Core/EU Risk Management Plan for Humira

AbbVie Inc. (AbbVie)

RMP version to be assessed as part of this application:

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Data lock point for this RMP: 08 April 2025

Date of final sign off: October 2025

Rationale for submitting an updated RMP:

Removal of completed Study M10-870 from the pharmacovigilance plan.

Removal of "Long-Term Safety Information in the Treatment of Children from 6 years to less than 18 years with UC" from Missing Information.

Updated exposure data (for specific indications as applicable) for registries, Study P10-023, Study P10-262, Study P11-282 and Study P11-292, through 31 December 2024, and for clinical trial, Study M10-870, through 08 April 2025.

Updated exposure data for post-authorization exposure through 31 December 2024.

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1: Product(s) Overview	September 2020	15.1_Core/EU
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	August 2022	16.0_Core
SII – Non-Clinical Part of the Safety Specification	August 2015	12.0_EU
SIII – Clinical Trial Exposure	October 2025	17.0_Core
SIV – Populations Not Studied in Clinical Trials	October 2025	17.0_Core
SV – Post-Authorisation Experience	October 2025	17.0_Core
SVI – Additional EU Requirements for the Safety Specification	November 2016	13.0_Core/EU
SVII – Identified and Potential Risks	October 2025	17.0_Core
SVIII – Summary of the Safety Concerns	October 2025	17.0_Core
Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)	October 2025	17.0_Core
Part IV: Plan for Post-Authorisation Efficacy Studies	September 2019	14.3_Core/EU
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	October 2025	17.0_Core
Part VI: Summary of the Risk Management Plan	October 2025	17.0_Core
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	October 2025	17.0_Core
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	October 2025	17.0_Core
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	August 2022	16.0_Core
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	September 2019	14.3_Core/EU
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	October 2018	14.2_Core/EU
Annex 7 – Other Supporting Data (Including Referenced Material)	October 2025	17.0_Core

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 8 – Summary of Changes to the Risk Management Plan Over Time	October 2025	17.0_Core
	Annex 9 – Local Currently-Approved Country Labeling	Not applicable	Not applicable
	Annex 10 – Local Risk Management/Mitigation Plan	Not applicable	Not applicable

Other RMP versions under evaluation:

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Details of the currently approved RMP:

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QPPV name: Sina Schader

QPPV oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

AE	adverse event
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransaminase
ARAMIS	American Rheumatism Association Medical Information System
AS	ankylosing spondylitis
ASAS	Assessment in Spondyloarthritis International Society
AZA	azathioprine
BD	Behçet's disease
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
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CRP	C-reactive protein
CT	computed tomography
CVA	cerebrovascular accident
DB	double-blind
DM	diabetes mellitus
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EM	erythema multiforme
EMA	European Medicines Agency
eow	every other week
EPAR	European Public Assessment Report

ERA	enthesitis-related arthritis
EU	European Union
5-ASA	5-aminosalicylic acid
GBS	Guillain-Barré syndrome
GPP	generalized pustular psoriasis
GPRD	General Practice Research Database
HCP	healthcare professional
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HL	Hodgkin's lymphoma
HR	hazards ratio
HS	hidradenitis suppurativa
HSTCL	hepatosplenic T-cell lymphoma
HTLV-I	human T-cell lymphoma/leukaemia virus type I
IBD	disease-modifying antirheumatic drug
IL	interleukin
ILAR	International League of Associations for Rheumatology
ILD	interstitial lung disease
IRR	incidence rate ratio
IV	intravenous
JIA	juvenile idiopathic arthritis
MCC	Merkel cell carcinoma
MI	myocardial infarction
MN	Minnesota
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTX	methotrexate
NA	not applicable
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
OLE	open-label extension
ON	optic neuritis
OR	odds ratio
pedCD	paediatric Crohn's disease
pedERA	paediatric enthesitis-related arthritis
pedPs	paediatric psoriasis
pedUC	paediatric ulcerative colitis
pedUV	paediatric uveitis
PFS	pre-filled syringe
PG	pyoderma gangrenosum
pJIA	polyarticular juvenile idiopathic arthritis
PL	package leaflet
PML	progressive multifocal leukoencephalopathy
Ps	psoriasis
PsA	psoriatic arthritis
PSC	primary sclerosing cholangitis
PSPs	patient support programs
PUVA	Psoralen + UVA treatment
PYs	patient-years
QPPV	qualified person for pharmacovigilance
RA	rheumatoid arthritis
ReA	reactive arthritis
RPLS	reversible posterior leukoencephalopathy syndrome
RR	risk ratio
6-MP	mercaptopurine
SC	subcutaneous
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology, and Ends Results
SIR	standardised incidence ratio
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMR	standardised mortality rate

SpA	spondyloarthritis
TB	tuberculosis
TBD	to be determined
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

The Product Overview reflects the currently approved Product Information for Humira.

Table 1. Product Overview

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AB04
Marketing Authorisation	AbbVie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Humira
Marketing authorisation procedure	Centralized procedure
Brief description of the product	Chemical class: Immunosuppressants – Tumor necrosis factor alpha (TNF-α) inhibitors (ATC Code: L04AA17)
	Summary of mode of action: Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.
	Important information about its composition: Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	Link to Product Information

Indication(s) in the EEA	**Current (if applicable):** **<u>Adults</u>** **Rheumatoid Arthritis (RA)** Humira® in combination with methotrexate (MTX), is indicated for: • the treatment of moderate to severe, active RA in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including MTX has been inadequate. • the treatment of severe, active and progressive RA in adults not previously treated with MTX. Humira can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Humira has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with MTX. **Psoriatic Arthritis (PsA)** Humira is indicated for the treatment of active and progressive PsA in adults when response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate. Humira has been shown to reduce the rate of progression of peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. **Axial Spondyloarthritis (Axial SpA)** • Ankylosing Spondylitis (AS) Humira is indicated for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy. • Axial spondyloarthritis without radiographic evidence of AS Humira is indicated for the treatment of adults with severe axial SpA without radiographic evidence of AS (also referred to throughout this Risk Management Plan [RMP] as non-radiographic axial SpA [nr-axSpA]) but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). **Crohn's Disease (CD)** Humira is indicated for treatment of moderately to severely active CD, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. **Psoriasis (Ps)** Humira is indicated for the treatment of moderate to severe chronic plaque Ps in adult patients who are candidates for systemic therapy.

	Ulcerative Colitis (UC) Humira is indicated for treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. **Hidradenitis Suppurativa (HS)** Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy. **Uveitis** Humira is indicated for the treatment of non-infectious intermediate uveitis, posterior uveitis, and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. **<u>Paediatrics</u>** **Polyarticular Juvenile Idiopathic Arthritis (pJIA)** Humira in combination with MTX is indicated for the treatment of active pJIA, in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. Humira can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Humira has not been studied in patients aged less than 2 years. **Paediatric Enthesitis-related Arthritis (pedERA)** Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. **Paediatric Crohn's Disease (pedCD)** Humira is indicated for the treatment of moderately to severely active CD in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. **Paediatric Psoriasis (pedPs)** Humira is indicated for the treatment of severe chronic plaque Ps in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

	Adolescent Hidradenitis Suppurativa (HS) Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. **Paediatric Uveitis (pedUV)** Humira 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. **Paediatric Ulcerative Colitis (pedUC)** Humira is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including corticosteroids and/or 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.
Dosage in the EEA	**Current (if applicable):** Dosing text is based on the 40 mg presentation of Humira. There are small modifications in the 20 mg and 80 mg presentations. **<u>Adults</u>** **Rheumatoid Arthritis** The recommended dose of Humira for adult patients with RA is 40 mg adalimumab administered every other week as a single dose via subcutaneous (SC) injection. MTX should be continued during treatment with Humira. Glucocorticoids, salicylates, NSAIDs, or analgesics can be continued during treatment with Humira. In monotherapy, some patients who experience a decrease in their response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. There may be a need for dose interruption, for instance before surgery or if a serious infection occurs. Available data suggest that re-introduction of Humira after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption. **Ankylosing Spondylitis, Axial SpA without Radiographic Evidence of AS, and PsA** The recommended dose of Humira 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 SC injection. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. **Crohn's Disease** The recommended Humira induction dose regimen for adult patients with moderately to severely active CD is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the Regimen 160 mg at Week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for two consecutive days), 80 mg at Week 2 (given as two 40 mg injections in 1 day), 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 SC injection. Alternatively, if a patient has stopped Humira and signs and symptoms of disease recur, Humira may be re-administered. There is little experience from re- administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg Humira every week or 80 mg every other week. Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. **Psoriasis** The recommended dose of Humira for adult patients is an initial dose of 80 mg administered SC, followed by 40 mg SC given every other week starting 1 week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week. Humira may be available in other strengths and/or presentations depending on the

	individual treatment needs.
	Ulcerative Colitis The recommended Humira induction dose regimen for adult patients with moderate to severe UC is 160 mg at Week 0 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days) and 80 mg at Week 2 (given as two 40 mg injections in 1 day). After induction treatment, the recommended dose is 40 mg every other week via SC injection. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg Humira every week or 80 mg every other week. Available data suggest that clinical response is usually achieved within 2 - 8 weeks of treatment. Humira therapy should not be continued in patients failing to respond within this time period. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. **Hidradenitis Suppurativa** The recommended Humira dose regimen for adult patients with 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 1 day). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in 1 day). Antibiotics may be continued during treatment with Humira 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 Humira. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Humira 40 mg every week or 80 mg every other week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. **Uveitis** The recommended dose of Humira 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. There is limited experience in the initiation of treatment with Humira alone. Treatment with Humira can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting 2 weeks after initiating treatment with Humira.

	It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. Humira may be available in other strengths and/or presentations depending on the individual treatment needs.
	Paediatrics **Juvenile Idiopathic Arthritis** Polyarticular juvenile idiopathic arthritis from 2 years of age The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight. Humira is administered every other week via SC injection. **Humira Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis** **Patient Weight** | **Dosing Regimen** 10 kg to < 30 kg | 20 mg every other week ≥ 30 kg | 40 mg every other week Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. There is no relevant use of Humira in patients aged less than 2 years for this indication. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. **Paediatric Enthesitis-related arthritis** The recommended dose of Humira for patients with enthesitis-related arthritis from 6 years of age is based on body weight. Humira is administered every other week via SC injection. **Humira Dose for Patients with Enthesitis-Related Arthritis** **Patient Weight** | **Dosing Regimen** 15 kg to < 30 kg | 20 mg every other week ≥ 30 kg | 40 mg every other week Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years. Humira may be available in other strengths and/or presentations depending on the individual treatment needs. **Paediatric Crohn's Disease** The recommended dose of Humira for patients with Crohn's disease from 6 to 17 years of age is based on body weight. Humira is administered via SC injection.

Humira Dose for Paediatric Patients with Crohn's disease

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

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

- < 40 kg: 20 mg every week
- ≥ 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 Humira in children aged less than 6 years for this indication.

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric Psoriasis

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

Humira Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week starting 1 week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting 1 week after the initial dose

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

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

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

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

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

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

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

The recommended Humira dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via SC injection.

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

Antibiotics may be continued during treatment with Humira 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 Humira.

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

Should treatment be interrupted, Humira 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 Humira in children aged less than 12 years in this indication.

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric Uveitis

The recommended dose of Humira for paediatric patients with uveitis from 2 years of age is based on body weight. Humira is administered via SC injection.

In paediatric uveitis, there is no experience in the treatment with Humira without concomitant treatment with MTX.

Humira Dose for Paediatric Patients with Uveitis

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

When Humira 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 Humira loading dose in children < 6 years of age.

There is no relevant use of Humira 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.

Humira may be available in other strengths and/or presentations depending on the individual treatment needs.

Paediatric Ulcerative Colitis

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

Humira Dose for Paediatric Patients with Ulcerative Colitis

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	• 40 mg every other week
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	• 80 mg every other week

* Paediatric patients who turn 18 years of age while on Humira 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 Humira in children aged less than 6 years in this indication.

	Humira may be available in different strengths and/or presentations depending on the individual treatment needs.
Pharmaceutical form(s) and strengths	Current for Humira (if applicable): <u>Pharmaceutic Forms and Strengths (50 mg/ml):</u> Clear solution for injection (vial) • Humira 40 mg/0.8 ml solution for injection for paediatric use Clear solution for injection in pre-filled syringe (PFS) • Humira 40 mg solution for injection in PFS Clear solution for injection in PFS with needle guard • Humira 40 mg solution for injection in PFS with needle guard Clear solution for injection in pre-filled pen • Humira 40 mg solution for injection in pre-filled pen A concentrated drug product formulation which contains adalimumab in a 0.4 mL (100 mg/mL) solution for SC injection has been approved. The concentrated formulation was achieved by excluding all but two of the excipients, i.e., mannitol and polysorbate-80 that are included in the approved formulation of Humira. <u>Pharmaceutic Forms and Strengths (100 mg/ml):</u> Clear solution for injection in PFS • Humira 40 mg/0.4 ml solution of injection in PFS Clear solution for injection in pre-filled pen • Humira 40 mg/0.4 ml solution for injection in pre-filled pen Clear solution for injection in a PFS with needle guard • Humira 40 mg/0.4 ml solution of injection in PFS with needle guard Clear solution for injection in PFS • Humira 80 mg/0.8 ml solution of injection in PFS Clear solution for injection in pre-filled pen • Humira 80 mg/0.8 ml solution of injection in pre-filled pen Clear solution for injection in a PFS with needle guard • Humira 80 mg/0.8 ml solution of injection in PFS with needle guard Clear solution for injection in PFS • Humira 20 mg/0.2 ml solution of injection in PFS Note: In the United States (US) and some other ex-European Union (EU) countries, a 10 mg PFS for the treatment of JIA is approved.
	Proposed (if applicable): NA
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety Specification

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

Indication #1: Rheumatoid Arthritis

Incidence

The reported annual incidence of RA in Europe ranged from 8 per 100,000 in Spain to 50 per 100,000 in Sweden (Alamanos 2006, Carbonell 2008, Englund 2010, Rodriguez 2009, and Rossini 2014). In North American countries the incidence of RA ranged 31 to 45 (Alamanos 2006 and Myasoedova 2010). The annual incidence of RA was reported to be 16 per 100,000 in Taiwan (Kuo 2013) and 42 per 100,000 in South Korea (Sung 2013). The incidence of RA tended to be lower in Southern European countries than in Northern European countries (Alamanos 2006).

Prevalence

Similarly, to incidence, the reported crude prevalence of RA appeared to be lower in Southern European countries (3.1 to 5.0 per 1,000) than in Northern European countries (4.4 per 1,000 to 8.0 per 1,000) (Alamanos 2006). The prevalence of RA appears to be lower in developing countries, ranging from 2.4 per 1,000 to 3.6 per 1,000 (Alamanos 2006). The prevalence of RA was reported to range from 7.2 per 1,000 to 10.7 per 1,000 in the US (Alamanos 2006 and Myasoedova 2010) and 6-10 per 1,000 in Japan (Yamanaka 2014). Modelled age-standardized prevalence (using the 2001 WHO standard population) for 2010 was highest in the Australasian region (0.46%), followed by Western Europe (0.44%) and North America (0.44%). The age-standardized prevalence was much lower in Asia and North Africa/Middle East (0.16%) (Cross 2014).

Demographics of target population

Both incidence and prevalence of RA increase with age and are approximately 2 to 3 times higher among females than among males (Alamanos 2006, Myasoedova 2010, and Cross 2014). Although earlier studies showed that the incidence of RA peaked earlier in men than in women (55-64 years old in men vs 75-84 years old in women) (Doran 2002c), another study found the incidence of RA peaked at 65 to 74 years of age in both sexes (Myasoedova 2010). Compared with white patients, Hispanic patients had higher disease activity levels; African American patients achieved lower rates of clinical remission; and both African American patients and Hispanic patients reported worse functional status (Greenberg 2013). Biologics have been used in about 15% of RA patients and the proportion of biologic use decreases with increased age (Neovius 2011). Of moderate and severe RA patients who initiated biologics, approximately 76% are female and 85% received non-biologic

disease-modifying antirheumatic drugs (DMARDs) at the time of biologics initiation (Kavanaugh 2017).

