacio since International Birth Date (02 Apr. 2019), it is unlikely that data generated from the RABBIT registry will provide any new significant safety information to the existing knowledge about the product.

Overall, it can be concluded that this early termination does not impact benefit risk profile of Idacio. Based on the cumulative assessment performed in the Addendum to the Clinical Overview (reporting period: 02 Apr. 2019-02 Mar. 2023, submitted as part of the Idacio renewal application), it was concluded that benefit-risk balance of Idacio in the approved indication remains favorable.

In addition, based on the latest PSUR (reporting period: 01 Jan. 2024 – 30 Jun. 2024) prepared for non-EU countries, no new safety information with IDACIO has been identified and therefore, the MAH concludes that the registry will not add any new information to the existing knowledge about the safety of Idacio. The MAH will continue to monitor the safety profile of Idacio through routine pharmacovigilance activities.

Following discontinuation, the final study report based on the available data with a cut-off date of 31-Dec-2024 will be provided in Q2'2026.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 9 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Participation in a Medical Society Registry established in one of the major EU markets for patients with Rheumatoid Arthritis (RA) following a prospective cohort design and collecting data on Idacio. Discontinued	The purpose of the study is to contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.	Serious infections, Tuberculosis (TB), Malignancies, Demyelinating disorders, Progressive multifocal leukoencephalopathy, Reversible posterior leukoencephalopathy syndrome	Category 3 Study open for enrollment: Q1 - 2020 End of participation in the registry: Q4 - 2024 Final study report of the Category 3 study: Q2 - 2026	Final report of study results: Q2-2026

Part IV: Plans for Post-authorization Efficacy Studies

No post authorization efficacy studies are planned.

Part V: Risk Minimization Plan (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Planned routine risk minimization measures are summarized by safety concern in the tables below.

Table 10 Routine Risk Minimization Measures

Safety concern	Routine risk minimisation activities
Serious infections	Routine risk communication: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population ≥65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC instructs to seek medical advice for signs or symptoms suggestive of clinically important infection. Guidance on when to suspect invasive fungal infection provided and start empiric anti-fungal therapy in consultation with a physician with expertise in the care of patients with invasive fungal infections. Other routine risk minimization measures: Prescription only medicine.
Tuberculosis (TB)	Routine risk communication: Text in SmPC: Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB

	In order to inform patients of these risks, corresponding text is also present in the package leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC: appropriate screening for active or inactive TB Section 4.3 and 4.4 of the SmPC: patients with active TB should not receive Idacio. Section 4.4 of the SmPC: In patient with latent TB, anti-tuberculosis prophylaxis treatment before the initiation of Idacio, and in accordance with local recommendations. Section 4.4 of the SmPC: Patients should be instructed to seek medical advice for specific signs/symptoms suggestive of a tuberculosis infection Other routine risk minimization measures: Prescription only medicine.
Malignancies	Routine risk communication: Text in SmPC: Section 4.4: Warning regarding lymphoma, HSTCL, leukaemia, NMSC, melanoma, MCC, and malignancies in the adult and paediatric population. Section 4.8: Information on incidence rates from clinical trials in lymphoma, NMSC, and melanoma. Information on incidence rates from postmarketing surveillance in HSTCL, leukaemia, and MCC. The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of AZA or 6-MP, and that the potential risk combination of AZA or 6-MP and Idacio should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states patients should be examined for the presence of nonmelanoma skin cancer prior to and during treatment with Idacio. Section 4.4 of the SMPC includes language on screening for colonic dysplasia before therapy and at regular intervals during therapy. (see also risk of adenocarcinoma of colon in UC) Other routine risk minimization measures: Prescription only medicine.
Demyelinating disorders (including multiple sclerosis	Routine risk communication: Text in SmPC

[MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON])	Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in postmarketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Idacio therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. Other routine risk minimization measures: Prescription only medicine.
BCG disease following live BCG vaccination in infants with in utero exposure to Idacio	Routine risk communication: Text in the SmPC: section 4.4 of the SmPC has section on vaccinations. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states Patients on Idacio may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. Administration of live vaccines (e.g., BCG) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. Other routine risk minimization measures: Prescription only medicine.
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk communication: Text in SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures: Prescription only medicine.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Routine risk communication: Text in SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures: Prescription only medicine.
Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk communication: Text in SmPC: Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), 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. Routine risk minimization activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC includes language on screening for colonic dysplasia before therapy and at regular intervals during therapy. Other routine risk minimization measures: Prescription only medicine.
Episodic treatment in UC	Routine risk communication: Text in SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures: Prescription only medicine.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk communication: Text in the SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures:

	Prescription only medicine.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk communication: Text in the SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures: Prescription only medicine.