Risk factors

RA results from an interaction of genetic and environmental factors (Scott 2011). Estimated from two major national twin studies in the UK and Finland, genetic factors account for 53% to 65% of risk of developing RA (Oliver 2006). Besides increased age and female gender, risk factors of RA include cigarette smoking, obesity, high birthweight, and lower socio-economic status. High vitamin D intake as well as alcohol consumption might reduce the risk of RA (Scott 2011 and Oliver 2006).

The main treatment options:

NSAIDs including cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, "traditional" DMARDs, such as MTX, sulfasalazine, anti-malarial drugs, leflunomide, cyclosporine A, gold, and D Penicillamine, as well as biologic DMARD therapies against specific targets interleukin receptor 1 (IL1; anakinra), TNF (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab), B cells (rituximab), T cell interactions (abatacept) and IL-6 receptor (tocilizumab) are now available to improve outcomes in RA. Another treatment option are targeted synthetic DMARDs with Janus kinase (JAK) inhibitors (tofacitinib, baricitinib and upadacitinib).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Mortality studies have consistently found increased mortality among individuals with RA (Naz 2007 and Sokka 2008). Median standardized mortality ratios for RA are in the range of 1.5 - 1.6 overall, 1.2 - 1.3 in inception cohort studies, and 1.6 - 1.7 in non-inception cohort studies (Sokka 2008). The distributions of the cause of death among RA patients are similar in studies conducted in the US and Western Europe (Sokka 2008). The distribution of attributed acute causes of death was cardiovascular disease (CVD, 39.6%), cancer (16.8%), infection (14.3%), musculoskeletal disease or rheumatoid arthritis (9.4%), respiratory disease (9.0%), renal disease (5.8%), gastrointestinal disease (5.1%), accidents/intoxication (4.2%), sudden death (3.1%), and other causes (12.9%). The percentage of deaths attributable to CVD among RA patients is similar to the source population from which they were identified, while pulmonary, gastrointestinal, renal disease and infection are more commonly observed in RA (Sokka 2008). RA may lead to joint destruction, deformity and disability. RA is also associated with extra-articular manifestations including vasculitis, pericarditis, aortitis, interstitial lung disease, Sjogren syndrome, pleuritis, episcleritis, scleritis, Felty's syndrome, glomerulonephritis, interstitial nephritis and rheumatoid nodules (Prete 2011).

Important co-morbidities:

Comorbidities of RA include CVD, malignancies (e.g., lymphoma, lung cancer, and skin cancer), lung disease (e.g., interstitial lung disease), infection, gastrointestinal ulcer disease, anemia, osteoporosis, and depression (Gabriel 2009). The most commonly reported comorbidity among RA patients in a large cohort study including patients from 17 countries worldwide was depression (past or current symptoms) with a mean prevalence of 15% (95% confidence interval [CI] 13.8 - 16.1) (Dougados 2014). Autoimmune disorders are often positively associated with RA; these include inflammatory bowel disease (IBD), type I diabetes mellitus and Hashimoto's thyroiditis (Cooper 2009).

Indication #2: Polyarticular Juvenile Idiopathic Arthritis

Incidence:

JIA has an annual incidence of 0.10 to 0.20 cases per 1,000 children (Andersson 1987, von Koskull 2001, Symmons 1996, Peterson 1996, Towner 1983, Kunnamo 1986, Kaipiainen-Seppanen 1996, Riise 2008, Pruunsild 2007) in the US and Europe and is more common in females (Andersson 1987, Towner 1983, Pruunsild 2007, Peterson 1996, Thierry 2014). In the US, incidence has not changed significantly since the 1960s (Krause 2016). Measures of juvenile arthritis vary widely in the literature. This is primarily due to differences in case ascertainment in study design (community-based surveys vs. clinical case studies), changes in disease classification over time, and the small sample sizes used in juvenile arthritis studies.

Prevalence:

Due to many of the reasons stated above relating to juvenile arthritis studies, estimates of the prevalence of juvenile arthritis vary widely in the literature. Estimated prevalence from Europe ranged from 0.04 to 4 per 1,000 children, with a prevalence of 0.19 per 1,000 female children and 0.11 per 1,000 male children (Thierry 2014). The National Arthritis Data Workgroup estimated that 294,000 American children have JIA after analyzing data collected through National Ambulatory and Medical Care Survey (Helmick 2008). Many studies estimate JIA prevalence to be less than 1 in 1,000 children (Andersson 1987, von Koskull 2001, Towner 1983, Khuffash 1990, Arguedas 1998, Hochberg 1983, Gewanter 1983, Prieur 1987). In Australia, a cross sectional study yielded a prevalence estimate of 4.0 juvenile chronic arthritis cases per 1,000 children 12 years of age and younger (Manners 1996).

Demographics of the target population:

By definition JIA onset occurs at 16 years of age or younger with disease persistence for 6 weeks or longer. Onset prior to 1 year of age is unusual. In a review by A. Ravelli (Ravelli 2007), he found that the frequency of JIA differs by International League of Associations for Rheumatology (ILAR) class, age of onset, and sex. In the US, peak incidence of JIA occurs in children aged 11 – 15 years (Harrold 2013). Oligoarthritis, RF-positive

and -negative arthritis, and psoriatic arthritis may present more often among females than males, while males more often experience enthesitis-related arthritis than females. Systemic arthritis incidence occurs throughout childhood. Oligoarthritis incidence peaks early in childhood, while RF-positive polyarthritis and enthesitis-related arthritis may peak later. RF-negative polyarthritis and psoriatic arthritis have bimodal peaks of incidence early in childhood (2 to 4 years of age) and in late childhood/preteen years.

Risk Factors:

Multiple risk factors for JIA are currently being studied but have not been established (Berkun 2010).

The main treatment options:

NSAIDs are the usual first-line treatment for JIA, since they are considered to be the least toxic agent in children. NSAIDs are not disease-modifying, but are used to treat pain, stiffness, and the fever associated with systemic arthritis (Hashkes 2005). Continuation of NSAID monotherapy (without additional therapy) for longer than 2 months is considered inappropriate for patients with active arthritis. NSAIDs are often used in conjunction with DMARDs such as MTX or sulfasalazine.

In patients with polyarticular JIA (pJIA), after starting MTX, the onset of response usually ranges from 3 to 6 months. Previous studies have shown that MTX used as DMARD monotherapy results in complete disease control in about 12% of patients (Ruperto 2004). In combination with steroids, hydroxychloroquine, or sulfasalazine, MTX use may result in remission in 20% to 45% of children (Wallace 1993, Wallace 1998). After withdrawal of MTX, many children have a disease relapse. MTX may exhibit a disease-modifying effect in pJIA, as the rate of radiographic damage was decreased in two small, uncontrolled series (Harel 1993, Ravelli 1998).

Systemic use of corticosteroids for JIA is less desirable due to many deleterious effects, especially on bone and growth. Intra-articular corticosteroid injections are recommended in JIA patients who have active arthritis regardless of the use of additional concomitant therapy (Beukelman 2011).

Biologic DMARD therapies against specific targets TNF (adalimumab, etanercept), T cell interactions (abatacept) and IL-6 receptor (tocilizumab) are used for moderate to severe disease states. Another treatment option are targeted synthetic DMARDs with Janus kinase (JAK) inhibitors (tofacitinib).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Two studies suggest that those patients with JIA may experience mortality at higher rates than the general population (French 2001, Thomas 2003). Uveitis, growth impairment, and

sequelae similar to rheumatoid cachexia are more prevalent in JIA (Asproudis 2010, Bechtold 2009, Heiligenhaus 2007).

Important co-morbidities:

Comorbidities of JIA include uveitis (Asproudis 2017 and Nordal 2017) and IBD (Virta 2013, Hugle 2017, and Barthel 2015).

Indication #3: Paediatric Enthesitis-Related Arthritis

Incidence:

Paediatric enthesitis-related arthritis (ERA) is a subtype of JIA (Colbert 2010). The incidence of pedERA has not been identified in the literature.

Prevalence:

The percentage of JIA patients classified as enthesitis related arthritis varies by demographic area and ethnic background. A Canadian study of 758 children with JIA found that 9.3% had ERA, and the proportion varied by ethnic background from 7.6% in those from European ancestry to 24.0% in those with Asian ancestry (Saurenmann 2007). Other studies have reported the proportion of JIA cases classified as enthesitis-related arthritis to be 10.4% in the US (Weiss 2012), 35.3% in West India (Kunjir 2010); 17.9% in Alsace, France (Danner 2006); 16.6% in western France (Solau-Gervais 2010); 6.4% in Germany (Krumrey-Langkammerer 2001); 7% in the United Kingdom (UK) (Thomas 2000a); 4% in Nordic countries (Berntson 2003); and 10.3% in Turkey (Yilmaz 2008).

Demographics of the target population:

Paediatric enthesitis-related arthritis (ERA) is a subtype of JIA (Colbert 2010). The demographics of JIA are presented above in the JIA section.

Risk Factors:

Paediatric ERA is a subtype of JIA (Colbert 2010). Multiple risk factors for JIA are currently being studied but have not been established (Berkun 2010).

The main treatment options:

The current treatment of ERA consists of NSAIDs, intra articular corticosteroid injections and/or second-line agents such MTX and sulfasalazine (Nistala 2008). NSAIDs offer symptomatic relief, particularly for enthesitis. Although most children respond to intra articular injections, there is often a need for a DMARD. In contrast to other types of JIA which generally favor use of MTX, sulfasalazine is recommended following glucocorticoid joint injection or an adequate trial of NASIDs in patients with enthesitis related arthritis (Beukelman 2011) who have moderate or high disease activity. All of these measures however, do not significantly modify

the disease course of ERA, especially the axial component of the disease. In patients refractory to NSAIDs and traditional DMARDs, adalimumab and etanercept have been shown to be effective in patients with ERA (Burgos-Vargas 2015, Horneff 2014).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Paediatric ERA is a subtype of JIA (Colbert 2010). The natural history of JIA is presented above in the JIA section.

Important co-morbidities:

Comorbidities of JIA include uveitis (Asproudis 2017 and Nordal 2017) and IBD (Virta 2013, Hugle 2017, and Barthel 2015).

Indication #4: Spondyloarthritis (Overall)

Spondyloarthritis (SpA) is a group of heterogeneous inflammatory diseases including ankylosing spondylitis (AS), reactive arthritis (ReA), PsA, arthritis associated with IBD (CD and UC), and undifferentiated spondyloarthritis (uSpA). This group of inter-related diseases can also be categorized based on the predominant manifestation as either axial SpA (AS and nr-axSpA) or peripheral SpA (PsA and non-PsA peripheral SpA).

Incidence:

Few studies have provided incidence rates for all types of SpA (Akkoc 2008, Stolwijk 2012). Two Finnish studies reported incidence rates of SpA that ranged from 19 to 52 per 100,000 population (Savolainen 2003, Kaipiainen-Seppanen 2000, Akkoc 2008). A higher incidence of SpA (62.5 per 100,000) was reported in a pilot registry study in Madrid, Spain (Munoz-Fernandez 2010). The incidence of SpA is much lower in Japanese because of low prevalence of HLA B27 and it was reported that the estimate incidence was 0.48 per 100,000 in a nationwide Survey (Hukuda 2001).

Prevalence:

The prevalence of SpA is estimated to be between 0.14 to 0.46 in France, between 0.56 to 2.9 in Germany, between 0.71 to 1.03 in China, and between 0.35 – 1.31 in the US (Braun 2005, Helmick 2008, Saraux 2005, Xiang 2009). Estimates of the prevalence of SpA vary from 0.01% in Japan to 2.5% in Alaskan Eskimos (Akkoc 2008, Farooqi 1998, Akkoc 2005, Hukuda 2001, Stolwijk 2012).

In the US National Health and Nutrition Examination Survey (NHANES) 2009 – 2010, the overall age-adjusted prevalence of definite and probable SpA was 0.9% (95% CI: 0.7 – 1.1) by the Amor criteria and 1.4% (95% CI: 1.0 – 1.9) by the European Spondylarthropathy Study Group criteria (Reveille 2012). In a US study including a chart review of at-risk patients

aged 18 to 44 years, the prevalence of axSpA was 0.70% (95% CI: 0.38 – 1.1) and the prevalence of nr axSpA was 0.35% (95 CI: 0.18 – 0.55) using the new Assessment in Spondyloarthritis International Society (ASAS) classification criteria (Strand 2013). In a German study of patients with back pain, among those with axSpA, 52.2% were diagnosed with AS and 47.8% were diagnosed with nr-axSpA. However, if the duration of back pain was a year or less, patients with axSpA were more frequently diagnosed with nr-axSpA (67.3%) than with AS. If the duration of back pain was between 6 and 9 years, patients diagnosed with axSpA were more likely to have AS (61.1%) than nr-axSpA (38.9%) (Poddubnyy 2012a).

The proportion of SpA accounted for by the different diseases also varies by study. In three European population-based studies AS and PsA constituted the greatest proportion of SpA (75% to 90% of all cases) (De Angelis 2007, Saraux 2005, Trontzas 2005).

ReA resolves in 20% to 45% of the cases of SpA depending on the triggering infection (Leirisalo-Repo 1998, Leirisalo-Repo 1988, Leirisalo-Repo 1997, Sairanen 1969); approximately 15 – 30% may progress to chronic arthritis (Hughes 1994, Keat 1999, Leirisalo-Repo 1998, Leirisalo-Repo 1988, Leirisalo-Repo 1997, Sairanen 1969, Sieper 2002).

Demographics of the target population:

Some studies show greater prevalence in males and other studies show similar or greater prevalence in females (Saraux 2005, Saraux 1999, Andrianakos 2003, Steven 1992).

Risk Factors:

Axial Spondyloarthritis (axial SpA):

The most established risk factors for axial SpA is family history for SpA and genetic predisposition (e.g., HLA B27) (Alamanos 2004, van der Linden 1984, Dai 2003, Reveille 2001, Khan 2002).

Peripheral Spondyloarthritis:

Genetic predisposition (e.g., IL12B, HLA Class 1) increases the risk of PsA (Nograles 2009). Risk of developing PsA has also been found to increase with increasing Body Mass Index (BMI) in individuals with and without preexisting psoriasis (Li 2012b, Love 2012).

Genetic predisposition (e.g., HLA-B27 positivity) increases the risk for non-PsA peripheral SpA (Dougados 2011, Mease 2015, Paramarta 2013). PsA has been estimated to occur in 20 – 30% of patients with Ps (Huynh 2015). Environmental factors, including infection (such as streptococcus, human immunodeficiency virus [HIV]), drug use, and joint trauma (mainly in children), are hypothesized to contribute to the development of PsA, while emotional stress plays an important role as a trigger for both skin and joint manifestations (Liu 2014).

The main treatment options:

Axial SpA:

Until recently, there were few treatment options other than physical therapy and NSAIDs. Published literature indicates that NSAIDs, but not corticosteroids or traditional DMARDs such as MTX and sulfasalazine, have efficacy and are first-line therapy in all axial SpA patients (AS and nr-axSpA) (Braun 2006, Braun 2011, van der Heijde 2011, Chen 2003). However, NSAID use in chronic conditions such as axial SpA can be associated with serious adverse gastrointestinal, cardiovascular, and renal events (Lanas 2010, Ofman 2002, Whelton 1991, Trelle 2011). As such, there is a significant unmet need for additional therapies for the treatment of patients with active axial SpA (AS and nr-axSpA). Several anti-TNF therapies, including adalimumab, have been shown to benefit AS patients who do not have adequate clinical response to NSAIDs and are currently approved for use in this population (van der Heijde 2006, van der Heijde 2005, Inman 2008, Davis 2003). Adalimumab and other anti TNF agents have also been shown to be effective in patients with nr axSpA (Haibel 2008, Sieper 2012a).

Peripheral Spondyloarthritis:

Treatment in PsA has previously consisted of using agents with proven efficacy in RA (Prasad 2004, Pipitone 2003). Patients are initially treated with NSAIDs for joint manifestations, and topical therapies for the skin. Conventional synthetic DMARD therapy is used both to treat pain and to attempt to control the progression of disease. Conventional synthetic DMARDs used include sulfasalazine, leflunomide, MTX, and cyclosporine. Cyclosporine is highly effective for skin disease, but less effective for joint manifestations, and is not widely used as it is potentially associated with serious systemic side effects (nephrotoxicity and hypertension). TNF-α antagonists, including adalimumab, etanercept, infliximab, golimumab, and certolizumab are also used, generally if patients fail to respond to at least one conventional synthetic DMARD (Felquer 2015, Ritchlin 2009).

Other approved drugs for PsA include apremilast, a phosphodiesterase 4 inhibitor, ustekinumab, an IL-12 and IL-23 inhibitor (Felquer 2015), and secukinumab, an IL-17A inhibitor (McInnes 2015).

Oral steroids are not widely used. Steroids may aggravate the skin disease in some PsA patients.

In the field of non-PsA peripheral SpA, 2 placebo controlled randomized controlled trials showed that adalimumab resulted in amelioration of signs and symptoms in patients who failed standard of care (Mease 2015, Paramarta 2013).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Mortality rates are increased in AS and PsA patients, the two most frequently occurring forms of SpA (Zochling 2008, Gladman 2008).

For further details, see Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity for axial SpA and for peripheral SpA in the sections below.

Important co-morbidities:

Comorbidities of AS include uveitis, psoriasis, IBD (Stolwijk 2015 and de Winter 2016), and CVD (Ahmed 2016 and Han 2006).

Indication #5: Axial Spondyloarthritis

Spondyloarthritis can be categorized based on the predominant manifestation as either axial SpA (AS and nr-axSpA) or peripheral SpA (PsA and non-PsA peripheral SpA).

Incidence:

The incidence of AS differs by sex (Kaipiainen-Seppanen 2000, Alamanos 2004, Carbone 1992) and closely follows the frequency of HLA class 1 molecule B27 in the population (Kaipiainen-Seppanen 2000, Alamanos 2004, van der Linden 1984, Bakland 2005).

A cohort study utilizing the Rochester Epidemiology Project found the age- and sex-adjusted incidence of AS in Rochester to be 7.3 per 100,000 person-years from 1935 through 1989 (Carbone 1992, Reveille 2001). A population-based study conducted in Northwest Greece that relied upon case identification through referrals to private rheumatology practices and inpatient/outpatient hospital rheumatology departments found the age-adjusted incidence of AS to be 1.5 cases per 100,000 individuals 16 years of age and older for the Period 1983 through 2002 (Alamanos 2004).

The annual incidence of AS was estimated for 5 hospital districts in Finland using Finnish linked medical record system. AS incidence equalled 6.3 per 100,000 (Kaipiainen-Seppanen 2000).

The annual incidence of AS was estimated using a regional hospital database representing medical catchment covering Tromsø and Finnmark counties in Northern Norway. AS incidence equalled 8.59 per 100,000 individuals (Bakland 2005).

Our review of the literature found no studies of the incidence of nr-axSpA.

Prevalence:

In a cross-sectional survey of the US population the prevalence of axial SpA was estimated to be between 0.9% and 1.4% (Reveille 2012). In a US study of patients aged 18 to 44 years

who were already seen in rheumatology offices, the prevalence of axSpA was 0.70% (95% CI: 0.38 – 1.1) with the prevalence of both AS and nr axSpA being 0.35% (95 CI: 0.18 – 0.55 for both) (Strand 2013). In a German study of patients with back pain, among those with axSpA, 52.2% were diagnosed with AS and 47.8% were diagnosed with nr axSpA. However, if the duration of back pain was a year or less, patients with axSpA were more frequently diagnosed with nr-axSpA (67.3%) than with AS. If the duration of back pain was between 6 and 9 years, patients diagnosed with axSpA were more likely to have AS (61.1%) than nr-axSpA (38.9%) (Poddubnyy 2012a).

The estimated prevalence of AS is 29.5 per 100,000 in Northwest Greece (Alamanos 2004), 310.0 per 100,000 females in Norway (Bakland 2005), 370.0 per 100,000 in the Marche region of Italy (De Angelis 2007).

The prevalence of AS in Asia is lower than North America and Europe. The age- and sex-adjusted prevalence of AS equalled 110 per 100,000 individuals in Shanghai, China (Dai 2003) and 120 per 100,000 in Iran (Davatchi 2008).

The French GAZEL cohort provided an overall prevalence estimate of 0.43% for SpA, of which 75% were patients who fulfilled the ASAS axial SpA criteria. Therefore, the prevalence of axial SpA is approximately 0.32% in this French population (Costantino 2015).

In a Norwegian study, the total prevalence of undiagnosed axial SpA was estimated to be 0.13%. The background prevalence of AS in this region was 0.4%, which combined with undiagnosed axial SpA gives a total prevalence of axial SpA in this population of 0.53% (Bakland 2013).

Demographics of the target population:

Symptoms of axSpA usually start in the teens and early 20s with initial symptoms rare after 45 years of age, however many patients are diagnosed at an older age (Khan 2002). The overall prevalence of axSpA is similar between males and females. Among axial SpA subtypes, nr axSpA is more frequent among females while AS is more frequent among males (Sieper 2013, Onen 2008, Bakland 2005, Stolwijk 2012, Rudwaleit 2009, Haibel 2008).

Risk Factors:

The most established risk factors for axial SpA are family history for SpA and genetic predisposition (e.g., HLA B27) (Alamanos 2004, van der Linden 1984, Dai 2003, Reveille 2001, Khan 2002).

The main treatment options:

Until recently, there were few treatment options other than physical therapy and NSAIDs. Published literature indicates that NSAIDs, but not corticosteroids or traditional DMARDs such as MTX and sulfasalazine, have efficacy and are first-line therapy in all axial SpA patients (AS

and nr-axSpA) (Braun 2006, Braun 2011, van der Heijde 2011, Chen 2003). However, NSAID use in chronic conditions such as axial SpA can be associated with serious adverse gastrointestinal, cardiovascular, and renal events (Lanas 2010, Ofman 2002, Whelton 1991, Trelle 2011). As such, there is a significant unmet need for additional therapies for the treatment of patients with active axial SpA (AS and nr-axSpA). Several anti-TNF therapies, including adalimumab, have been shown to benefit AS patients who do not have adequate clinical response to NSAIDs and are currently approved for use in this population (van der Heijde 2006, van der Heijde 2005, Inman 2008, Davis 2003). Adalimumab and other anti TNF agents have also been shown to be effective in patients with nr axSpA (Haibel 2008, Sieper 2012a). Another treatment option are targeted synthetic DMARDs with Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Data indicate that the progression rate from nr-axSpA to AS over 2 years is approximately 12% and is probably 20% in patients with active inflammation on MRI of the SI joints and/or CRP elevation at baseline (Poddubnyy 2011, Sieper 2013).

Factors predicting radiographic progression from nr axSpA to AS include extended active sacroiliitis on MRI, male gender, elevated CRP levels and smoking (Bennett 2008, Oostveen 1999, Rudwaleit 2009, Poddubnyy 2011). In AS patients, syndesmophytes have the strongest predictive role for further radiographic progression along with elevated CRP, male gender and smoking (Poddubnyy 2012b, van Tubergen 2012).

AS patients experience increased mortality compared to the general population (Brown 1965, Khan 1981, Radford 1977). Significant increases in mortality due to various cancers, cardiovascular disease, nephritis/nephrosis, aplastic anaemia, and pneumonia have been consistently reported among AS patients (Brown 1965, Kaprove 1980, Smith 1982). AS may lead to disability and decreased physical functioning (Boonen 2001a, Boonen 2001b).

Important co-morbidities:

Comorbidities of AS include uveitis, psoriasis, IBD (Stolwijk 2015 and de Winter 2016), and CVD (Ahmed 2016 and Han 2006).

Indication #6: Peripheral Spondyloarthritis

Spondyloarthritis can be categorized based on the predominant manifestation as either axial SpA (AS and nr-axSpA) or peripheral SpA (PsA and non-PsA peripheral SpA).

Incidence:

Estimates of PsA annual incidence are similar in the US and Europe (6 per 100,000 in Denmark [Pedersen 2008], 6.8 per 100,000 in Finland [Kaipiainen-Seppanen 2000], 3.02 per 100,000 in

Northwest Greece [Alamanos 2003], 8 per 100,000 in Kronoberg County, Sweden [Soderlin 2002], and 6.6 per 100,000 in the USA [Shbeeb 2000]).

A review of annual PsA incidence rates in various countries shows rates of 0.1/100,000 in Japan, 3.0/100,000 in Greece, 23.1/100,000 in Finland, 7.2/100,000 in US, and 6.3/100,000 in Argentina (Liu 2014).

Our review of the literature found no studies of the incidence of non-PsA peripheral SpA.

Prevalence:

Estimates of PsA prevalence do not vary greatly among European countries, US, and Australia (0.25 per 100 in the USA [Gelfand 2005a], 0.14 to 0.15 per 100 in Denmark [Pedersen 2008], 0.139 per 100 in Iceland [Love 2007], 0.42 per 100 in Italy [De Angelis 2007, Liu 2014], 0.5 per 100 among Australian Aborigines in North Queensland, Australia [Minaur 2004], 0.56 per 100 in Northwest Greece [Alamanos 2003], 0.17 per 100 in all of Greece [Liu 2014], 0.195 per 100 in Western Norway [Madland 2005], 0.19 per 100 in France [Liu 2014]), and 0.29 per 100 in Germany [Liu 2014]). The proportion of Ps patients presenting with PsA can vary by geography and patient populations studied (Gelfand 2005a, Kawada 2003, Baek 2000, Jamshidi 2008).

In China and Japan, annual PsA prevalence rates are 0.02 per 100 and 0.001 per 100, respectively (Liu 2014).

Among 1,036 patients diagnosed with SpA in a Brazilian epidemiological study, 10.7% had exclusively peripheral involvement (Sampaio-Barros 2011).

Demographics of the target population:

Many studies have found no difference in incidence of PsA with respect to sex (Pedersen 2008, Alamanos 2003, Gelfand 2005a, Madland 2005, Jamshidi 2008, Duarte 2012).

Our review of the literature found no studies that differentiated the demographics of non-PsA peripheral SpA from other forms of SpA.

Risk Factors:

Genetic predisposition (e.g., IL-12B, HLA Class 1) increases the risk of PsA (Nograles 2009). Risk of developing PsA has also been found to increase with increasing BMI in individuals with and without preexisting psoriasis (Li 2012b, Love 2012).

Genetic predisposition (e.g., HLA-B27 positivity) increases the risk for non-PsA peripheral SpA (Dougados 2011, Mease 2015, Paramarta 2013). PsA has been estimated to occur in 20 – 30% of patients with Ps (Huynh 2015). Environmental factors, including infection (such as streptococcus, HIV), drug use, and joint trauma (mainly in children), are hypothesized to

contribute to the development of PsA, while emotional stress plays an important role as a trigger for both skin and joint manifestations (Liu 2014).

The main treatment options:

Patients are initially treated with NSAIDs for joint manifestations, and topical therapies for the skin. Conventional synthetic DMARD therapy is used both to treat pain and to attempt to control the progression of disease. Conventional synthetic DMARDs used include sulfasalazine, leflunomide, MTX, and cyclosporine. Cyclosporine is highly effective for skin disease, but less effective for joint manifestations, and is not widely used as it is potentially associated with serious systemic side effects (nephrotoxicity and hypertension). TNF-α antagonists, including adalimumab, etanercept, infliximab, golimumab, and certolizumab are also used, generally if patients fail to respond to at least one conventional synthetic DMARD (Felquer 2015, Ritchlin 2009).

Other approved drugs for PsA include apremilast, a phosphodiesterase 4 inhibitor, ustekinumab, an IL-12 and IL-23 inhibitor (Felquer 2015), secukinumab, an IL-17A inhibitor (McInnes 2015), ixekizumab, a monoclonal antibody, and tofacitinib, a JAK inhibitor (Gladman 2017, Remicade 2019).

Oral steroids are not widely used. Steroids may aggravate the skin disease in some PsA patients.

In the field of non-PsA peripheral SpA, 2 placebo controlled randomized controlled trials showed that adalimumab resulted in amelioration of signs and symptoms in patients who failed standard of care (Mease 2015, Paramarta 2013).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

All-cause mortality rates do not appear increased in PsA (SMR = 0.56, 0.14 – 2.25) (Ali 2007). PsA patients may experience increased disability and decreased physical functioning (Gladman 2005).

Important co-morbidities:

The incidence rate of uveitis in PsA patients increased compared to the reference (Egeberg 2015).

Indication #7: Psoriasis (Adult and Paediatric)

Incidence:

The annual incidence of psoriasis equalled 78.9 per 100,000 population in Olmsted County, Minnesota, USA (Icen 2009) and 140 per 100,000 person-years in the General Practice Research Database in the UK (Huerta 2007). The incidence of Ps in Olmsted County has

increased over time (Icen 2009). Among paediatric patients aged < 18 years, the annual incidence of psoriasis was 40.8 per 100,000 (95% CI: 36.6 – 45.1) in Olmsted County, Minnesota, USA (Tollefson 2010). Lifetime incidence of nail psoriasis in patients with psoriasis was estimated to be between 80 and 90%, and only 1 – 5% of nail psoriasis cases occur in the absence of cutaneous disease (Tan 2012, Reich 2009, Augustin 2010).

Prevalence:

In Europe, the prevalence of psoriasis was estimated to be 1.5 per 100 in the UK (Gelfand 2005c), 2.1 per 100 in Germany (Schaefer 2008), 3.1 per 100 in Italy (Naldi 2004), and 1.43 per 100 in Spain (Ferrandiz 2001). In the UK, the prevalence of psoriasis among those aged 0 to 9 years and those aged 10 to 19 years was estimated to be 0.55 per 100 and 1.37 per 100, respectively (Gelfand 2005c). Prevalence for nail involvement in psoriasis was approximately 40 – 75% (Augustin 2010, Armesto 2011, Radtke 2011, Brazzelli 2012). A study of paediatric psoriasis patients found 15.7% had nail involvement. In the subgroup of European patients, 12.5% of children were diagnosed with nail psoriasis (Piraccini 2015).

An analysis of NHANES 2003 – 2004 estimated that 5 million Americans 20 – 59 years of age have been diagnosed with psoriasis. The addition of undiagnosed cases identified through the medical exam component of NHANES yields an estimated prevalence of 5.6 to 8.6 million cases (3.55% to 5.43% of Americans 20 to 59 years of age). Additionally, 11.38% of psoriasis cases present as moderate psoriasis (3% to 10% BSA affected) and 5.25% of cases present as severe psoriasis (> 10% BSA affected) (Kurd 2008). Another nationally representative survey conducted in the USA found psoriasis prevalence in the USA to be 2.5 per 100 among Caucasians and 1.3 per 100 among blacks in the USA (Gelfand 2005b).

Demographics of the target population:

Psoriasis incidence and prevalence is similar in both sexes (Icen 2009, Kurd 2008, Gelfand 2005c). Psoriasis prevalence is highest in those 20 to 50 years of age (Gelfand 2005b, Schaefer 2008, Ferrandiz 2001). It appears that the prevalence of psoriasis is highest in Northern Europe and lowest in East Asia (Gupta 2014). Nail psoriasis occurs more often in adult patients with more severe psoriasis, and there is a positive correlation between the severity of nail lesions and the severity of joint and skin symptoms (Piraccini 2015).