V.2 Additional Risk Minimization Measures

Fresenius Kabi has an additional risk minimization program to remind patients about key risks associated with the use of Idacio. The additional risk minimization measures are outlined below.

Patient Material

Additional Risk Minimization measure: **Patient (including pediatric) Reminder Card**

Objectives: The objective of the measure is to remind patients (or caregivers) on the key risks for adalimumab. These include serious infections, Tuberculosis (TB), demyelinating disorders, malignancies, and the risk of BCG disease following live BCG vaccination in infants with in utero exposure to Idacio. In addition, the patient reminder card can also serve as information that a patient can provide to any HCPs that may treat the patient (i.e., non Idacio prescribing HCP), so that the HCP is aware that the patient is being treated with adalimumab and can take this into consideration.

Rationale for the Additional Risk Minimization Activity (Patient Material):

The targeted risks are believed to be those which patients need to be aware of and in which signs/symptoms may be used to help patients recognize when they should seek medical advice.

Implementation Plan (including Target Audience and Planned Distribution Path):

The patient reminder card is distributed to prescribers (HCPs) of Idacio (regardless of indication of use) who then distributes it to their patients.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

In accordance with the PRAC's assessment of the RMP for reference product Humira® (version 11.2_EU within procedure EMEA/H/C/481/II/134), ongoing routine pharmacovigilance activities are considered sufficient to monitor the effectiveness of the additional risk minimization measures.

V.3 Summary of Risk Minimization Measures

Table 11 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Idacio: • Patient Reminder Card	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Tuberculosis (TB)	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Idacio: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Malignancies	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Idacio: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Specific adverse reaction follow-up questionnaires for malignancies and premalignancies. Additional pharmacovigilance activities: None.
Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON])	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: To remind patients about the risk of demyelinating disorders associated with the use of Idacio. • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
BCG disease following live BCG vaccination in infants with in-utero exposure to Idacio	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: To remind patients about the risk of BCG disease following live BCG vaccination in infants with in-utero exposure to Idacio. • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.

Progressive Multifocal Leukoencephalopathy (PML)	Routine risk minimization measures: The SmPC currently contains no text regarding PML. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Routine risk minimization measures: The SmPC currently contains no text regarding reversible posterior leukoencephalopathy syndrome. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Adenocarcinoma of colon in ulcerative colitis (UC) patients	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None
Episodic treatment in UC	Routine risk minimization measures: The SmPC currently contains no text regarding Episodic treatment in UC. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk minimization measures: Labelling as detailed in Table 10. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Idacio (adalimumab)

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

Idacio's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Idacio should be used.

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

I. The Medicine and What it is used for

Idacio is authorized for use in adults in the treatment of:

- Rheumatoid Arthritis (RA),
- Psoriatic Arthritis (PsA)
- Axial Spondyloarthritis (Axial SpA)
- Crohn's Disease (CD),
- Psoriasis,
- Ulcerative Colitis (UC),
- Hidradenitis Suppurativa, and
- Uveitis.

Idacio is authorised for use in paediatrics for the treatment of:

- Polyarticular Juvenile Idiopathic Arthritis (pJIA),
- Paediatric Enthesitis-related Arthritis (pedERA);
- Pediatric Crohn's Disease (pedCD);
- Pediatric Psoriasis (pedPs);
- Adolescent Hidradenitis Suppurativa (HS);
- Paediatric Uveitis (pedUV)
- Paediatric Ulcerative Colitis

Refer to SmPC for the full indications. It contains adalimumab as the active substance and it is given by subcutaneous (SC) injection.

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

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

Measures to minimize 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 authorized 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 minimize its risks.

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

In the case of Idacio, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Idacio is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Idacio are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Idacio. 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 infections • Tuberculosis (TB); • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS], and optic neuritis [ON])

List of important risks and missing information	
	• BCG disease following live BCG vaccination in infants with in utero exposure to Idacio
Important potential risks	• Progressive multifocal leukoencephalopathy (PML); • Reversible posterior leukoencephalopathy syndrome (RPLS); and • Adenocarcinoma of colon in ulcerative patients (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD; • Episodic treatment in UC; • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

II.B Summary of Important Risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Serious infections has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly Population ≥65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Idacio: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Tuberculosis has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g., pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections (Institute of Medicine: National Academy Press 1992).
Risk minimization measures	Routine risk minimization measures:

	Text in SmPC: Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Idacio: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Malignancies has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01 - 13.9) (Beaugerie 2009). Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks may or may not be applicable to HSTCL which is rare (Kotlyar 2011, Parakkal 2011). Risk factors for leukemia depend on the type of leukemia. In general, factors associated with an increased risk of leukemia include smoking, exposure to certain chemicals such as benzene, exposure to radiation, past treatment with chemotherapy or radiation therapy, having certain inherited or genetic disorders, having certain blood disorders, and having a family history of leukemia (National Cancer Institute 2014). Factors associated with an increased risk of skin cancer include radiation (e.g., sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants, thiopurines [Peyrin-Biroulet 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic (National Cancer Institute 2011b). Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis (National Cancer Institute 2011b). Factors associated with an increased risk of melanoma include UV radiation (e.g., sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g., antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune

	system, dysplastic nevus, and having many common moles (National Cancer Institute 2011b). Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g., organ transplant, HIV), other cancers (e.g., squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure (Becker 2010a).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Warning regarding lymphoma, HSTCL, leukaemia, NMSC, melanoma, MCC, and malignancies in the adult and paediatric population. Section 4.8: Information on incidence rates from clinical trials in lymphoma, NMSC, and melanoma. Information on incidence rates from postmarketing surveillance in HSTCL, leukaemia, and MCC. The SmPC also highlights that some of the cases of HSTCL occurred with concomitant use of AZA or 6-MP, and that the potential risk combination of AZA or 6-MP and Idacio should be carefully considered. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Idacio: • Patient Reminder Card.
Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON])	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barre syndrome [GBS] and optic neuritis [ON]) has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (e.g., HLA-DR2 [HLA-DRB1*15], ethnic origin [being white], female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors) (Ramagopalan 2010). Factors associated with an increased risk of GBS include male sex, Campylobacter jejuni infection, some vaccines, and increased age (Sejvar 2011). Subjects with intermediate uveitis have a high prevalence of demyelination (Burkholder 2012, Zein 2004, Llorenc 2012, Messenger 2015).
Risk minimization measures	Routine risk minimization measures: Text in SmPC:

	Section 4.4: Warnings on demyelinating disorders are included. Further details for the uveitis patient population are also included. Section 4.8: Demyelinating disorders are also listed as adverse reaction identified in postmarketing surveillance. In order to inform patients of these risks, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of demyelinating disorders associated with the use of Idacio. • Patient Reminder Card.
Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Idacio	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. BCG disease following live BCG vaccination in infants with in utero exposure to Idacio has been classified as an identified risk for Idacio in accordance with the reference product.
Risk factors and risk groups	No epidemiological data available.
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: Section 4.4 of the SmPC has section on vaccinations. Instructions for preparing and giving an injection of adalimumab are outlined in the Package Leaflet. Prescription only medicine. Additional risk minimization measures: To remind patients about the risk of live vaccines associated with the use of Idacio and the risk of live vaccines in infants exposed to Idacio in utero: • Patient Reminder Card.
Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Progressive Multifocal Leukoencephalopathy has been classified as a potential risk for Idacio in accordance with the reference product
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. A descriptive analysis of PML cases identified through claims found approximately 40% of patients were aged 40 to 49 years and 75% were male (Eng 2006). Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS (Weber 2008). Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukaemia (Carson 2009). Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other

	rheumatic diseases (Eng 2006, Carson 2009, Calabrese 2007, Bartt 2006, Govindappa 2007).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Important potential risk: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Reversible Posterior Leukoencephalopathy Syndrome has been classified as a potential risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Suspected etiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) (Lee 2008).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients	
Evidence for linking the risk to the medicine	Idacio is a biosimilar medicine to the reference product Humira®. Adenocarcinoma of colon in ulcerative colitis (UC) patients has been classified as a potential risk for Idacio in accordance with the reference product.
Risk factors and risk groups	Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid PSC (Van Assche 2013), diet, and cigarette smoking (National Cancer Institute 2006).
Risk minimization measures	Routine risk minimization measures: Text in SmPC: Section 4.4: Recommendation that all patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), 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. Prescription only medicine. Additional risk minimization measures: None.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Episodic treatment in UC	
Risk minimization measures	Routine risk minimization measures: Text in SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine. Additional risk minimization measures: None.

II.C Post-authorization Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of the invented name.

II.C.2 Other Studies in the Post-Authorization Development Plan

Observational registry (RABBIT) Study #1 ((Study Identifier: FKS0-000-RAB)-A prospective, observational cohort study (sample size of at least 150 subjects foreseen) whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumor necrosis factor-inhibitor therapies in the treatment of RA.