A German study conducted in 2010 on 3531 patients with psoriasis found that 46.0% of males and 34.8% of females had nail involvement, indicating that nail psoriasis is 11.2% more prevalent in German males compared to females (Augustin, 2010).

Risk Factors:

High BMI, exposure to tobacco smoke at home, and stressful life events may be risk factors for paediatric psoriasis, and smoking may be a risk factor for adult psoriasis (Ozden 2011, Li 2012a). Genetic predisposition (e.g., HLA-Cw*06) is also an important factor (Li 2009). The

presence of nail psoriasis is also associated with the severity of the skin condition and joint involvement in patients with psoriasis (Williamson 2004, Brazzelli 2012, Hallaji 2012).

The main treatment options:

Topical corticosteroids are commonly used for mild to moderate cases. Keratolytic agents, anthralin, coal tar, vitamin D analogs, and retinoids are also used as topical medications. For more widespread disease, phototherapy such as ultraviolet B (UVB) or psoralen + UVA treatment (PUVA) is commonly used. Systemic therapy, including MTX, cyclosporine and synthetic retinoids may be effective in patients with severe disease. Due to the toxicity of systemic agents, these medications are generally administered in rotation to avoid long-term or cumulative toxicities.

The traditional treatment paradigm in managing psoriasis patients is that those with limited disease are treated with topical agents such as corticosteroids, calcipotriene, or dithranol. In moderate to severe cases, or where topical therapy has proven ineffective, phototherapy or systemic treatment are available options. Exposure to UVB phototherapy may be effective but is often inconvenient due to the frequency of treatments, which are usually administered in a physician's office. Chronic therapy with traditional systemic treatments for moderate and severe psoriasis, including oral retinoids, MTX, and cyclosporine, can be limited by lack of efficacy or precluded by dose dependent side effects. Oral retinoids can cause hypertriglyceridemia and hepatitis; MTX can cause bone marrow suppression, pneumonitis, and cirrhosis; cyclosporine can cause hypertension and renal toxicity. Due to the toxicity of systemic agents, these medications are generally administered in rotation to avoid long-term or cumulative toxicities (Menter 1996).

TNF-α antagonists, including adalimumab, etanercept, and infliximab, are also used to treat Ps, particularly in cases in which other systemic therapy has failed. Other approved and/or recommended drugs for Ps include ustekinumab, an IL-12 and IL-23 inhibitor, apremilast, a phosphodiesterase 4 inhibitor, IL-17A inhibitors (secukinumab, ixekizumab), an IL-17 receptor A antagonist (brodalumab), and an IL-23 inhibitor (guselkumab, risankizumab, tildrakizumab).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Inpatient death records suggest the mortality rate among hospitalized psoriasis patients in the USA is 0.64 deaths per 100,000 psoriasis patients per year (Pearce 2006). Mortality in psoriasis may be associated with disease severity. Analyses of the General Practice Research Database (GPRD) database found increased mortality rates among severe psoriasis patients (hazards ratio [HR] = 1.5) but not among mild psoriasis patients (HR = 1.0). The mortality rate among those with mild and severe psoriasis in this study equalled 12.0 and 21.3 deaths per 1,000 person-years, respectively (Gelfand 2007). In Finland, the all-cause SMR identified

through Finland's inpatient register equalled 1.62 for males and 1.54 for females with psoriasis (Poikolainen 1999).

Important co-morbidities:

Comorbidities of Ps include PsA (Strohal 2014), depression (Strohal 2014), CVD (Strohal 2014 and Kaye 2008), uveitis (Strohal 2014 and Kaye 2008), and malignancies including lymphoma and skin cancer (Boffetta 2001, Brauchli 2009b, Chen 2011, and Ji 2009).

Indication #8: Hidradenitis Suppurativa (Adult and Adolescent)

Incidence:

A study of patients in the Rochester Epidemiology Project in Olmsted County, Minnesota between 1968 and 2008 determined that the overall annual age-and sex-adjusted incidence was 6.0 per 100,000. The annual incidence in women (8.2 per 100,000) was significantly higher than in men (3.8 per 100,000). The highest annual incidence was in women 20 – 29 years of age (18.4 per 100,000) and the annual incidence was 2.7 per 100,000 in those under 20 years of age (4.4 and 1.0 per 100,000 for females and males, respectively) (Vazquez 2013).

Prevalence:

In the US, the prevalence of HS was 0.053% in a retrospective analysis of healthcare claims data, including patients who were enrolled for the entire year of 2007. The prevalence for patients younger than 18 years old was 0.017% (Cosmatos 2013). A study of patients in the Rochester Epidemiology Project in Olmsted County, Minnesota between 1968 and 2008 showed that the total sex- and age-adjusted prevalence was 0.13%. The prevalence was 0.005% for those aged below 20 years (Shahi 2014).

In France and Copenhagen County, Denmark, the 1-year prevalence of symptomatic HS was estimated to be 0.97% and 1.0%, respectively (Revuz 2008, Jemec 1996).

Demographics of the target population:

Most studies describe a predominance of HS among females compared to males (Revuz 2008, von der Werth 2000, Lapins 2001, Buimer 2009, Alikhan 2009) and an average age of onset for HS patients in their early 20s. Postmenopausal onset is rare (Buimer 2009). HS has been associated with current smoking (Revuz 2008, Buimer 2009) and increased BMI (Revuz 2008). HS may lessen in severity with the onset of menopause (von der Werth 2000).

Risk Factors:

Female sex, age 11 to 30 years, smoking, and obesity may be risk factors for HS (Revuz 2008, von der Werth 2000, Lapins 2001, Buimer 2009, Alikhan 2009, Sartorius 2009).

The main treatment options:

Humira is the only approved treatment for this condition. Treatment guidelines for this condition have recently been developed and recommendations for mild or limited forms of the disease consist of topical clindamycin, short courses of systemic antibiotics, or intralesional steroids. Successful use of oral retinoids, anti-androgens, or immunosuppressants for recalcitrant cases has been described in case reports and series, but no controlled studies have been conducted with these agents. Humira is typically reserved for moderate to severe disease.

In more advanced cases, a multifaceted approach may be adopted, where surgical therapy is used to remove the chronic components of HS which are not expected to respond to medical therapy (e.g., scarring, fistulas, and sinus tracts), and long term systemic medical therapy is used to treat the acute or sub chronic manifestations of HS (e.g., inflammatory lesions [abscesses and/or nodules]).

Immunosuppressive therapy can be considered as an option for long-term systemic medical therapy in the event that topical and/or oral antibiotic therapy fails to reduce disease activity (Jemec 2006). Given that HS is more common in women of child-bearing potential and the teratogenicity associated with oral retinoid and with anti-androgen therapy, one of the key safety issues related to current treatments is the risk of teratogenicity for patients who use isotretinoin or anti-androgen therapy off-label. Medical therapies causing immunosuppression may increase risk of superinfection of pre-existing HS lesions, cellulitis, and sepsis.

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Our review of the literature found no studies of mortality in the overall HS population. Among HS inpatients in Sweden, the rates of non-melanoma skin (standardised incidence ratio [SIR] = 4.6), buccal (SIR = 5.5), and liver cancer (SIR = 10.0) were significantly increased compared to the general population (Lapins 2001). HS may be associated with IBD with 14% of UC and 17% of CD patients reporting a history of recurrent, painful boils in the axillae and/or groin areas (van der Zee 2010).

Important co-morbidities:

Comorbidities of HS include IBD (Church 1993, van der Zee 2010, Janse 2016, van der Zee 2014), malignancies such as NMSC, buccal cancer, and liver cancer (Lapins 2001, Lavogiez 2010), metabolic syndrome (Sabat 2012, Gold 2014), spondyloarthritis (Richette 2014), depression and anxiety (Shavit 2015, Onderdijk 2013).

Indication #9: Crohn's Disease (Adult and Paediatric)

Incidence:

The reported annual incidence of CD is highest in Europe and North America. In North America, the annual incidence ranges from 6.3 to 13.4 per 100,000 individuals (Herrinton 2008, Loftus 2007, Bernstein 2006).

In Europe, the annual incidence is estimated to be 5.6 (95% CI: 2.8 – 8.3) cases per 100,000 population aged 15 to 64 years with countries in Northern Europe reporting higher incidences of Crohn's disease than countries in Southern Europe (7.0 [95% CI: 4.2 – 9.8] and 3.9 [95% CI: 1.1 – 6.7] per 100,000, respectively) (Shivananda 1996).

Asian countries have historically reported very low incidence rates of CD with reported annual incidence equaling 0.28 cases per 100,000 in China (Zheng 2005), 0.51 to 1.2 cases per 100,000 in Japan (Morita 1995, Yao 2000), and 1.34 per 100,000 in Seoul, South Korea (Yang 2008).

Authors of recent studies conducted in various geographic regions have noted an increasing trend in the incidence of CD (Loftus 2007, Jacobsen 2006, Molinie 2004, Yao 2000, Yang 2008).

Reported annual incidence rates among children in Europe are: 2.3 per 100,000 in northern France (Auvin 2005), 3.6 per 100,000 in Akershus County, Norway (Perminow 2006), 2.1 per 100,000 in The Netherlands (van der Zaag-Loonen 2004), 1.25 to 2.69 per 100,000 in the Czech Republic (Kolek 2004, Pozler 2006), 2.3 per 100,000 in Scotland (Armitage 2004), 5.4 per 100,000 in Stockholm, Sweden, and 1.2 to 1.3 per 100,000 in Sweden (Hildebrand 1991, Lindberg 2008). In North America, annual incidence rates ranged from 4.6 per 100,000 in Wisconsin to 12 per 100,000 in Nova Scotia, Canada (Loftus 2007, Kugathasan 2003).

Prevalence:

As with incidence, the prevalence of CD is highest in North America and Europe. In the US, estimates of CD prevalence range from 96.3 per 100,000 individuals in Northern California (Herrinton 2008) to 173.8 per 100,000 individuals in Olmsted County, Minnesota (Loftus 2007). In Canada, the prevalence of CD was estimated to be 233.7 cases per 100,000 individuals (Bernstein 2006). In Hungary, the prevalence of CD equaled 52.9 per 100,000 (Lakatos 2004). In England CD prevalence equaled 130 per 100,000 (Stone 2003). In Israel, the prevalence of CD was found to be 112.99 per 100,000 (Zvidi 2009). The prevalence of CD in Asia is relatively low. Studies conducted in China and Japan estimate the prevalence of CD to be 1.38 and 13.5 per 100,000, respectively (Zheng 2005, Morita 1995, Yao 2000, Yang 2008).

Among children, the prevalence of CD equaled 4.8 per 100,000 in Sweden (Hildebrand 1991) and 13.7 per 100,000 in Scotland (Armitage 2001). The prevalence in the US for children under 20 ranged from 43 to 114.9 per 100,000, with the highest prevalence found in a study conducted in Olmsted County, Minnesota (Loftus 2007, Kappelman 2007). The prevalence in Canada ranged from 30.5 per 100,000 in Manitoba to 71.1 per 100,000 in Alberta (Bernstein 2006).

Japan has the lowest reported prevalence CD in paediatric populations (0.2 and 0.1 per 100,000 in males and females less than 10 years of age, respectively, and 8.2 and 4.5 per 100,000 in males and females 10 to 19 years of age, respectively) (Yao 2000).

Demographics of the target population:

The incidence of CD is similar between males and females (Herrinton 2008, Shivananda 1996, Vind 2006, Molinie 2004) in most areas except in Asia, where incidence is greater among males (Yao 2000, Yang 2008).

Risk Factors:

Smoking, female sex, and chronic obstructive pulmonary disease (COPD) independent of smoking status may be risk factors for CD (Hovde 2012, Mendall 2011, Marshall 2008, Ekbom 2008). Appendectomy is associated with a decreased risk of CD early in life but may be associated with an increased risk of CD later in life (Hovde 2012).

The main treatment options:

Systemic corticosteroid therapy is highly effective in inducing clinical remission in patients with moderately to severely active CD but is associated with considerable toxicity. At present, budesonide is advocated in preference to systemic corticosteroids (e.g., prednisolone) if the disease distribution is appropriate (terminal ileal or ileocecal disease) (Dignass 2010).

The conventional approach to steroid-refractory or steroid dependent patients has been the introduction of AZA or 6-MP. In recent years, the association of the thiopurines with an increased risk of lymphoma and NMSC has resulted in the recommendation of MTX instead for steroid sparing and in combination with anti-TNF therapy to reduce the appearance of anti-drug antibodies. Immunosuppressants are effective in maintaining remission and have a steroid sparing effect (Candy 1995). The most widely used purine antimetabolite is AZA which is usually prescribed at a maintenance dose of 2.5 mg/kg/day. The rate of remission (Crohn's disease Activity Index [CDAI] < 175) at Month 15 has been reported to be 42% in the AZA group compared to 7% in the placebo group (Candy 1995).

Efficacy of AZA has been limited by a 3- to 4-month therapeutic delay in the onset of action (Candy 1995).

Elemental or polymeric diets appear less effective than corticosteroids in inducing clinical remission.

Other biologic therapies are available for active CD, including the TNF-α antagonists adalimumab, infliximab, and certolizumab, and vedolizumab (a monoclonal anti-integrin α4β7 antibody), and ustekinumab (an anti-IL-12/23 agent) (Feagan 2016). Recently, risankizumab (a selective p19 anit-IL-23 antibody) was approved for adult patients with moderately to severely active CD.

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

A population-based cohort study of patients in the Quebec Administrative Health Database determined that all-cause mortality was significantly increased in CD compared to the general population (SMR = 1.45 [95% CI: 1.34 – 1.58]) (Bitton 2016), while data from Copenhagen County, Denmark suggests a slight increase in all-cause mortality (SMR = 1.3 [95% CI: 1.01 – 1.56]) (Jess 2002). A systematic meta-analysis concluded that the all-cause mortality was increased in CD (SMR = 1.38 [95% CI: 1.23 – 1.55]) (Bewtra 2013). However, other studies did not identify a significantly increased mortality in patients with CD compared to the general population (Selinger 2013, Hovde 2014, Manninen 2012, Probert 1992).

Important co-morbidities:

Comorbidities of CD include uveitis (Hofley 1993, Bernstein 2001c, Turkcapar 2006, Zippi 2014, Vavricka 2011), pyoderma gangrenosum (Bernstein 2001c, Veloso 1996, Turkcapar 2006, Vavricka 2011), and spondyloarthritis (Shivashankar 2012, Bernstein 2001c, Palm 2002, Salvarani 2001, Turkcapar 2006, Beslek 2009, de Vlam 2000).

Indication #10: Ulcerative Colitis (Adult and Paediatric)

Incidence:

The reported annual incidence of UC is highest in Europe and North America. In North America, the annual incidence ranges from 7.6 per 100,000 to 12.0 per 100,000 individuals (Herrinton 2008, Loftus 2007, Bernstein 2006, Loftus 2000). In Europe, the annual incidence is estimated to be 10.4 cases per 100,000 population with countries in Northern Europe reporting higher incidences of UC per 100,000 compared to countries in Southern Europe (11.8 and 8.7 per 100,000, respectively) (Shivananda 1996). Some epidemiologic studies have yielded similar annual incidence estimates (17.0 per 100,000 in Jutland County, Denmark [Jacobsen 2006], 11.01 per 100,000 in Hungary [Lakatos 2004], 11.2 per 100,000 in Greece [Ladas 2005], 13.4 per 100,000 in Copenhagen [Vind 2006]), while others have reported lower incidence rates (3.5 per 100,000 in Northern France [Molinie 2004], 1.7 per 100,000 in Estonia [Salupere 2001], 4.3 per 100,000 in Primorsko goranska County Croatia [Sincic 2006], 5.2 per 100,000 in Huelva, Spain [Garrido 2004], 3.9 per 100,000 in Southern Germany [Ott 2008]).

In much of Asia, the annual incidence of UC is lower than in North America and Europe (1.95 per 100,000 people in Japan [Morita 1995] and 3.08 per 100,000 people in Korea [Yang 2008]).

Reported annual incidence rates among children less than 17 years of age in Europe are: 0.8 per 100,000 in northern France (Auvin 2005), 2.05 per 100,000 in Akershus County, Norway (Perminow 2006), 1.6 per 100,000 in The Netherlands (van der Zaag-Loonen 2004), 1.84 in Eastern Czech Republic (Kolek 2004), 1.8 per 100,000 in Northern Scotland (Armitage 2004), 1.6 per 100,000 in Southern Scotland (Armitage 2004), 2.1 per 100,000 persons in Northern Stockholm, Sweden (Askling 1999), 1.7 per 100,000 in Sweden (Hildebrand 1991), and 3.2 per 100,000 in Sweden (14 counties) (Lindberg 2008). In North America, incidence rate equalled 2.14 per 100,000 in Wisconsin (Kugathasan 2003).

Prevalence:

As with incidence, the prevalence of UC is highest in North America and Europe. A study utilizing data from Olmsted County, Minnesota found a prevalence to be 213.9 per 100,000 individuals (Loftus 2007), while a study conducted using administrative health records from a northern California managed care organization found the prevalence of UC equal to 155.8 per 100,000 (Herrinton 2008). In Canada, the prevalence of UC equalled 193.7 per 100,000 (Bernstein 2006). In England UC prevalence equalled 243 per 100,000 (Stone 2003).

Among children less than 16 years of age, the prevalence of UC equalled 7.5 per 100,000 in Sweden (Hildebrand 1991) and 9.2 per 100,000 in Scotland (Armitage 2001). The prevalence in the US for children under 20 ranged from 28 to 106.7, with the highest prevalence found in a study conducted in Olmsted County, Minnesota (Loftus 2007, Kappelman 2007). In Canada the prevalence of UC among patients diagnosed before age 20 ranged from 17.5 per 100,000 in British Columbia to 30.7 per 100,000 in Alberta (Bernstein 2006). In a recent analysis of 2 large databases in the US, the standardized prevalence of UC in children 2 - 17 years of age increased significantly from 2007 to 2016 (8.6 to 21.6 per 100,000) (Ye 2019).

Demographics of the target population:

UC incidence appears to peak between 20 and 39 years of age among females and between 40 and 59 years of age among males (Herrinton 2008, Loftus 2007). However, more recent data from Southern Germany collected between 2004 and 2005 suggest the incidence is highest in those 16 to 25 years of age (Ott 2008).

Risk Factors:

Among those over age 50, male sex may be a risk factor for UC (Marshall 2008).

The main treatment options:

Conventional therapies for the induction of remission have included anti-inflammatory agents (5-aminosalicylic acid [5-ASA] derivatives and corticosteroids) and the immunomodulatory agent cyclosporine. Aminosalicylates (which come in numerous formulations and delivery systems) are generally started with in mild-to-moderate UC. Intolerance to 5-ASA drugs occurs in up to 15%, gastrointestinal symptoms are relatively frequent, and renal impairment may rarely occur. Additionally, corticosteroids are given for induction therapy. These agents are not adequate, however, for the maintenance of remission and also have serious systemic toxicities such as adrenal suppression, Cushing syndrome, lymphopenia, infections, osteoporosis, psychopathological alterations, gastrointestinal bleeding, hypertension, and cataract. If intravenous (IV) corticosteroids fail in patients with severe colitis, treatment with IV cyclosporine is sometimes used in order to avoid colectomy. However, the risk of clinical relapse remains high in the first year after treatment, and the occurrence of opportunistic infection is a main concern. Other adverse events related to cyclosporine may be hypertension, paraesthesia, renal impairment, or gastrointestinal upset (Kornbluth 2004, Travis 2008).

5-ASA derivatives, as well as immunomodulatory agents (AZA or 6 MP), have been used for the maintenance of remission (Harrison 2002). Significant adverse events of thiopurines are myelo-/hematotoxicity and hepatotoxicity. Furthermore, intake of thiopurines has been established as an independent risk factor for the development of lymphoma and NMSC in IBD (Beaugerie 2009, Kandiel 2005, Peyrin-Biroulet 2011).

Biologic therapies available for adult patients with moderately to severely active UC include the TNF-alpha inhibitors infliximab, adalimumab and golimumab, the monoclonal anti-integrin α4β7 antibody vedolizumab (Feagan 2013), the IL-12/IL-23 antagonist ustekinumab (Sands 2019), the JAK inhibitor tofacitinib (Sandborn 2017), and the sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist ozanimod (Sandborn 2021). Recently, upadacitinib (a selective inhibitor of the Janus kinase 1 [JAK1] enzyme) was approved for adult subjects with moderate to severe UC.

The pharmacological treatment for pedUC is largely similar to adults. However, the only biological therapies available for pediatric patients with moderately to severely active UC are the TNF-alpha inhibitors infliximab and adalimumab. Infliximab as an IV therapy may pose a burden to paediatric patients.

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Similar to CD, studies have reported inconsistent results regarding the risk of mortality in UC.

A population-based cohort study of patients in the Quebec Administrative Health Database determined that all-cause mortality was significantly increased in UC compared to the general

population (SMR = 1.21 [95% CI: 1.12 – 1.32]) (Bitton 2016). A systematic meta-analysis concluded that the all-cause mortality was increased in UC (SMR = 1.19 [95% CI: 1.06 – 1.35]) (Bewtra 2013). However, data from Copenhagen County, Denmark suggests no increase in all-cause mortality rate (SMR = 1.05 [95% CI: 0.92 – 1.19]) among patients with UC compared with the general population. Causes of death that occurred at higher rates among male and female UC patients in Copenhagen included pneumonia (SMR = 3.04) and gastrointestinal disease (SMR = 2.55) (Winther 2003).

Important co-morbidities:

Comorbidities of UC include colorectal cancer (Bernstein 2001b, Goldacre 2008, Palli 1998, de Ridder 2014, Turner 2018), uveitis (Bernstein 2001c, Veloso 1996, Turkcapar 2006, Rychwalski 1997, Zippi 2014, Vavricka 2011, Jose 2009), pyoderma gangrenosum (Monsen 1990, Bernstein 2001c, Veloso 1996, Vavricka 2011, Jose 2009), seronegative spondyloarthritis (Shivashankar 2013, Bernstein 2001c, Palm 2002, Salvarani 2001, Turkcapar 2006, Beslek 2009, de Vlam 2000, Bardazzi 1997, Jose 2009), and primary sclerosing cholangitis (Broome 1994, Vind 2006, Bernstein 2001c, Aitola 1994, Olsson 1991, Terg 2008, Christodoulou 2002, Lakatos 2003, Lindberg 2008, Lunder 2016, Jose 2009).

Indication #11: Uveitis (Adult and Paediatric)

Incidence:

Most uveitis studies describe patients seen in subspecialty referral practices and likely underestimate the true incidence of uveitis. From these studies, uveitis incidence is widely reported to be around 20 per 100,000 (London 2010). In Northern California, the annual incidence of uveitis equalled 52.4 cases per 100,000 person-years (Gritz 2004). There is some evidence that incidence and prevelance of uveitus seem to increase with age (Gritz 2004). In a US sample of Medicare recipients, the annual incidence of uveitis equalled 340.9 cases per 100,000 person-years. In this sample, the mean annual incidence of posterior uveitis equalled 76.6 per 100,000 while the mean annual incidence of panuveitis/endophthalmitis equalled 41.7 per 100,000 (Reeves 2006). A retrospective population-based cohort study using data from patients enrolled in Kaiser Permanente Hawaii reported the incidence of uveitis equalled 24.9 per 100,000. The incidence of posterior/panuveitis equalled 3.9 per 100,000 person-years while the incidence of intermediate uveitis equalled 0.7 per 100,000 person-years (Acharya 2013).

The reported annual incidence of uveitis equalled 51.91 cases per 100,000 inhabitants in Spanish study (Llorenc 2015).

The incidence of uveitis in children is lower than in adults. In Northern California, the incidence of uveitis was approximately 5 per 100,000 person-years in children younger than 15 years old, and the incidence increased to over 30 per 100,000 person years in those aged 15 –

24 years (Gritz 2004). In southwestern Finland, the annual incidence of uveitis was reported to be 2.6 per 100,000 children under 10 years old and 8.5 per 100,000 children and young adults aged 10 – 19 years (Saari 1995).

Prevalence:

The reported prevalence of uveitis in adults equalled 144.85 cases per 100,000 inhabitants in a Spanish study. In this study, 23% of patients had posterior uveitis, 15% had panuveitis, and 9% had intermediate uveitis (Llorenc 2015). In Northern California, the prevalence (during a period of a year) of uveitis equalled 115.3 cases per 100,000 (Gritz 2004). In a US sample of Medicare recipients, the prevalence of uveitis equalled 567.3 cases per 100,000 person-years (Reeves 2006). A study using a large US study of administrative insurance claims database found that the prevalence of noninfectious uveitis among adults was 121 cases per 100,000 persons (Thorne 2016). A retrospective population-based cohort study using data from patients enrolled in Kaiser Permanente Hawaii reported the prevalence of uveitis equalled 58.0 per 100,000 persons in 2007. The prevalence of intermediate uveitis in this population equalled 2.8 per 100,000 persons, while that of posterior/panuveitis equalled 6.9 per 100,000 (Acharya 2013).

The prevalence of uveitis determined by studies conducted in referral clinics is approximately 200 per 100,000 in developed countries. This variation is largely attributed to differences in the background prevalence of etiologic factors in the patient populations studied (e.g., sarcoidosis in the USA, Behçet's disease in Asian and Mediterranean countries, toxoplasmosis in Colombia) (London 2010).

In an Italian study including 1,064 consecutive uveitis patients, anterior uveitis was most common (51.2%) followed by posterior uveitis (23.4%), panuveitis (19.6%), and intermediate uveitis (5.8%), respectively (Cimino 2010).

Pediatric uveitis accounts for 5 – 16% of all uveitis cases in most tertiary clinics (Tsirouki 2016, Jones 2015, Bajwa 2015). Of pedUV patients, approximately 17.0 – 58.4% have anterior uveitis, 17.5 – 25.1% have intermediate uveitis, 13.8 – 50.4% have posterior uveitis, and 2.0 – 15.0% have panuveitis. Approximately 5.1 – 41.5% of pedUV patients have JIA (Tsirouki 2016).

Demographics of the target population:

Studies have produced conflicting results regarding the importance of age and sex in the epidemiology of uveitis (Gritz 2004). Gritz et al found the incidence of uveitis was positively associated with female sex and increasing age (Gritz 2004). Many studies conducted in referral settings have found relatively equal distributions with regard to sex, and age of onset occurring most often between 35 to 45 years of age (London 2010).

Risk Factors:

Male sex, increasing age, and smoking may be risk factors for uveitis (Hwang 2012, Lin 2010).

The main treatment options:

Corticosteroids have been the mainstay of treatment for non-infectious uveitis due to their immediate efficacy. These can be administered either in a topical, oral or injectable form. However, ocular and/or systemic adverse effects of long-term corticosteroid therapy limit its use in the treatment of uveitis (Jabs 2000, Cervantes-Castaneda 2007).

For JIA-associated uveitis, the main cause of non-infectious uveitis in children, it is recommended that treatment follows 3 phases: 1) treatment with topical corticosteroids, 2) treatment with nonbiologic immunosuppressive agents, and 3) addition of a second nonbiologic immunosuppressive agent (e.g., MTX or cyclosporine) or a biologic immunomodulator (e.g., infliximab or adalimumab) (Heiligenhaus 2012).

The type and severity of the uveitis dictate the route of administration of corticosteroids and the likelihood of requiring additional immunosuppressive therapy (Jabs 2000, Smith 2002). Topical corticosteroid eye drops may be sufficient to successfully control anterior uveitis, however, while in inflammation involving the posterior segment of the eye may require systemic or injectable corticosteroid administration.

The most commonly used immunosuppressive agents in uveitis are cyclosporine, mycophenolate mofetil, AZA and tacrolimus (Jabs 2000, Cervantes-Castaneda 2007). Based on the published recommendations of an expert panel, immunosuppressive agents should be considered for the management of ocular inflammatory disorders in the following situations: 1) the disease worsens on high dose prednisone, 2) a response is not obtained after 2 to 4 weeks of high-dose prednisone, 3) the disease is not completely controlled after 4 weeks of high-dose prednisone, 4) chronic suppression of disease activity requires much more than 10 mg/day of prednisone (or its equivalent), 5) the type of uveitis requires immediate combination therapy with high-dose steroids and an immunosuppressive agent, 6) in the presence of corticosteroid side effects, or 7) requirement for doses of systemic corticosteroids that are highly likely to result in corticosteroid complications (Jabs 2000).

Natural history of the indicated disease/condition in the untreated population, including mortality and morbidity:

Our literature review did not identify any studies of mortality associated with uveitis.

Uveitis is a leading cause of vison loss, accounting for 10 – 25% of blindness worldwide (Dick 2016, Venkatesh 2016).

Chronicity and high complication rates tend to be associated with paediatric uveitis. In about one-third of children, uveitis leads to severe visual loss (Tsirouki 2016).

Important co-morbidities:

Comorbidities of uveitis include sarcoidosis (Barisani-Asenbauer 2012, Jakob 2009, Llorenc 2015, Smith 2004, Grajewski 2015, Jones 2015, Bajwa 2015), Behçet's disease (Barisani Asenbauer 2012, Jakob 2009, Llorenc 2015, Smith and Rosenbaum 2004, Grajewski 2015), Vogt–Koyanagi–Harada (VKH) syndrome (Barisani-Asenbauer 2012, Jakob 2009, Llorenc 2015, Smith 2004, Grajewski 2015), and demyelinating disorder (Zein 2004, Llorenc 2012, Messenger 2015, Barisani-Asenbauer 2012, Jakob 2009, Llorenc 2015, Smith 2004, Guo 2018).