Purpose of the study: To contribute to the overall evidence base in support of adalimumab, in particular the estimation of incidence rates of adverse events of special interest for adalimumab as identified in the summary of safety concerns in the risk management plan.

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Part VII Annexes

Annex 1 **EudraVigilance Interface**

Not applicable. Submission of Annex 1 suspended per EMA instruction.

Annex 2 **Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme**

Refer to Annex 2

Annex 3 **Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan**

Refer to Annex 3

Annex 4 **Specific Adverse Drug Reaction Follow-up Forms**

Refer to Annex 4

Annex 5 **Protocols for Proposed and Ongoing Studies in RMP Part IV**

Not applicable

Annex 6 **Details of Proposed Additional Risk Minimisation Activities**

Refer to Annex 6

Annex 7 **Other Supporting Data (including Referenced Material) (see References)**

Annex 8 **Summary of Changes to the Risk Management Plan over Time**

Refer to Annex 8

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

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Follow-up forms

Malignancy and Pre-malignancy Follow-up Questionnaire

Patient Details

Initials:	Age (at the time of adverse event onset):
Date of Birth:	Sex:

Event Details:

Reported Event: _____

Qualifying criterion as a Serious Adverse Event:

☐ Death (autopsy: ☐ Yes ☐ No)
☐ Life-threatening
☐ Hospitalization or prolonged hospitalization
☐ Persistent or significant disability/incapacity
☐ Congenital anomaly/birth defect
☐ Important medical event

Onset Date (dd/mmm/yyyy): _____

Resolution of the event:
☐ Unknown
☐ Complete recovery
☐ Recovered with sequelae
☐ Not yet recovered
☐ Recovering

If recovered, date of recovery Date (dd/mmm/yyyy): _____

Exact diagnosis & localisation: _____

(Initial) Symptoms: _____

Onset of Symptoms (dd/mmm/yyyy)**:**

Initial diagnosis of the current event (dd/mmm/yyyy)**:**

Histopathologic classification: ** _____

TNM: ** _____ **UICC:** _____ **Grading:** _____

The current event: ☐ Premalignancy ☐ initial event ☐ recurrence ° ☐ metastasis ° ☐ 2° malignancy

°In case the event qualifies as a recurrence or metastasis:

Diagnosis of the current tumor/event: _____

Date of diagnosis (dd/mmm/yyyy)**:**

Histopathologic classification ** _____

TNM: ** _____ **UICC:** _____ **Grading:** _____

History of any other malignancies? ☐ yes : ☐ no ☐ not known

If yes, start date (dd/mmm/yyyy): stop date (dd/mmm/yyyy):

If so, diagnosis _____Treatment _____

Additional relevant information from the patient history (e.g. family history, occupational exposure, other co-morbidities, smoking)**:** _____

_____

☐ No/Unknown

Therapy *(Tick all that apply)*

☐ Chemotherapy ☐ Radiotherapy ☐ Surgical

☐ Discontinuation of Biologics- / DMARD ☐ unknown

☐ other: _____

Outcome of the Therapy: ☐ Complete remission ☐ Partial remission ☐ Progression ☐ un-assessable

Hospitalized? ☐ No ☐ Yes from _____ to _____

***** ***Please send us any relevant additional reports, if available***

Annex 6 Details of Proposed Additional Risk Minimisation Activities

Key messages of the additional risk minimisation measures

The Patient Reminder Cards (adult and paediatric) contain the following key elements:

- Before initiating treatment with Idacio, patient should tell his or her doctor about any health problems and any medicines they take. The patients should tell their doctor if they:
    - Have an infection or have symptoms of an infection (such as fever, wounds, feeling tired, dental problems)
    - Have tuberculosis or have been in close contact with someone with tuberculosis
    - Have or have had cancer
    - Have any numbness or tingling or have a problem that affects the nervous system, such as multiple sclerosis
- Patients on Idacio may receive concurrent vaccinations, except for live vaccines. Also, if the patient receives Idacio while pregnant, the baby should not receive a 'live vaccine', such as BCG within 5 months following their last Idacio injection during pregnancy.
- A description of the serious risks, and their sign and symptoms, associated with the use of Idacio namely:
    - Infections
    - Cancer
    - Nervous system problems
- A description of the best course of action if sign and symptoms of those risks present themselves (e.g. How to reach your doctors).
- A remark that patient should read the Idacio package leaflet for more information.
- Dedicated space to fill the contact details of the prescriber, date of first and last dose of the Idacio injection (if no longer taking Idacio).