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	**Relevance To Human Usage**
Toxicity	It is important to keep in mind that adalimumab neutralizes both human TNF-α as well as cynomolgus monkey (non-human primate [NHP]) TNF-α, but does not bind to rat TNF-α. Therefore, toxicology studies in NHP can assess potential mechanistic (on-target) and non-mechanistic (off target) effects of adalimumab. Studies in rats will assess primarily non-mechanistic effects.
Single and repeat dose toxicity Single IV doses up to 898 mg/kg adalimumab to rats or mice were well tolerated. Chronic weekly IV dosing of cynomolgus monkey (NHP) up to 39 weeks at dosages of up to 215 mg/kg/week were well tolerated. There was no evidence of an increased risk of infections and all the findings observed were the consequence of exaggerated pharmacology (i.e., effects on the immune system: minimal changes in the lymphoreticular system; changes in cellularity).	Serum concentrations at the no observable adverse effects level in NHP were at least 70-fold higher than in patients. Because the findings observed in the toxicology studies were driven by exaggerated pharmacology of adalimumab (i.e., neutralization of TNF-α), it can be assumed that these findings are also relevant for humans.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
Reproductive and developmental toxicity In a developmental toxicity study conducted in cynomolgus monkeys, there was no indication of maternal toxicity, embryotoxicity, or teratogenicity at weekly IV dosing up to 100 mg/kg. Preclinical data on postnatal toxicity and fertility effects of adalimumab are not available.	Limited clinical data on exposed pregnancies are available in humans. Due to its inhibition of TNF-α, adalimumab administered during pregnancy could affect normal immune responses in the newborn and, therefore, administration of adalimumab is not recommended during pregnancy. Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last adalimumab treatment. It can be assumed that adalimumab will cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may have an increased risk for infection.
Nephrotoxicity There was no evidence of renal toxicity in animal studies.	Studies in NHP were not indicative of any nephrotoxicity risk for humans.
Hepatotoxicity There was no evidence of hepatotoxicity in animal studies.	Studies in NHP were not indicative of any hepatotoxicity risk for humans.
Genotoxicity Adalimumab was negative in the in vitro Ames test and in the in vivo mouse micronucleus test. These studies were conducted prior to ICH S6 and are irrelevant tests for a biologic because it can be assumed that these molecules will not interact with deoxyribonucleic acid (DNA) or chromosomes like small molecules.	Genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and, therefore, are not needed. Moreover, the administration of large quantities of peptides/proteins may yield uninterpretable results. It is not expected that these substances would interact directly with DNA or chromosomal material.
Carcinogenicity A dedicated study was not conducted because there was no evidence of any preneoplastic changes in the chronic NHP study. Furthermore, there was a lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and rodents developed neutralizing anti-drug antibodies.	In clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF antagonist compared with control patients; however, the occurrence was rare. Cases of leukaemia have been reported in patients treated with a TNF-antagonist. With the current knowledge, a possible risk for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Key Safety Findings (from Non-Clinical Studies)	Relevance To Human Usage
General Safety Pharmacology	
Cardiovascular Electrocardiogram (ECG) measurements and heart rate were measured in a 39-week chronic toxicology study in NHP; dosing with adalimumab did not show any effects. Adalimumab treatment of Beagle dogs also did not affect cardiovascular and respiratory parameters or body temperature.	Based on animal studies, no effects of adalimumab on cardiovascular or respiratory parameters are expected in humans.
Nervous system No effects (e.g., locomotor activity, hexobarbital induced sleep, and convulsion) were observed in several mice studies conducted to observe for potential effects on the central nervous system (CNS) in mice exposed to doses of adalimumab up to 786 mg/kg.	Based on the animal studies, no effects of adalimumab on CNS parameters are expected in humans.
Other systems (dependent on the product's pharmacological activity)	None known at this time.
Mechanisms for drug interactions Cytokines (e.g., IL-6, TNFα) have been shown to alter the expression of many cytochrome P450 (CYP450) enzymes in vitro. Thus, patients with infections or inflammatory diseases may have altered CYP450 activities due to elevated cytokine levels. No dedicated in vitro or in vivo study in animals on drug-drug interactions was conducted with adalimumab.	When an anti-cytokine antibody, such as adalimumab, is given to patients who are stabilized on drugs with CYP450 mediated metabolism, adalimumab has the potential to alter the clearance of co-administered drugs due to reversal of cytokine effects on CYP expression, which may require dose adjustment of the coadministered drug. Upon initiation or discontinuation of adalimumab in patients being treated with drugs that are CYP450 substrates which also have a narrow therapeutic index, monitoring of the effect (e.g., bleeding time with warfarin use) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the coadministered drug may be adjusted, as needed.
Local tolerance Both the commercial formulation (50 mg/mL) and the high concentration formulation (100 mg/mL) have been tested on local tolerance (IV and SC) in rabbits with no evidence for local intolerability.	Based on animal studies, no local intolerability of adalimumab is expected in humans.

Non-Clinical Safety Findings that are Included as Safety Concerns

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

Module SIII Clinical Trial Exposure

Summaries of total adalimumab exposure are presented in Table 2, Table 3, Table 4, and Table 5 for any subject who received adalimumab for the treatment of RA, PsA, AS, nr-axSpA, non-PsA peripheral SpA, CD, Ps, generalized pustular Ps (GPP), pedPs, UC, pedUC, JIA (pJIA and pedERA combined), pedCD, HS, uveitis, intestinal Behçet's disease (BD), or pyoderma gangrenosum (PG). Data cut-off for exposure is 31 December 2024 except for Study M10-870; data cut-off for Study M10-870 is 08 April 2025.

In Annex 7, exposure data (n,%) are provided by indication in tables by duration; dose; age group and sex; and racial origin for both the randomised, blinded trial population only and for all trial populations together (any adalimumab). Indications are presented in the following order: RA, JIA, PsA, AS, CD, pedCD, Ps, pedPs, generalized pustular psoriasis (GPP), UC, pedUC, nr-axSpA, non-PsA peripheral SpA, HS, uveitis, intestinal BD, and PG.

Person time data (100 [patient-years] PYs) are presented for the randomised, blinded trial population as well as for the population who received any adalimumab, with the exception of exposure by dose. For exposure by dose, person time is presented for the randomised, blinded population only due to the fact that the doses are not consistent across the population receiving any adalimumab. This is because some adalimumab studies allow subjects to increase or decrease dose as needed for efficacy.

A list of studies per indication, which were used to calculate the exposures, is also included in Annex 7.

Table 2. Duration of Exposure

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Person**	**Person Years**
Any Adalimumab – Randomized-Blinded Exposure[a]		
≤ 4 weeks	609	41.9
> 4 to 12 weeks	3052	584.1
> 12 to 24 weeks	2618	875.0
> 24 to 36 weeks	1962	1038.2
> 36 to 48 weeks	327	256.9
> 48 to 60 weeks	824	842.0
> 60 to 72 weeks	27	34.4

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Person**	**Person Years**
> 72 to 84 weeks	153	230.5
> 84 to 96 weeks	12	20.5
> 96 to 108 weeks	370	739.5
> 108 to 120 weeks	5	10.6
Total Person Time	9959	4673.6
Any Adalimumab – All Trial Exposure		
≤ 4 weeks	878	54.3
> 4 to 12 weeks	3263	598.6
> 12 to 24 weeks	7562	2682.2
> 24 to 36 weeks	5638	3074.3
> 36 to 48 weeks	2768	2232.9
> 48 to 60 weeks	3361	3436.1
> 60 to 72 weeks	1019	1287.0
> 72 to 84 weeks	825	1232.9
> 84 to 96 weeks	363	623.0
> 96 to 108 weeks	498	986.9
> 108 to 120 weeks	313	687.6
> 120 to 132 weeks	359	863.9
> 132 to 144 weeks	421	1124.4
> 144 to 156 weeks	543	1563.7
> 156 to 168 weeks	505	1561.7
> 168 to 180 weeks	466	1549.0
> 180 to 192 weeks	412	1469.5
> 192 to 204 weeks	316	1202.3
> 204 to 216 weeks	260	1046.5
> 216 to 228 weeks	216	919.2
> 228 to 240 weeks	212	954.1
> 240 to 252 weeks	241	1140.2
> 252 to 264 weeks	258	1287.7
> 264 to 276 weeks	162	837.9
> 276 to 288 weeks	138	745.1
> 288 to 300 weeks	169	955.3
> 300 to 312 weeks	115	674.3

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Person**	**Person Years**
> 312 to 324 weeks	107	650.3
> 324 to 336 weeks	65	410.7
> 336 to 348 weeks	84	549.8
> 348 to 360 weeks	32	217.2
> 360 to 372 weeks	48	336.3
> 372 to 384 weeks	57	413.6
> 384 to 396 weeks	85	635.6
> 396 to 408 weeks	63	484.9
> 408 to 420 weeks	120	956.8
> 420 to 432 weeks	44	359.3
> 432 to 444 weeks	29	243.0
> 444 to 456 weeks	29	250.4
> 456 to 468 weeks	79	703.7
> 468 to 480 weeks	39	352.9
> 480 to 492 weeks	16	149.4
> 492 to 504 weeks	33	317.1
> 504 to 516 weeks	83	810.6
> 516 to 528 weeks	329	3287.8
> 528 to 540 weeks	100	1024.0
> 540 to 552 weeks	21	219.1
> 552 to 564 weeks	19	202.9
> 564 to 576 weeks	62	678.7
> 576 to 588 weeks	4	44.5
> 588 to 600 weeks	3	34.1
> 600 to 612 weeks	0	0.0
> 612 to 624 weeks	4	47.7
> 624 to 636 weeks	12	144.5
Total Person Time	32848	48315.6
Any Adalimumab – Registry Exposure		
≤ 4 weeks	701	30.5
> 4 to 12 weeks	632	103.2
> 12 to 24 weeks	1286	432.2
> 24 to 36 weeks	1113	631.8

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Person**	**Person Years**
> 36 to 48 weeks	840	674.8
> 48 to 60 weeks	916	950.9
> 60 to 72 weeks	668	844.7
> 72 to 84 weeks	1104	1670.6
> 84 to 96 weeks	659	1127.3
> 96 to 108 weeks	585	1148.2
> 108 to 120 weeks	420	913.5
> 120 to 132 weeks	429	1038.0
> 132 to 144 weeks	411	1083.6
> 144 to 156 weeks	374	1078.2
> 156 to 168 weeks	420	1299.9
> 168 to 180 weeks	352	1175.5
> 180 to 192 weeks	368	1311.0
> 192 to 204 weeks	280	1064.1
> 204 to 216 weeks	357	1436.8
> 216 to 228 weeks	277	1176.7
> 228 to 240 weeks	352	1581.0
> 240 to 252 weeks	389	1839.5
> 252 to 264 weeks	1096	5453.9
> 264 to 276 weeks	882	4548.1
> 276 to 288 weeks	331	1788.2
> 288 to 300 weeks	288	1621.9
> 300 to 312 weeks	581	3421.0
> 312 to 324 weeks	795	4829.9
> 324 to 336 weeks	299	1886.5
> 336 to 348 weeks	153	1002.2
> 348 to 360 weeks	126	854.4
> 360 to 372 weeks	124	868.6
> 372 to 384 weeks	77	558.4
> 384 to 396 weeks	101	754.4
> 396 to 408 weeks	104	801.7
> 408 to 420 weeks	100	794.1
> 420 to 432 weeks	106	864.1

Cumulative for All Indications (Person Time)		
Duration of Exposure	**Person**	**Person Years**
> 432 to 444 weeks	78	654.7
> 444 to 456 weeks	85	733.2
> 456 to 468 weeks	114	1011.1
> 468 to 480 weeks	115	1045.1
> 480 to 492 weeks	114	1062.4
> 492 to 504 weeks	147	1403.4
> 504 to 516 weeks	231	2259.5
> 516 to 528 weeks	456	4561.7
> 528 to 540 weeks	161	1644.6
> 540 to 552 weeks	43	449.0
> 552 to 564 weeks	13	138.8
> 564 to 576 weeks	6	65.2
> 576 to 588 weeks	3	33.2
Total Person Time	19662	67721.7

a. PedCD exposure data were not included in this cumulative category because the only pedCD study that would potentially be included in this cumulative category (Study M06-806) did not have a control group.

Note: PedCD and GPP are only included in the Cumulative All Trial Exposure group.

Table 3. Exposure by Age Group and Gender

Cumulative for All Indications (Person Time)						
	Male		**Female**		**Unknown**	
Age Group	**Persons**	**Person Years**	**Persons**	**Person Years**	**Persons**	**Person Years**
Randomised-Blinded Exposure (Any Adalimumab)						
2 – 6	8	3.4	11	5.3	--	--
7 – 11	26	10.2	41	19.2	--	--
12 – 17	75	29.8	81	37.3	--	--
≥ 18	4120	1779.2	5597	2789.2	--	--
< 40 years	1760	679.1	1850	835.2	--	--
40 to 64 years	2117	961.5	3151	1605.2	--	--
65 to 75 years	310	158.9	603	342.5	--	--
76 to 85	41	22.9	122	66.2	--	--

Cumulative for All Indications (Person Time)						
	Male		Female		Unknown	
Age Group	Persons	Person Years	Persons	Person Years	Persons	Person Years
> 85	1	0.1	4	1.9	--	--
All Trial Exposure (Any Adalimumab)						
2 – 6	15	30.4	45	107.1	--	--
7 – 11	69	191.4	110	300.6	--	--
12 – 17	205	510.1	234	604.2	--	--
≥ 18	12546	18368.3	19623	28203.3	--	--
< 40 years	5080	7438.5	5984	8119.8	--	--
40 to 64 years	6650	10165.1	11156	17208.0	--	--
65 to 75 years	981	1367.7	2444	3353.6	--	--
76 to 85	122	127.4	421	529.1	--	--
> 85	2	1.4	7	4.6	--	--
Unknown	--	--	--	--	1	0.3
Registry Trial Exposure (Any Adalimumab)[a]						
2 – 6	16	81.6	54	202.9	--	--
7 – 11	100	388.1	125	409.1	--	--
12 – 17	539	1599.6	532	1535.8	--	--
≥ 18	8022	30786.9	10276	32717.7	--	--
< 40 years	3611	12789.9	4349	13080.3	--	--
40 to 64 years	4356	17593.6	5362	17970.8	--	--
65 to 75 years	627	2230.2	1073	3347.2	--	--
76 to 85	83	242.4	195	450.9	--	--
> 85	--	--	6	16.4	--	--

Note: PedCD and GPP are only included in the Cumulative All Trial Exposure group.

Table 4. Total Exposure by Dose

Cumulative for All Indications (Person Time)		
Dose	**Persons**	**Person Years**
Randomised-Blinded Exposure		
Control	6505	2769.3
20 mg eow	375	119.3
20 mg weekly	396	255.6
40 mg eow	6419	3410.3
40 mg weekly	1004	392.7
Other adalimumab doses	1802	495.7

eow = every other week

Table 5. Exposure by Ethnic Origin

Cumulative for All Indications (Person Time)		
Ethnic Origin	**Persons**	**Person Years**
Randomised-Blinded Exposure (Any Adalimumab)[a]		
White	7163	3614.0
Black	300	139.2
Asian	1992	662.6
Other	226	113.8
Unknown	278	144.0
All Trial Exposure (Any Adalimumab)		
White	27655	41263.0
Black	807	1257.2
Asian	3425	4420.0
Other	693	1236.6
Unknown	268	138.8
Registry Trial Exposure (Any Adalimumab)		
White	18087	62584.8
Black	424	1240.36
Asian	395	1403.0
Other	591	1681.2
Unknown	165	812.4

a. PedCD exposure data were not included in this category because the only pedCD study that would potentially be included in this category (Study M06-806) did not have a control group.

Note: PedCD and GPP is only included in the cumulative All Trial Exposure group.

Module SIV Populations Not Studied in Clinical Trials

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

There were, and still are, a number of exclusion criteria applied to clinical studies for the benefit of patients participating and to allow clear interpretation of study results. These criteria, which are outlined below, are not contraindications for therapy for approved indications. Some of these criteria are mentioned in the label as situations in which caution should be used in the use of the product, including the use of screening tests and appropriate follow up, and other criteria are not recommended but not explicitly contraindicated.

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 Humira 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: Positive Opinion issued in the EU on 28 June 2018 for the Type II variation to update product labeling for pregnancy based on final results of the OTIS pregnancy registry and postmarketing data and for lactation based on literature (EMEA/H/C/000481/II/0170).

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 the Clinical Development Program

The most current estimate of total patient exposure to adalimumab in clinical trials is 48,315.6 PYs. Additionally, 67,721.7 PYs exposure to adalimumab have accumulated in AbbVie conducted registries. The estimated cumulative postmarketing patient exposure since the International Birth Date (31 December 2002) through 31 December 2024 is 12,395,087 patient treatment years. This volume of patient exposure spanning 22 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 AbbVie has more than 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 Development Program

Table 6. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Pregnant and Breastfeeding women	Pregnant women are excluded from Humira clinical trials. 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]).	The decision to use Humira during pregnancy lies with the patient and her physician in regard to assessing the benefit versus the risk of discontinuing Humira. Language in the current SmPC addresses use in pregnancy as well as breastfeeding. The data do not indicate an increased risk of adalimumab treatment compared to the disease-matched untreated control group with respect to the primary endpoint of major birth defects and secondary endpoints of minor birth defects, spontaneous abortion, preterm birth, birth size and serious or opportunistic infections. No stillbirths or malignancies were reported. Positive opinion issued in the EU on 28 Jun 2018 for the Type II variation to update product labeling for pregnancy based on final results of the OTIS pregnancy registry and postmarketing data and for lactation based on literature (EMEA/H/C/000481/II/0170). It is not to be considered missing information.

Type of special population	Exposure	Implications
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Patients with hepatic or renal impairment have not been directly studied in Humira clinical trials.	Since Humira is a protein, it is likely to be metabolized in a similar fashion as other human antibodies, which is not significantly impaired even in patients with end stage liver or kidney disease. Patients with hepatic and renal exclusionary labs with hepatic or renal impairment were not evaluated during clinical trials. Labeling currently states this. PSUR review of safety data in these populations has not generated a safety signal of concern. This is not considered missing information. Humira is contraindicated in patients with moderate to severe heart failure.
Population with relevant different ethnic origin	Adalimumab has been extensively studied in subject populations that included men and women of a variety of racial backgrounds and ages in clinical trials (SIII).	None.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms that affect metabolism, degradation or pharmacological effects of TNF inhibitors including Humira.	None.

Type of special population	Exposure	Implications
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	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 our 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 (Table 3) and postmarketing (Module SV, Post-Authorisation Experience) experience in the elderly age group. The majority of these patients have RA.	Population information for patients with UC receiving episodic treatment is considered to be missing information.

Type of special population	Exposure	Implications
	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 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 Humira therapy and should be amenable to standard of care treatment. Patients in Ps and JIA indications receiving episodic treatment have been adequately characterized in the clinical development program and the completed studies, Study P10-262 and Study P10-023. Intermittent treatment populations were included in both studies. No unexpected trends were observed for the Intermittent Treatment Population and the overall safety of the Intermittent Treatment Population was comparable with that of the Humira All Treated Population. Patients in the UC indication receiving episodic treatment have not been well characterized.	

Module SV Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Since the approval of adalimumab for RA in the US in December 2002 and in September 2003 in the EU, considerable global postmarketing exposure has accrued.

The estimated cumulative patient exposure from the International Birth Date (31 December 2002) to 31 December 2024 was approximately 12.4 million patient treatment years. This estimate was based on distribution data that included the number of syringes/pens of adalimumab sold worldwide and distributed through AbbVie Special Access Programs. All postmarketing events were evaluated using data obtained from the International Birth Date (31 December 2002) to 31 December 2024, which corresponds with adalimumab PSUR (31 December 2024).

Patient treatment years were calculated by dividing the number of syringes (syringes and pens) distributed by AbbVie's estimated 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 an analysis of US healthcare utilization data from Symphony Healthcare Solution and European utilization experience. An estimated average annual dose of 28 syringes was used in the calculation of patient treatment years.

Estimates of distribution statistics in the US by age, sex and indication were derived from AbbVie's analysis of US healthcare utilization data from Symphony Healthcare Solution. Symphony Healthcare Solution data consists of a large number of US prescription claims processed through commercial networks. The percentage distribution by age was based on patients that were treated with adalimumab that have age and sex recorded. The percentage distribution by indication was based on prescriptions for patients treated with adalimumab who also had a diagnosis recorded.

SV.1.2 Exposure

Exposure by geographic area in patient treatment years for the most recent 5 years and the total since the International Birth Date is summarized in Table 7.

Table 7. Adalimumab Post-Marketing (Non-Study) Exposure – Number of Patient Treatment Years by Region and Year

Region	2020	2021	2022	2023	2024	IBD – 2024
EEME&A	57,346	54,522	51,145	43,754	40,620	602,594
JAPAC	92,203	92,717	98,989	90,293	84,428	961,432
Latin America	69,113	78,393	72,489	51,040	30,067	839,241
United States	496,773	552,211	580,681	483,743	392,915	6,021,244
Western Europe/ Canada	256,036	243,246	205,488	179,456	158,590	3,970,576
Total	**971,471**	**1,021,089**	**1,008,793**	**848,285**	**706,620**	**12,395,087**

Data cut-off for postmarketing exposure data is 31 December 2024.

Note: Patient treatment years are calculated by dividing the total number of syringes sold or distributed by the average number of syringes used by a patient for a year. AbbVie estimates that patients use on average 28 syringes per year.

Patient treatment years by country and year for the most recent 5 years are presented in Table 8.

Table 8. Adalimumab Post-Marketing (Non-Study) Exposure – Number of Patient Treatment Years by Country and Year

Country	2020	2021	2022	2023	2024
EEME&A	[redacted]				
Algeria					
Armenia					
Bahrain					
Belarus					
Bosnia and Herzegovina					
Botswana					
Bulgaria					
Croatia					
Czechia					
Egypt					
Estonia					
Hungary					
Iraq					
Jordan					

Country	2020	2021	2022	2023	2024
Kazakhstan					
Kenya					
Kuwait					
Latvia					
Lebanon					
Libya					
Lithuania					
Malta					
Mauritius					
Moldova, Republic of					
Montenegro					
Morocco					
Namibia					
Oman					
Palestine, State of					
Poland					
Qatar					
Romania					
Russian Federation					
Saudi Arabia					
Serbia					
Slovakia					
Slovenia					
South Africa					
Tunisia					
Ukraine					
United Arab Emirates					
JAPAC					
Australia					
China					
Hong Kong					
Indonesia					
Japan					
Korea, Republic of					

Country	2020	2021	2022	2023	2024
Malaysia					
New Zealand					
Philippines					
Singapore					
Taiwan, Province of China					
Viet Nam					
LATIN AMERICA					
Argentina					
Aruba					
Bahamas					
Barbados					
Bermuda					
Brazil					
Cayman Islands					
Chile					
Colombia					
Costa Rica					
Curaçao					
Dominican Republic					
Ecuador					
El Salvador					
Guatemala					
Honduras					
Jamaica					
Mexico					
Nicaragua					
Panama					
Paraguay					
Peru					
Puerto Rico					
Sint Maarten (Dutch part)					
Trinidad and Tobago					

Country	2020	2021	2022	2023	2024
Uruguay	[redacted]				
UNITED STATES					
United States of America					
WESTRN EUROPE/CANADA					
Austria					
Belgium					
Canada					
Cyprus					
Denmark					
Finland					
France					
Germany					
Gibraltar					
Greece					
Iceland					
Ireland					
Israel					
Italy					
Netherlands					
Norway					
Portugal					
Spain					
Sweden					
Switzerland					
Turkey					
United Kingdom of Great Britain and Northern Ireland					
Total	**971,471**	**1,021,089**	**1,008,793**	**848,285**	**706,620**

Data cut-off for postmarketing exposure data is 31 December 2024.

Note: Patient treatment years are calculated by dividing the total number of syringes sold or distributed by the average number of syringes used by a patient for a year. AbbVie estimates that patients use on average 28 syringes per year.

Estimates of usage by indication are presented in Table 9.

Table 9. Estimated Percentage Range of Humira Usage in the United States from 2020 to 2024 by Indication and Year

Indication	2020 %	2021 %	2022 %	2023 %	2024 %
Rheumatoid Arthritis[a]	26.6-35.3	27-35.7	29.1-39.2	28.3-37.2	30.7-39.9
Psoriatic Arthritis	10-11.3	9.3-10.4	5.1-5.5	5.4-5.9	4.5-4.8
Psoriasis	18.6-29.6	17.8-28.5	16.7-27.6	18.8-25.6	17.3-24.4
Ankylosing Spondylitis	4.4-9.7	4.7-9.8	4.9-10.5	5.0-10.2	5.3-10.6
Crohn's Disease	21.6-24.9	21.3-24.4	20.2-23.4	20.7-23.8	20.0-22.7
Ulcerative Colitis	13.7-16.3	13.8-16.4	13.4-16.3	13.7-16.3	13.5-16.0
Hidradenitis Suppurativa	4.0-5.6	5.1-6.8	6.2-8.7	6.8-9.0	7.0-9.3
Uveitis	1.0-2.2	1.2-2.4	1.4-3.4	1.5-3.0	1.9-3.9

a. Includes JIA.

Note: Estimates based on AbbVie's analysis of Symphony Health Solutions data. Company Confidential. Lower bound of percent usage calculated using individuals without comorbid indications, while the upper bound accounts for comorbidities.

Estimated US exposure by age, by sex, and by sex and age together is contained in Table 10 and Table 11.

Table 10. Estimated Percentage Usage of Humira by Age and Sex Within Year in the United States

Category	2020 %	2021 %	2022 %	2023 %	2024 %
0 – 17	4	4	2.5	3.3	4.5
18 – 39	28	28	26.2	27.2	27.3
40 – 64	55	54	53.3	53.1	52.5
65 – 75	14	11	14.0	12.8	12.1
76+	--	3	4.0	3.6	3.6
Total	100	100	100	100	100
Male	43	42	41	41	40
Female	57	58	59	59	60
Total	100	100	100	100	100

Note: Estimates based on AbbVie's analysis of Source Healthcare Analytics data. Company Confidential.

Table 11. Estimated Percentage Usage of Humira by Age Within Sex and Year in the United States

Sex/Age	2020 %	2021 %	2022 %	2023 %	2024 %
Female					
0 – 17	4	4	2.5%	3.1%	4.1%
18 – 39	26	27	25.1%	26.1%	26.2%
40 – 64	55	55	53.8%	53.7%	53.3%
65 – 75	15	11	14.2%	13.0%	12.4%
76+	0	3	4.4%	4.0%	4.0%
Total	100	100	100	100	100
Male					
0 – 17	4	4	2.6%	3.5%	4.9%
18 – 39	30	30	27.8%	28.9%	28.9%
40 – 64	54	54	52.5%	52.2%	51.3%
65 – 75	13	10	13.8%	12.4%	11.8%
76+	0	2	3.4%	3.1%	3.1%
Total	100	100	100	100	100

Note: Estimates based on AbbVie's analysis of Source Healthcare Analytics data. Company Confidential.

Ongoing review of data included in Humira PSURs for patients with hepatic and renal failure shows no unique safety concerns in those patient populations. Humira is contraindicated in patients with moderate to severe heart failure.

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.

Module SVII Identified and Potential Risks

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

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

See Section SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP for Important identified and Important Potential Risks which were removed and now categorized below.

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 disorders
- Intestinal perforation
- Intestinal stricture in Crohn's Disease

- Liver failure and other liver events
- Elevated alanine aminotransferase levels
- Autoimmune Hepatitis
- Immune reactions (including Lupus-like Reactions and Allergic reactions)
- Medication errors and maladministration
- Off label use
- Infections in infants exposed to adalimumab in utero (see also new identified risk of BCG disease following live BCG vaccination in infants with in utero exposure to Humira under SVII.1.2)

Known risks that do not impact the benefit-risk 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: the 20 mg/0.2 ml pre-filled syringe was approved in the EU on 08 December 2017 to support a fixed dose regimen in pediatric patients (EMEA/H/C/000481/X/0164/G). The MAH intends to phase out the vial subject to the appropriate regulatory approvals in other dependent markets.
- Opportunistic infections: this risk is covered under the identified risk of serious infections.

SVII.1.2 Risks/Missing Information Considered Important for Inclusion 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 defense 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 defense 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 Humira Reason for Inclusion: As requested by the EMA per the Type II variation for the ARTIS registry, Type II variation for the pregnancy and lactation labeling update, and PSUR (01 January 2014 to 31 December 2016).

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

Information 1: 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-Authorisation: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activity: Registry for pedCD patients (Study P11-292). Monitoring to better understand the effects of adalimumab in longer-term treatment of pedCD. Evaluate the long-term safety of adalimumab in paediatric patient population with CD.
Information 2: Episodic treatment in Ps, UC and JIA Reason for Inclusion: Routine pharmacovigilance surveillance is being performed. Data to be Collected Post-Authorisation: Treatment interruptions in registry studies will be evaluated.
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-Authorisation: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activity: Long-term uveitis data from the ongoing JIA registry (Study P10-262).
Information 4: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC Reason for Inclusion: Safety profile in this population requires more characterization. Data to be Collected Post-Authorisation: Routine pharmacovigilance surveillance is being performed. Evaluate long-term ped UC data from the ongoing extension study (Study M10-870).

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

Removed Missing Information

Missing Information 4: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC Reason for Removal: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC has been reviewed through the completion of Study M10-870. Overall, the long-term safety data in paediatric patients with UC were comparable to those observed in previous Humira clinical trials and in line with the observed safety profile for Humira. No new safety concerns were identified. The benefit-risk profile is favourable in paediatric patients with UC treated with Humira.

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

Important Identified risk 1: Serious infections

Potential mechanisms:

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

Evidence Sources and Strength of Evidence:

Data from adalimumab trials and registries as described below and from the company postmarketing safety database.

Characterization of the Risk:

Frequency by Incidence

In controlled trials, the rate of serious infection in subjects treated with adalimumab was 4.1/100 PYs. It ranged from 0/100 PYs in the nr-axSpA and peripheral SpA indication to 13.6/100 PYs in the pedUC indication (Study M11-290). In the pedUC Study M10-870, the rate of serious infection was 2.7/100 PYs. Apart from 1 subject with meningitis, study drug was not interrupted because of these infections.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal adverse events (AEs) occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, 62 were due at least in part to serious infection.

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 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-α 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 Humira, 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:

With appropriate risk minimization measures currently in place, the benefit-risk 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-α.

Evidence Sources and Strength of Evidence:

Data from adalimumab trials and registries as described below and from the company postmarketing safety database.

Characterization of the Risk:

Frequency by Incidence

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 0.4E/100 PYs. It ranged from 0/100 PYs in the JIA, PSA, AS, CD, Ps, pedPs, HS, and peripheral SpA indications to 5.5/100 PYs in the PedUC indication, and 3.0/100 PYs in the uveitis indication.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 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:

With appropriate risk minimization measures currently in place, the benefit-risk 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 Sources and Strength of Evidence:

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, like Humira.

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

If you take Humira, the risk of getting lymphoma, leukaemia, or other cancers may increase. The risk can increase if you take AZA or 6-MP.

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

Information from Company postmarketing safety database.

On rare occasions, a specific and severe type of lymphoma, called HSTCL, has been seen in patients on Humira. This is a very rare specific form of lymphoma involving the blood cells, liver, and spleen. Some patients who developed HSTCL were also treated with AZA or 6-MP.

Cases of NMSC have been observed in patients taking Humira.

Characterization of the Risk:

Frequency by Incidence

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), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, 90 (0.2%) were due 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).

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 2001b). 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). Similarly, analyses of the GPRD (1988 – 1997) in the United Kingdom found no increased incidence in lymphoma in UC patients (lymphoma SIR 1.11, 95% CI: 0.51 – 2.19) (Lewis 2001). 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 1 year 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).

HSTCL:

The frequency of this aggressive form of lymphoma is exceedingly rare. Accurate incidence rates are not available.

For Humira-indicated populations, the background prevalence and mortality of HSTCL are not well described.

Leukaemia:

RA

The incidence rate of leukaemia 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 leukaemia 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 leukaemia 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 leukaemia 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 leukaemia 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 leukaemia as 1.15 (95% CI: 0.69 – 1.92) compared to the general population (von Roon 2007).

The SIR of leukaemia 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 leukaemia 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 leukaemia 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 leukaemia as 1.2 (95% CI: 0.2 – 3.4) (Mellemkjaer 2000).

The standard morbidity ratio for leukaemia 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 leukaemia/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 2001b). The IRR of leukaemia/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 2001b).

Ps

The SIR for leukaemia 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) ≥ 1 year after last Ps hospitalization (Ji 2009).

The SIR for leukaemia 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 leukaemia 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 leukaemia 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 leukaemia/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 2001b). The IRR of leukaemia/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 2001b).

A study of 6,990 hospitalized English UC patients reported an adjusted RR of lymphoid leukaemia 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 leukaemia was 2.15 (95% CI: 1.02 – 4.03) (Goldacre 2008).

In Sweden, the SIR for leukaemia 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 Humira-indicated populations, the background prevalence of leukaemia 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 SCC was 1.4 (95% CI: 1.1 – 1.9) for the same cohort (Mellemkjaer 1996).

The SIR of SCC 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).

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).

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 SCC 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 SCC 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).

For Humira-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 2001b). 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 2001b).

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) ≥ 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) ≥ 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).

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

MCC:

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). In a case-control study using Surveillance, Epidemiology, and Ends Results (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 (≥ 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/leukaemia virus type I (HTLV-I), and hepatitis C), and age (over 60 years) (National Cancer Institute 2008b).

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 2008b).

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).

Leukaemia:

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).

NMSC:

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).

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 2011b).

MCC:

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).

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 Humira.

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 Humira.

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 Humira and on an annual basis while on Humira, especially if you have a history of extensive immunosuppressive therapy or if you are a psoriasis patient with a history of PUVA treatment.

Your physician should educate your patient about sunscreen use and the importance of prompt detection of lesions.

Impact on the Risk-Benefit Balance of the Product:

With appropriate risk minimization measures currently in place, the benefit-risk balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Important Identified Risk 4: Demyelinating Disorders (Including Multiple Sclerosis, Guillain Barré Syndrome, and Optic Neuritis)

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 Sources and Strength of Evidence:

Data from adalimumab trials as described below.

Characterization of the Risk:

Frequency by Incidence

In controlled trials, the rate of demyelinating disorders in subjects treated with adalimumab was < 0.1/100 PY. It ranged between 0/100 PYs in the PSA, JIA, AS, CD, Ps, pedPs, UC, pedUC, HS, nr-axSpA, and peripheral SpA indications and 0.6/100 PYs in the uveitis indication.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, none were due at least in part to demyelinating disorders.

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 equalled 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 equalled 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) (data on file).

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 2004).

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

For Humira-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-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).
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 Humira. Show your Patient Reminder Card to any healthcare professional that you consult.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures currently in place, the benefit-risk 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 Humira
Potential mechanisms: Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.
Evidence Sources and Strength of Evidence: Data from adalimumab trials and registries as described below and from the company postmarketing safety database.
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.
Risk Factors and Risk Groups: Infants who are exposed to Humira intrauterine.
Preventability: Live vaccines should not be given to patients using Humira, and infants exposed to Humira in utero should not receive live vaccines (e.g., BCG) for 5 months following mother's last Humira dose.

Impact on the Risk-Benefit Balance of the Product:

With appropriate risk minimization measures currently in place, the benefit-risk balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Important Potential Risk 1: Progressive Multifocal Leukoencephalopathy

Potential mechanisms:

Reactivation of Polyomavirus JC (often called JC virus).

Evidence Sources and Strength of Evidence:

Potential source data from adalimumab trials as described below and from the company postmarketing safety database.

Characterization of the Risk:

Frequency by Incidence

There were no reports of PML in all controlled, non-registry, and registry clinical trials.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, none were due at least in part to PML.

Severity and nature of risk

Severe neurological disabilities and death.

Background incidence/prevalence/mortality

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 naïve patients, and 2.3 (0.1 – 71) per 100,000 person-years among RA biologic-treated patients (Arkema 2012).

The mortality of PML in the US (estimated from analysis of national mortality and acquired immune deficiency syndrome (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. 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).

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:

With appropriate risk minimization measures currently in place, the benefit-risk balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

Important Potential Risk 2: Reversible Posterior Leukoencephalopathy Syndrome

Potential mechanisms:

Unknown.

Evidence Sources and Strength of Evidence:

Potential source data from adalimumab trials as described below and from the company postmarketing safety database.

Characterization of the Risk:

Frequency by Incidence

There were no reports of RPLS in all controlled, non-registry, and registry clinical trials.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, none were due at least in part to RPLS.

Severity and nature of risk

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

Background incidence/prevalence/mortality

For Humira-indicated populations, the background incidence and prevalence of and the mortality from RPLS are 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:

With appropriate risk minimization measures currently in place, the benefit-risk 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 Patients

Potential mechanisms:

Unknown.

Evidence Sources and Strength of Evidence:

Potential source data from adalimumab trials as described below.

Characterization of the Risk:

Frequency by Incidence

In non-registry clinical trials, 10 (< 0.1%) instances of adenocarcinoma of colon were observed in the adalimumab group. No cases were observed in pedUC.

Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 376 deaths with associated fatal AEs occurred among 47,982 (0.8%) subjects. Of the 376 deaths with associated fatal AEs, 2 (< 0.1%) were due at least in part to adenocarcinoma of colon in UC.

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).

The age-adjusted incidence rate of rectal cancer as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada from 1984 to 1997 was 56.7 per 100,000 PYs (95% CI not reported) (Bernstein 2001b). In this study, the IRR comparing the population-based cohort of 2,673 UC patients in Manitoba, Canada with a non-UC cohort matched on age, sex, and postal area of residence for rectal cancer was 1.90 (95% CI: 1.05 – 3.43) (Bernstein 2001b).

Excluding the first year after initial UC hospitalization, the adjusted RR of rectal cancer among 6,990 English patients with an inpatient diagnosis of UC between 01 Jan 1963 through 31 Mar 1999 and followed through 31 Mar 1999 was 1.00 (95% CI: 0.50 – 1.81) when compared to hospitalized patients without IBD (Goldacre 2008).

For Humira-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:

With appropriate risk minimization measures currently in place, the benefit-risk balance remains positive.

Public Health Impact:

There is no potential public health risk or impact.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD
The population is in need of further characterization. Routine pharmacovigilance surveillance is being performed. Additionally, a registry for pedCD patients (Study P11-292) is ongoing.
Missing information 2: Episodic treatment in UC
The population is in need of further characterization. Routine pharmacovigilance surveillance is being performed. Additionally, treatment interruptions in registry studies will be evaluated.

Module SVIII Summary of the Safety Concerns

Table 12. Summary of Safety Concerns

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

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Not applicable.

III.2 Additional Pharmacovigilance Activities

PASS summary

Study Short Name and Title:

P11-292: A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Pediatric Patients with Moderately to Severely Active Crohn's Disease – (CAPE)

Rationale and Study Objectives:

To evaluate long-term safety of Humira in pediatric patients with moderately to severely active CD who are prescribed and treated according to routine clinical practice. Patients being prescribed and treated with immunosuppressant therapy with no concurrent biologic use will be enrolled as a reference group.

Study Design:

Registry P11-292 is an ongoing, multicenter, postmarketing, observational registry of pediatric patients (between the ages of 6 and 17 years inclusive at the time of enrollment) with moderately to severely active CD treated according to routine clinical practice with Humira (monotherapy or combination therapy with IMM) prescribed and administered per the local Humira label or IMM (MTX, MP or AZA; without concurrent biologic at the time of enrollment) prescribed and administered per local clinical practice.

Study Population:

Approximately 800 pediatric patients with moderately to severely active CD who will be treated with Humira and approximately 500 patients with moderately to severely active CD who will be treated with IMM non-biologic therapy will be enrolled in the EU countries and additional countries after marketing authorisation is obtained in these regions.

Milestones:

Annual interim analysis: Reporting August through 2019

Biennial interim analysis: Reporting from 2019 through 2027

10-year final report: 3Q 2028

Study Short Name and Title:

P11-282: A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis (UC)

Rationale and Study Objectives:

The objectives of this observational study are to evaluate the long-term safety of Humira in adult patients (18 years of age or older) with moderately to severely active UC who are treated per routine clinical practice.

Study Design:

A multicenter, non-interventional Registry of patients with moderately to severely active UC treated in a routine clinical setting with registry drug.

Study Population:

An adult patient (18 years of age or older) who has been prescribed HUMIRA® for moderately to severely active UC as per the physician's assessment, without or in combination with an IMM (6-MP or AZA), according to routine clinical practice. Additionally, an adult patient (18 years of age or older) who has been prescribed IMM (6-MP or AZA) therapy for moderately to severely active UC as per the physician's assessment, is currently taking IMM (6-MP or AZA) therapy without a concurrent biologic.

Approximately 8,250 patients (approximately 5,500 patients prescribed HUMIRA®, either with or without concurrent IMM (6-MP or AZA) therapy, and approximately 2,750 patients prescribed IMM with no concurrent biologic use will be enrolled after decision to prescribe drug was made.

Milestones:

Next interim report due: 2026. Additional interim reports only required biennially if new safety signal identified.

Final report: 2Q 2031

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 13. Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
Ped CD Patient Registry (Study P11-292) ongoing	To evaluate long-term safety of Humira in pediatric patients with moderately to severely active CD who are prescribed and treated according to routine clinical practice. Patients being prescribed and treated with immunosuppressant therapy with no concurrent biologic use will be enrolled as a reference group.	Captured specific data on the identified and potential risks detailed in Module SVII.3.	Annual interim analysis	Reporting August through 2019
			Biennial interim analysis	Reporting from 2019 through 2027
			10-year final report	3Q 2028
UC Patient Registry (Study P11-282) ongoing	The objectives of this observational study are to evaluate the long-term safety of Humira in adult patients (18 years of age or older) with moderately to severely active UC who are treated per routine clinical practice.	Captured specific data on the identified and potential risks detailed in Module SVII.3.	Next interim report	2026. Additional interim reports only required biennially if a new safety signal identified.
			Final report	2Q 2031

Part IV: Plans for Post-Authorisation Efficacy Studies

Table 14. Planned and Ongoing Post-Authorisation Efficacy Studies that Are Conditions of the Marketing Authorisation or that Are Specific Obligations

Study and Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
NA				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA				

NA = not applicable

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

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 15. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization 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.

Safety Concern	Routine Risk Minimization Activities
Tuberculosis	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 Humira Section 4.4 of the SmPC: In patient with latent TB, anti-tuberculosis prophylaxis treatment before the initiation of Humira, 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 Humira 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 Humira. 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.

Safety Concern	Routine Risk Minimization Activities
Demyelinating Disorders	Routine risk communication: 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. 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 Humira 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 Humira	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 Humira 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. As part of the procedure EMEA/H/C/000481/II/0170 for the pregnancy and lactation labeling update (Positive Opinion issued on 28 June 2018), section 4.4 of the SmPC was updated to state Patients on Humira may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g., BCG) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. Other routine risk minimization measures: Prescription only medicine.

Safety Concern	Routine Risk Minimization Activities
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	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 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.
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 SmPC: None. Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other routine risk minimization measures: Prescription only medicine.

Safety Concern	Routine Risk Minimization Activities
Episodic Treatment in UC	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

AbbVie has an additional risk minimization program to remind patients about key risks associated with the use of adalimumab (Humira®). 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 Humira. 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-Humira prescribing HCP), so that the HCP is aware that the patient is being treated with adalimumab and are aware of these risks.

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 Humira (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 (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. The effectiveness of the Humira risk minimization activities in the EU was assessed annually between 2008 and

2010 in terms of prescriber awareness of the key risks associated with use of Humira. Results of each annual survey were submitted to the EMA. Based on this, no further formal evaluation of the effectiveness of additional risk minimization measures was proposed. The extent to which each of the risk minimization tools is being distributed (i.e., number distributed, how distributed, when and by whom) will continue to be monitored.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 16. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Serious infections	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: To remind patients about the risk of serious infections associated with the use of Humira: • Patient Reminder Card	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Additional pharmacovigilance activity: monitoring as an event of special interest in registry studies.
Tuberculosis (TB)	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: To remind patients about the risk of TB associated with the use of Humira: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Additional pharmacovigilance activity: monitoring as an event of special interest in registry studies.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Malignancies	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: To remind patients about the risk of malignancies associated with the use of Humira: • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: monitoring as an event of special interest in registry studies.
Demyelinating disorders (including MS, GBS, and ON)	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: To remind patients about the risk of demyelinating disorders associated with the use of Humira. • 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 Humira	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: To remind patients about the risk of BCG disease following live BCG vaccination in infants with in utero exposure to Humira. • Patient Reminder Card.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: None.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
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 UC patients	Routine risk minimization measures: Labelling as detailed in Table 15. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Monitoring as an event of special interest in registry for UC patients (Study P11-282).

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
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 15. Additional risk minimization measures: None.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance surveillance is being performed. Additional pharmacovigilance activities: Registry for pedCD patients (Study P11-292).
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: Treatment interruptions in registry studies will be evaluated.

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Humira

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

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

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

Important new concerns or changes to the current ones will be included in updates of Humira RMP.

I The Medicine and What it Is Used For

Humira is authorised for use in adults for the treatment of:

Rheumatoid Arthritis (RA);

Psoriatic Arthritis (PsA);

Axial Spondyloarthritis (Axial SpA);

Crohn's Disease (CD);

Psoriasis (Ps);

Ulcerative Colitis (UC);

Hidradenitis Suppurativa (HS);

Uveitis.

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

Polyarticular Juvenile Idiopathic Arthritis (pJIA);

Paediatric Enthesitis-related Arthritis (pedERA);

Paediatric Crohn's Disease (pedCD);

Paediatric Psoriasis (pedPs);

Adolescent Hidradenitis Suppurativa (HS);

Paediatric Uveitis (pedUV);

Paediatric Ulcerative Colitis (pedUC).

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

Further information about the evaluation of Humira's benefits can be found in Humira's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124.

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

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

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

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

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

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

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

II.A List of Important Risks and Missing Information

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

II.B Summary of Important Risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the company postmarketing safety database.
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 Humira: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the company postmarketing safety database.
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 Humira: • Patient Reminder Card.
Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Data from adalimumab trials. No reports of this specific form of lymphoma were received from any clinical trial, open-label (OL) or controlled. Information from Company postmarketing safety database.
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 Humira 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 Humira: • Patient Reminder Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Demyelinating disorders (including MS, GBS, and ON)	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
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 Humira. • Patient Reminder Card.
Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Humira	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
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 that includes recommendations to avoid administration of live vaccines to infants exposed to adalimumab in utero for 5 months following the mother's last adalimumab injection during pregnancy. 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 Humira and the risk of live vaccines in infants exposed to Humira in utero: • Patient Reminder Card.

Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the company postmarketing safety database.
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	Potential source data from adalimumab trials and from the company postmarketing safety database.
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 UC patients	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials.

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: Monitoring as an event of special interest in registry studies. See Section II.C of this summary for an overview of the post-authorisation development plan.
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 SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry for pedCD patients (Study P11-292). See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Episodic treatment in UC	
Risk minimization measures	Routine risk minimization measures: Text in the SmPC: None. Prescription only medicine. Additional risk minimization measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Treatment interruptions in registry studies will be evaluated.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

Not applicable.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: Study P11-292

Purpose of the study: a long-term non-interventional registry to assess safety and effectiveness of Humira in paediatric patients with moderately to severely active CD.

Study short name: Study P11-282

Purpose of the study: a long-term non-interventional registry to assess safety and effectiveness of Humira in patients with moderately to severely active UC.

Part VII: Annexes

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-Up Forms
Annex 5	Protocols for Proposed and Ongoing Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Activities (If Applicable)
Annex 7	Other Supporting Data (Including Referenced Material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time
Annex 9	Local Currently Approved Country Labeling
Annex 10	Local Risk Management/Mitigation Plan

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Not applicable

Annex 6. Details of Proposed Additional Risk Minimization Activities

Key messages of the additional risk minimization measures

Patient Material:

- Patient Reminder Card

Patient Reminder Card:

- Contact details of the Humira prescriber.
- That the Patient Reminder Card can be carried by the patient and shared with healthcare professionals involved in their treatment.
- A message for the patient that they should undergo screening for TB before taking Humira and reminder that they should record the TB screening results on the card.
- Inform the patient concerning key risks (i.e., serious infections, Tuberculosis (TB), demyelinating disorders, malignancies, and BCG disease following live BCG vaccination in infants with in-utero exposure to Humira) and the need to be vigilant for symptoms associated with them
- A message for the patient to not receive live vaccinations while using Humira and to warn of BCG disease following live BCG vaccination in infants with in utero exposure to Humira, so if they took Humira while pregnant, their baby should not receive a 'live vaccine,' such as BCG (used to prevent tuberculosis) within 5 months following your last adalimumab injection during pregnancy.
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional