PF-06410293 (ADALIMUMAB) RISK MANAGEMENT PLAN

RMP Version number: 2.2

Data lock point for this RMP (Pfizer post-marketing safety data): 28 February 2025

(Data lock point for Innovator RMP on which this RMP is partially based: 31 Dec 2021)

Date of final sign off:

Rationale for submitting an updated RMP: The purpose of the update is to align with the current Innovator RMP (version 16.2 dated September 2024).

Summary of significant changes in this RMP: The missing information " Long Term Safety Information in the Treatment of Children with Uveitis " has been removed and missing information “Episodic treatment in Ps, UC and JIA” has been changed to “Episodic treatment in UC” to align with the current Humira RMP. Post-marketing exposure and safety data have been updated.

Other RMP versions under evaluation: Not Applicable

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EU Centralised Procedure

Date of approval (opinion date): 19 September 2024

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the applicant’s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

5-ASA	5-Aminosalicylic Acid
6-MP	6-mercaptopurine
ADA-EU	Adalimumab sourced in the European Union (Humira)
ADA-PF	Pfizer's Adalimumab
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AR	Adverse Reaction
ARAMIS	North American Rheumatism Association Medical Information System
ARTIS	Antirheumatic Therapies in Sweden
AS	Ankylosing Spondylitis
ATC	Anatomical Therapeutic Chemical
AxSpA	Axial Spondyloarthritis
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin
BW	Body Weight
CD	Crohn's Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
CRP	C-Reactive Protein
CSR	Clinical Study Report
CYP450	Cytochrome P450
DLP	Data-Lock Point
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
eow	every other week
EPAR	European Public Assessment Report
ERA	Enthesitis-Related Arthritis
EU	European Union
GBS	Guillain-Barré Syndrome
GPRD	General Practice Research Database
HBV	Hepatitis B Virus
HCP	Healthcare Professional

HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HLA	Human Leukocyte Antigen
HMA	Heads of Medicines Agencies
HS	Hidradenitis Suppurativa
HSTCL	Hepatosplenic T-Cell Lymphoma
HTLV	Human T-Cell Leukaemia-Lymphoma Virus
IBD	Inflammatory Bowel Disease
ICH	International Committee on Harmonization
IL	Interleukin
INN	International Nonproprietary Name
IRR	Incidence Rate Ratio
IV	Intravenous
JCV	Polyoma Virus JC (John Cunningham Virus)
JIA	Juvenile Idiopathic Arthritis
kg	kilogram
MAH	Marketing Authorization Holder
MCC	Merkel Cell Carcinoma
MedDRA	Medical Dictionary of Regulatory Activities
mg	milligram
mL	milliliter
MN	Minnesota
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTX	Methotrexate
n or N	number
NHL	Non-Hodgkin's Lymphoma
NHP	Non-Human Primate
NMSC	Non-Melanoma Skin Cancer
nr-axSpA	Non-Radiographic Axial Spondyloarthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
OL	Open Label
ON	Optic Neuritis
OTIS	Organization of Teratology Information Specialists
OR	Odds Ratio
PCR	Polymerase Chain Reaction
pedCD	Paediatric Crohn’s Disease
pedERA	Paediatric Enthesitis-Related Arthritis

pedPs	Paediatric Psoriasis
pedUC	Paediatric Ulcerative Colitis
PFP	Pre-Filled Pen
PFS	Pre-Filled Syringe
pJIA	Polyarticular Juvenile Idiopathic Arthritis
PK	Pharmacokinetic
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
Ps	Psoriasis
PsA	Psoriatic Arthritis
PSC	Primary Sclerosing Cholangitis
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
PT	Preferred Term
PUVA	Psoralen + Ultraviolet A treatment
PV	Pharmacovigilance
PY	Patient Year
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
ROW	Rest of World
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RR	Rate Ratio
SAE	Serious Adverse Event
SC	Subcutaneous
SCC	Squamous Cell Carcinoma
SEER	Surveillance, Epidemiology and End Results
SIR	Standardised Incidence Ratio
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SMR	Standardised Mortality Rate
SpA	Spondyloarthritis
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
UK	United Kingdom

USA	United States of America
UV	Ultraviolet
WHO DDD	World Health Organization Defined Daily Dose

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PART I. PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AB04
Marketing Authorisation Applicant	Pfizer Europe Marketing Authorization European Economic Interest Grouping
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area	Amsparity
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Pharmacotherapeutic group: Immunosuppressants-TNF-α inhibitors (ATC Code: L04AA17).
	Summary of mode of action Adalimumab binds specifically TNF and neutralises 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 Qualitative Composition: Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells
Hyperlink to the Product Information:	Module 1.3.1.
Indication(s) in the EEA	Current: **Adults** **Rheumatoid Arthritis:** Adalimumab in combination with MTX is indicated for: • The treatment of moderate to severe, active RA in adult patients when the response to DMARDs including MTX has been inadequate.

	• The treatment of severe, active and progressive RA in adults not previously treated with MTX. Adalimumab can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with MTX. **Psoriatic Arthritis:** Adalimumab is indicated for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. Adalimumab 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:** • Ankylosing Spondylitis Adalimumab 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 Adalimumab is indicated for the treatment of adults with severe AxSpA without radiographic evidence of AS [also referred to throughout this RMP as nr-axSpA] but with objective signs of inflammation by elevated CRP and/or MRI who have had an inadequate response to, or are intolerant to NSAIDs. **Enthesitis-Related Arthritis:** Adalimumab is indicated for the treatment of active ERA in adult patients, who have had an inadequate response to, or who are intolerant of, conventional therapy. **Crohn's Disease:** Adalimumab 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:** Adalimumab is indicated for the treatment of moderate to severe chronic plaque Ps in adult patients who are candidates for systemic therapy. **Ulcerative Colitis:** Adalimumab 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/or 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. **Hidradenitis Suppurativa:** Adalimumab is indicated for the treatment of active moderate to severe HS (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

	Uveitis: Adalimumab is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. **<u>Paediatrics</u>** **Polyarticular Juvenile Idiopathic Arthritis:** Adalimumab 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 1 or more DMARDs. Adalimumab can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Adalimumab has not been studied in patients aged less than 2 years. **Paediatric Enthesitis-Related Arthritis:** Adalimumab is indicated for the treatment of active ERA in paediatric 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:** Adalimumab 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 Plaque Psoriasis:** Adalimumab 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:** Adalimumab is indicated for the treatment of active moderate to severe HS (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy. **Paediatric Uveitis:** Adalimumab 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:** Adalimumab is indicated for the treatment of moderately to severely active UC (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: **Adults** **Rheumatoid Arthritis:** The recommended dose of adalimumab for adult patients with RA is 40 mg adalimumab administered eow as a single dose via SC injection. MTX should be continued during treatment with adalimumab. **Ankylosing spondylitis, AxSpA without radiographic evidence of AS, and PsA.** The recommended dose of adalimumab for patients with AS, AxSpA without radiographic evidence of AS and PsA is 40 mg adalimumab administered eow as a single dose via SC injection. **Crohn's Disease:** The recommended adalimumab 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 of 160 mg at Week 0 (given as four 40 mg injections in 1 day or two 40 mg injections per day for 2 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 AEs is higher during induction. After induction treatment, the recommended dose is 40 mg eow via SC injection. **Psoriasis:** The recommended dose of adalimumab for adult patients with Ps is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given eow starting 1 week after the initial dose. Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosage to 40 mg every week. If adequate response is achieved with 40 mg every week, the dosage may subsequently be reduced to 40 mg eow. **Ulcerative Colitis:** The recommended adalimumab 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 eow via SC injection. **Hidradenitis Suppurativa:** The recommended adalimumab 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 (2) weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg eow (given as two 40 mg injections in 1 day). **Uveitis:** The recommended dose of adalimumab for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given eow starting 1 week after the initial dose.

	<u>Paediatrics</u> **Polyarticular Juvenile Idiopathic Arthritis:** The recommended dose of adalimumab for patients with pJIA from 2 years of age is based on BW. For patients weighing 10 kilogram (kg) to < 30 kg, the dosing regimen is 20 mg eow. For patients weighing ≥ 30 kg, the dosing regimen is 40 mg eow. **Paediatric Enthesitis-Related Arthritis:** The recommended dose of adalimumab for adult and paediatric patients from 6 years of age is based on BW. For patients weighing 15 kg to < 30 kg, the dosing regimen is 20 mg eow. For patients weighing ≥ 30 kg, the dosing regimen is 40 mg eow. **Paediatric Crohn's Disease:** The recommended dose of adalimumab for patients with paediatric Crohn's disease from 6 to 17 years of age is based on BW. Patients weighing less than 40 kg should receive 40 mg at Week 0 and 20 mg at Week 2. The maintenance dose should be 20 mg eow, starting at week 4. 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. Patients weighing ≥ 40 kg should receive 80 mg at Week 0 and 40 mg at Week 2. The maintenance dose should be 40 mg eow, starting at week 4. 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. Patients who experience insufficient response may benefit from an increase in dosage: • < 40 kg: 20 mg every week • ≥ 40 kg: 40 mg every week or mg 80 eow **Paediatric Psoriasis:** The recommended dose of adalimumab for patients from 4 to 17 years of age is based on BW). For patients weighing 15 kg to < 30 kg, the initial dose is 20 mg, followed by 20 mg given eow starting one week after the initial dose. For patients weighing ≥ 30 kg, the initial dose is 40 mg, followed by 40 mg given eow starting one week after the initial dose. **Adolescent Hidradenitis Suppurativa:** Adolescent HS (from 12 years of age, weighing at least 30 kg): The recommended adalimumab dose is 80 mg at Week 0 followed by 40 mg eow starting at Week 1 via SC injection. In adolescent patients with inadequate response to adalimumab 40 mg eow, an increase in dosage to 40 mg every week may be considered. **Paediatric Uveitis:** For patients weighing < 30 kg, the dose is 20 mg eow in combination with methotrexate. For patients weighing ≥ 30 kg, the dose is 40 mg eow in combination with MTX.

	When adalimumab therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy.
	
	Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and psoriatic arthritis:
	
	There is no relevant use of adalimumab in the paediatric population for the indications of ankylosing spondylitis and psoriatic arthritis.
	
	Paediatric Ulcerative Colitis:
	
	For treatment using the 40 mg solution for injection formulation only. The recommended adalimumab induction dose regimen for paediatric patients (from 6 to 17 years of age) with UC is based on BW. Adalimumab is administered via SC injection.
	
	• < 40 kg:
	  o Induction dose 80 mg at Week 0 and 40 mg at Week 2
	  o Maintenance dose (starting at week 4) 40 mg eow
	• ≥ 40 kg:
	  o Induction dose 160 mg at Week 0 and 80 mg at Week 2
	  o Maintenance dose (starting at week 4) 80 mg eow
	
	Paediatric patient who turn 18 years of age while on adalimumab should continue prescription maintenance dose.
	
	Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.
	
	There is no relevant use of adalimumab in children aged less than 6 years in this indication.

Pharmaceutical form(s) and strengths	• PF-06410293 40 mg/0.8 mL solution for injection • PF-06410293 20 mg solution for injection in prefilled syringe • PF-06410293 40 mg solution for injection in prefilled syringe • PF-06410293 40 mg solution for injection in prefilled pen
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

PF-06410293 has been developed as a biosimilar to the Innovator's product Humira (adalimumab). Humira was developed and is currently marketed by AbbVie. Humira was approved in the European Union (EU) in September 2003.

The currently well-established efficacy and safety profile of Humira in the approved indications have been demonstrated during clinical development and use in post-marketing.

The clinical development programme for PF-06410293 was to establish biosimilarity in the expected PK, safety, efficacy, and immunogenicity between PF- 06439535 and Humira.

As such, safety specifications for this RMP are aligned with the RMP developed by Abbvie, version 16.2 dated September 2024, with a data-lock point of 31 December 2021.

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

This section is not required for biosimilars.

Module SII. Non-Clinical Part of the Safety Specification

Amsparity (PF-06410293) is a biosimilar to Humira, and information in this section is largely based on information from the Humira RMP dated August 2022 (there have been no updates to this section in the Innovator's RMP). There were no findings in the non-clinical testing that warrant inclusion among the summary of safety concerns.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-Clinical Studies	Relevance to Human Usage
Toxicity: • Acute toxicity In single-dose toxicity studies undertaken by the Innovator, single intravenous (IV) doses up to 898 mg/kg adalimumab to rats or mice were well tolerated.	It is important to keep in mind that adalimumab neutralizes both human TNF-α as well as cynomolgus monkey (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.
• Repeat-dose toxicity In repeat-dose toxicity studies undertaken by the Innovator, 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 for infections and all the findings observed were the consequence of exaggerated pharmacology (ie, 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 (ie, neutralisation of TNF-α), it can be assumed that these findings are also relevant for humans.
• Reproductive and developmental toxicity In a developmental toxicity study undertaken by the Innovator 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.
• Genotoxicity In genotoxicity studies undertaken by the Innovator, 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 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

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-Clinical Studies	Relevance to Human Usage
	would interact directly with DNA or chromosomal material.
• Carcinogenicity A dedicated study was not conducted by the Innovator because they had no evidence of any preneoplastic changes in the chronic NHP study. Furthermore, they determined that there was a lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and rodents developed neutralising 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.
• Nephrotoxicity: There was no evidence of renal toxicity in animal studies.	Studies performed by the Innovator in NHP were not indicative of any nephrotoxicity risk for humans.
• Hepatotoxicity: There was no evidence of hepatotoxicity in animal studies.	Studies performed by the Innovator in NHP were not indicative of any hepatotoxicity risk for humans.
Safety Pharmacology as applicable: • Cardiovascular and respiratory: The following results were obtained in studies performed by the Innovator: ECG measurements and heart rate were measured in a 39-week chronic toxicology study in NHP; dosing with adalimumab did not show any effects. Humira treatment of Beagle dogs also did not affect cardiovascular and respiratory parameters or body temperature.	Based on the animal studies, no effects of adalimumab on cardiovascular or respiratory parameters are expected in humans.
• Nervous system: No effects (eg, locomotor activity, hexobarbital-induced sleep, and convulsion) were observed in several mice studies conducted by the Innovator to observe for potential effects on the CNS in mice exposed to doses of Humira up to 786 mg/kg.	Based on the animal studies, no effects of adalimumab on CNS parameters are expected in humans.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-Clinical Studies	Relevance to Human Usage
Mechanisms for drug interactions: Cytokines [eg, IL-6, TNFα] have been shown to alter the expression of many 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 Humira by the Innovator.	When an anti-cytokine antibody, such as adalimumab, is given to patients who are stabilised 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 co-administered 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 (eg, bleeding time with warfarin use) or drug concentration (eg, cyclosporine or theophylline) is recommended and the individual dose of the co-administered 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 conducted by the Innovator, no local intolerability of adalimumab is expected in humans.
Other systems (dependent on the product's pharmacological activity)	None known at this time.

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

The PF-06410293 clinical development programme is comprised of 3 single dose trials (B5381001, B5381007 and B5381005) in healthy adult subjects and 1 multi-dose phase III trial (B5381002) in patients with moderate to severe Rheumatoid Arthritis with inadequate response to MTX.[1,2,3]

Exposure data for PF-06410293 from the Phase III trial are presented below. This study was also designed to evaluate clinical response, safety, and immunogenicity after study drug transition (randomized blind single transition) from adalimumab-EU to PF-06410293 after 6 or 12 months of adalimumab-EU treatment. As trial B5381002 investigated use of PF-06410293 in one indication (rheumatoid arthritis) and one dose (40 mg SC injection every two weeks), indication and dose-specific exposure tables are not provided below.

Table 2. Duration of Exposure by Treatment

Study	Treatment Group	Duration of Exposure	Persons	Time (person months)
B5381005 (device study)	ADA-PF: PFS	≤ 1 day	81	2.66
	ADA-PF: PFP	≤ 1 day	83	2.73
B5381001, B5381007 (PK studies)	ADA-PF	≤ 1 day	190	6.24
B5381002 (phase III study)	ADA-PF (Subjects with no prior exposure to ADA-EU)	≤ 8 weeks	5	4.43
		> 8 weeks - ≤ 16 weeks	2	5.62
		> 16 weeks - ≤ 26 weeks	9	43.50
		> 26 weeks - ≤ 34 weeks	10	65.34
		> 34 weeks - ≤ 42 weeks	4	33.94
		> 42 weeks - ≤ 52 weeks	10	111.17
		> 52 weeks - ≤ 60 weeks	6	73.36
		> 60 weeks - ≤ 68 weeks	5	74.44
		> 68 weeks - ≤ 78 weeks	239	4184.95
		> 78 weeks	7	126.05
		Total	297	4722.80
	ADA-PF (Subjects with prior exposure to ADA-EU)	≤ 8 weeks	7	3.55
		> 8 weeks - ≤ 16 weeks	4	12.91
		> 16 weeks - ≤ 26 weeks	114	627.96
		> 26 weeks - ≤ 34 weeks	7	44.61
		> 34 weeks - ≤ 42 weeks	1	7.85
		> 42 weeks - ≤ 52 weeks	117	1347.67
		> 52 weeks	3	36.76
		Total	253	2081.31
	ADA-PF (All Subjects)	≤ 8 weeks	12	7.98
		> 8 weeks - ≤ 16 weeks	6	18.53
		> 16 weeks - ≤ 26 weeks	123	671.45
		> 26 weeks - ≤ 34 weeks	17	109.95
		> 34 weeks - ≤ 42 weeks	5	41.79
		> 42 weeks - ≤ 52 weeks	127	1458.84
		> 52 weeks - ≤ 60 weeks	9	110.12
		> 60 weeks - ≤ 68 weeks	5	74.44
		> 68 weeks - ≤ 78 weeks	239	4184.95

Table 2. Duration of Exposure by Treatment

Study	Treatment Group	Duration of Exposure	Persons	Time (person months)
		> 78 weeks	7	126.05
		Total	550	6804.11

Table 3. Total Exposure by Age Group and Sex

			Persons		Time (person months)	
Study	**Treatment Group**	**Age Group (years)**	**Male**	**Female**	**Male**	**Female**
B5381005 (device study)	ADA-PF: PFS	18-44	27	34	0.89	1.12
		45-64	11	9	0.36	0.30
		≥ 65	0	0	0.00	0.00
		Total	38	43	1.25	1.41
	ADA-PF: PFP	18-44	34	27	1.12	0.89
		45-64	10	12	0.33	0.39
		≥ 65	0	0	0.00	0.00
		Total	44	39	1.45	1.28
B5381001 (PK study)	ADA-PF	18-44	57	0	1.87	0.00
		45-64	12	0	0.39	0.00
		≥ 65	0	0	0.00	0.00
		Total	69	0	2.27	0.00
B5381007 (PK study)	ADA-PF	18-44	71	46	2.33	1.51
		45-64	3	1	0.10	0.03
		≥ 65	0	0	0.00	0.00
		Total	74	47	2.43	1.54
B5381002 (phase III study)	ADA-PF (Subjects with no prior exposure to ADA-EU)	18-44	12	69	192.64	1152.23
		45-64	28	136	426.87	2124.61
		≥ 65	16	36	272.86	553.58
		Total	56	241	892.38	3830.42
	ADA-PF (Subjects with prior exposure to ADA-EU)	18-44	15	52	126.22	450.10
		45-64	31	103	288.76	800.59
		≥ 65	16	36	143.13	272.50
		Total	62	191	558.11	1523.19
	ADA-PF (All Subjects)	18-44	27	121	318.86	1602.33
		45-64	59	239	715.64	2925.20
		≥ 65	32	72	416.00	826.08
		Total	118	432	1450.49	5353.61

Table 4. Total Exposure by Ethnic Origin

Study	Treatment Group	Ethnic Origin	Persons	Time (person months)
B5381005 (device study)	ADA-PF: PFS	Hispanic or Latino	41	1.35
		Non-Hispanic or Latino	40	1.31
		Total	81	2.66
	ADA-PF: PFP	Hispanic or Latino	53	1.74
		Non-Hispanic or Latino	30	0.99

Table 4. Total Exposure by Ethnic Origin

Study	Treatment Group	Ethnic Origin	Persons	Time (person months)
		Total	83	2.73
B5381001, B5381007 (PK studies)	ADA-PF	Hispanic or Latino	42	1.38
		Non-Hispanic or Latino	79	2.60
		Not Reported	69	2.27
		Total	190	6.24
B5381002 (phase III study)	ADA-PF (Subjects with no prior exposure to ADA-EU)	Hispanic or Latino	25	412.61
		Non-Hispanic or Latino	272	4310.18
		Total	297	4722.80
	ADA-PF (Subjects with prior exposure to ADA-EU)	Hispanic or Latino	23	185.87
		Non-Hispanic or Latino	230	1895.43
		Total	253	2081.31
	ADA-PF (All Subjects)	Hispanic or Latino	48	598.49
		Non-Hispanic or Latino	502	6205.62
		Total	550	6804.11

Module SIV. Populations Not Studied in Clinical Trials

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

PF-06410293 is a biosimilar to Humira, and information in this section is largely based on information from the Humira RMP [version 16.0 with a DLP of 31 December 2021]. 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. Some of these criteria are mentioned in the label as situations in which caution should be applied in the use of the product, including the use of screening tests and appropriate follow up, and other criteria that are not recommended but not explicitly contraindicated.

Table 5. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Being an Exclusion Criterion	Missing Information/Rationale if not considered missing information
Chronic recurring infections and history of invasive infection (eg, listeriosis and histoplasmosis)	Criterion to avoid a potential safety bias in the study at Baseline.	Not considered missing information in the RMP. Comprehensive wording concerning infections (including chronic infections) is currently in section 4.4 "Special warnings and precautions for use" of the SmPC.
Prior exposure to natalizumab (Tysabri®) or efalizumab (Raptiva®)	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.	Not considered missing information in the RMP. The current SmPC, section 4.4 "Special warnings and precautions for use" recommends not to administer other biologics concurrently with adalimumab due to the increased risk of infections.
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 (eg, presence or history of snowbanking or snowballs) and symptoms and/or MRI findings suggestive of a demyelinating disease, such as multiple sclerosis.	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.	Not considered missing information in the RMP. 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.

Table 5. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Being an Exclusion Criterion	Missing Information/Rationale if not considered missing information
History of HIV or HIV positive test	Use in patients with HIV, which results in an immunocompromised state, is not recommended.	Yes, considered missing information in the RMP.[2]
Hepatitis B: HBs antigen positive (+) or detected sensitivity on the HBV DNA PCR qualitative test for HBc Ab/HBs ab positive subjects	Reactivation of hepatitis B has occurred in patients receiving TNF-antagonists.	Not considered missing information in the RMP. Reactivation of hepatitis B is currently addressed in section 4.4 "Special warnings and precautions for use" of the SmPC.
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	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.	Not considered missing information in the RMP. Comprehensive wording concerning malignancy is currently in section 4.4 "Special warnings and precautions for use" of the SmPC.
Women who are pregnant, nursing, or who plan to become pregnant	Pregnant women are rarely enrolled in a clinical trial unless a product is specifically indicated for a pregnancy-related indication.	Not considered missing information in the RMP. 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 post-marketing data and for lactation based on literature (EMEA/H/C/000481/II/0170).
History of clinically significant drug or alcohol abuse in the last 12 months	Criterion to avoid a potential safety bias in the study at Baseline.	Yes, considered missing information in the RMP.[2]
Known hypersensitivity to adalimumab or its excipients	Patients with known hypersensitivity to adalimumab or excipients should not use.	Not considered missing information in the RMP. Use in this population is contraindicated in the label.
Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections	To avoid any possible impact by adalimumab, in relationship with its immunosuppressant	Not considered missing information in the RMP.

[2] This is no longer considered missing information but is included here as it was part of the initial Innovator RMP

Table 5. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Being an Exclusion Criterion	Missing Information/Rationale if not considered missing information
	effect, on the treatment of a current or recent infection.	Use in this population is contraindicated in the label.
History of moderate to severe congestive heart failure (New York Heart Association Class III or IV)	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.	Not considered missing information in the RMP. Use in this population is contraindicated in the label.

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

The Innovator reports that the estimate of total patient exposure to Humira in clinical trials through 31 December 2021 is 48,262.4 PYs. Additionally, 65,813.2 PYs exposure to adalimumab have accumulated in AbbVie conducted registries. The estimated cumulative post-marketing patient exposure since the International Birth Date (31 December 2002) through 31 December 2021 is 9,827,466 PYs. Pfizer experience includes 1124 clinical trial participants exposed to Pfizer's adalimumab as well as an estimated 16,532 PY of post-marketing exposure, through 28 February 2025. 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 ARs that may be due to prolonged exposure to adalimumab
- Identification of ARs with long latency
- Identification of ARs due to cumulative effects, if any

New patient populations are constantly being added through approval of new indications and new age groups. Although there is more than 22 years of post-marketing observation of patients taking adalimumab, safety data continues to be monitored for the appearance of new adverse reactions.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 6. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

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 enrolment criteria [exposure series cohort]).	The decision to use adalimumab during pregnancy lies with the patient and her physician with regard to assessing the benefit versus the risk of discontinuing adalimumab. 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. A positive opinion was 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 post-marketing data and for lactation based on literature (EMEA/H/C/000481/II/0170). It is not to be considered missing information.
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 adalimumab clinical trials.	Since adalimumab is a protein, it is likely to be metabolized in a fashion similar to that of 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. Adalimumab 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.	None
Subpopulations carrying relevant	There are no known relevant genetic polymorphisms that affect metabolism, degradation or	None

Table 6. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure	Implications
genetic polymorphisms	pharmacological effects of TNF inhibitors including adalimumab.	
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 post-marketing 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 EMA Paediatric Committee has agreed to grant waivers for the following patient population: • 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 post-marketing (Module SV, Post-Authorisation Experience) experience in the elderly age group. The majority of these patients have RA. Comorbid conditions including cardiac disorders, diabetes, and the use of multiple concomitant medications have been explored in clinical trials and post-marketing 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	Population information for patients in the UC indication receiving episodic treatment is considered missing information.

Table 6. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure	Implications
	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 the Ps, UC, and JIA indications 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

The cumulative estimated patient exposure is based on the audited pharmacy and/or wholesaler sales data of adalimumab received from the IQVIA (formerly the [IMS]) database from IBD through the third quarter of 2024, estimated to be 17,511,456 mg, which has been extrapolated to the end of reporting period. The extrapolated sales were divided by the WHO DDD of 2.9 mg and further by 365.25 (average days in a single year).

SV.1.2. Exposure

The worldwide exposure to adalimumab since the product was first approved through 28 February 2025 is estimated to be 16,532 patient-years for the MAH.

Cumulative estimated exposure by indication, region, country, age and gender extrapolated from applicable data provided by IQVIA for the period IBD through 28 February 2025 are summarized in Table 1. There is 1 formulation of Pfizer's adalimumab, the 50 mg/mL solution, which is available as a 10 mg, 20 mg, and 40 mg PFS, a 40 mg PFP, and a 40 mg/0.8 mL solution for injection. Note that data on age and gender is available in fewer countries than region.

Table 7 Cumulative Estimated Exposure for Adalimumab (IBD through 28 February 2025) - Patient Years

Indication	Age		Gender		Region	
	17-65	>65	M	F	EU	ROW
Other rheumatoid arthritis	4764	3883	5677	2970	3266	5381
Seropositive rheumatoid arthritis	-	-	-	-	5203	-
Ankylosing spondylitis	101	1,560	101	1,560	1,093	568
Other inflammatory spondylopathies	-	-	-	-	393	-
Psoriasis	-	-	-	-	337	-
Total Others	3120	3103	3711	2513	291	-

Table 8 Cumulative Estimated Exposure for Adalimumab (IBD through 28 February 2025) - Patient Years

Country	Patient Years
Australia	2
Brazil	467
Canada	13,427
France	1786
Switzerland	774
USA	2
Germany	-
Malaysia	19

Table 8 Cumulative Estimated Exposure for Adalimumab (IBD through 28 February 2025) - Patient Years

Romania	16
Thailand	40

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

Not Applicable

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

Not Applicable

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

Not Applicable

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

No new important identified or potential risks have been added or reclassified since the previous RMP (version 2.1).

Removed Missing Information: Long Term Safety Information in the Treatment of Children with Uveitis.

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

Changed missing information: from Episodic treatment in Ps, UC and JIA to Episodic treatment in UC.

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

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

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks:

- Serious infections
- Tuberculosis
- Malignancies
- Demyelinating disorders (including MS, GBS and ON)

- Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Important Potential Risks:

- Progressive multifocal leukoencephalopathy
- Reversible posterior leukoencephalopathy syndrome
- Adenocarcinoma of colon in UC patients

SVII.3.1.1. Serious Infections

Serious infections are an important identified risk based on clinical data (summarised below). For this RMP, AEs indicative of infections are defined as TEAEs with a customized PT search (see Annex 7). Table 9 summarises information relevant to this important identified risk.

Table 9. Important Identified Risk: Serious Infections

Potential mechanisms	Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.
Evidence source and strength of evidence	Data from adalimumab clinical trials (Innovator and Pfizer), registries as describe below, and from Innovator post-marketing data.
Characterisation of the risk	**Frequency by Incidence** In Innovator 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 and 13.6/100 PYs in the pedUC indication. The pedUC data studies had 6/69 subjects with a serious infection including gastroenteritis (2 subjects) bronchitis, urinary tract infection, pharyngitis and aseptic meningitis. Apart from 1 subject with meningitis, study drug was not interrupted because of these infections. **Seriousness/Outcomes** In all Innovator 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, 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]).[4] In the ARAMIS database, the rate of serious infection requiring hospitalization among individuals with RA equalled 3.1 per 100 person-years. The rate among RA patients receiving no treatment equalled 1.1 per 100 person-years, while the rate among those receiving DMARDs equalled 2.9 (RR = 2.7 [95% CI: not reported]).[5] 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).[6]

Table 9. Important Identified Risk: Serious Infections

	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.[7] 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.[8] **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.[9,10,11,12,13] 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.[14] **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[15] and sulfasalazine therapy.[16] Incidence of serious infection in paediatric patients (<18 years) with UC exposed not to TNF-α inhibitors was approximately 6.5 events per 100 person years.[17] **Pfizer Clinical Trials** For both the safety populations *All Subjects that Received PF-06410293* (N=904), and *Humira (Adalimumab-EU)-Naïve Subjects Treated with PF-06410293* (N=651), the incidence, seriousness, severity, and outcome of treatment-emergent adverse events (all causalities) for serious infections are presented in Annex 7. The vast majority of events were reported as mild in severity with an outcome of resolved. There was 1 event in the *All Subjects* dataset, Urinary tract infection, that was reported as severe. There were no fatalities in these datasets. The most commonly reported events in the *All Subjects* dataset were Nasopharyngitis (78, incidence 8.63) Upper respiratory tract infection (31, incidence 3.43), Urinary tract infection (22, incidence 2.43), Bronchitis, and Pharyngitis (20 each, incidence is 2.21). The most frequently reported events in the *Humira-Naïve Subjects* dataset were Nasopharyngitis (48, incidence 7.37), Pharyngitis (13, incidence 2.0), and Upper respiratory tract infection (12, incidence 1.84). **Pfizer Post-Marketing Data** In the post-marketing experience, since first approval through 28 February 2025, there have been 2011 cases received by the MAH reporting 2932 relevant AEs, including 969 cases reporting 1389 relevant AEs that were reported as serious. Frequently reported (>20) serious relevant infection-related events were Pneumonia (199), Uveitis (62), Infection (58), Lower respiratory tract infection (46), Urinary tract infection (43), Abscess (41), Nasopharyngitis (34), Anal abscess, Cellulitis (31 each), Clostridium difficile infection, Sinusitis (30 each), Bronchitis (28), Sepsis (27), Ear infection (22), and Folliculitis (21). Outcomes for serious relevant infection-related events were reported as resolved or resolving (354), resolved with sequelae (4), not resolved (415), fatal (142), or were not reported (474).
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 (eg, pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections. [18]

Table 9. Important Identified Risk: Serious Infections

	While taking adalimumab, the risk for infection might increase, particularly for those over 65 years of age, taking immunosuppressive treatment (eg, 6-MP, AZA), those who are heavy smokers, 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.

SVII.3.1.2. Tuberculosis

Tuberculosis is an important identified risk based on clinical data (summarised below). For this RMP, AEs indicative of tuberculosis are defined as TEAEs with a customized PT search (see Annex 7). Table 10 summarises information relevant to the important identified risk of tuberculosis.

Table 10. Important Identified Risk: Tuberculosis

Potential mechanisms	Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.
Evidence source and strength of evidence	Data from adalimumab clinical trials (Innovator and Pfizer), registries as described below, and from Innovator post-marketing data.
Characterisation 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 between 0/100 PYs in the pedUC, JIA, PsA, AS, CD, Ps, pedPs, HS, and peripheral SpA indications and 3.0/100 PYs in the uveitis indication. **Seriousness/Outcomes** In all clinical trials with adalimumab (non-registry and registry trials), 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).[19]

Table 10. Important Identified Risk: Tuberculosis

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]).[20]

In South Korea, the rate of TB among RA patients not taking TNFα 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]).[21]

Pfizer Clinical Trials

For the safety population *All Subjects that Received PF-06410293* (N=904), the incidence, seriousness, severity, and outcome of treatment-emergent adverse events (all causalities) for tuberculosis - safety population are presented below. There were no events reported as severe (grade 4-5), and no fatalities in this dataset. There were also no reported outcomes of resolved or resolved with sequelae.

			Seriousness	Severity		Outcome	
Reported PTs	Number of subjects	Incidence (95% CI) (%)	SAEs (n)	Mild (Grade 1-2) (n)	Moderate (Grade 3) (n)	Present (n)	Unknown (n)
Latent tuberculosis	11	1.22	0	10	1	8	3
Mycobacterium tuberculosis complex test positive	2	0.22	0	2	0	1	1
Total	13	1.44 (0.82,2.47)	0	12 (92.3%)	1 (7.7%)	9 (69.2%)	4 (30.8%)

MedDRA version 16.1, 19, 18 and 20.1 were used for coding AEs to PTs included in CSRs for studies B5381001, B5381005, B5381007 and B5381002 respectively, and the most recent MedDRA version 21.1 was used for coding AEs to PTs included within Important identified risks and Important Potential risks.

For the safety population *Humira (Adalimumab-EU)-Naïve Subjects Treated with PF-06410293* (N=651), incidence, seriousness, severity, and outcome of treatment-emergent adverse events (all causalities) for tuberculosis - safety population are presented below. There were no events reported as severe (grade 4-5), and no fatalities in this dataset. There were also no reported outcomes of resolved or resolved with sequelae.

Reported PTs	Number of subjects	Incidence (95% CI) (%)	SAEs (n)	Mild (Grade 1-2) (n)	Moderate (Grade 3) (n)	Present (n)	Unknown (n)
Latent tuberculosis	8	1.23	0	7	1	5	3
Mycobacterium tuberculosis complex test positive	1	0.15	0	1	0	0	1
Total	9	1.38 (0.69, 2.65)	0	8 (88.9%)	1 (11.1%)	5 (55.6%)	4 (44.4%)

MedDRA version 16.1, 19, 18 and 20.1 were used for coding AEs to PTs included in CSRs for studies B5381001, B5381005, B5381007 and B5381002 respectively, and the most recent MedDRA version 21.1 was used for coding AEs to PTs included within Important identified risks and Important Potential risks.

Pfizer Post-Marketing Data

In the post-marketing experience, since first approval through 28 February 2025, there have been 25 cases received by the MAH reporting 25 relevant AEs. Of the 25 relevant AEs reported, 23 were assessed as serious. Relevant reported AEs were Tuberculosis (10), Disseminated tuberculosis (5), Cutaneous tuberculosis, Mycobacterium

Table 10. Important Identified Risk: Tuberculosis

	tuberculosis complex test positive, Oral tuberculosis, Pulmonary tuberculosis (2 each), Tuberculin test positive, and Tuberculosis of central nervous system (1 each). AE outcomes were reported as resolved or resolving (8), fatal (1), not resolved (3), or not reported (13).
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 (eg, pneumonia, influenza, and tuberculosis), bacteremia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections.[18]
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.

SVII.3.1.3. Malignancies

Malignancies are an important identified risk based on clinical data (summarised below). For this RMP, AEs indicative of malignancies are defined as TEAEs with a customized PT search (see Annex 7). Table 11 summarises information relevant to the important identified risk of malignancies.

Table 11. Important Identified Risk: Malignancies

Potential mechanisms	Adalimumab may alter T-cell mediated immunity, which may influence the appearance of malignancy, but the mechanism is unknown.
Evidence source and strength of evidence	Data from adalimumab clinical trials (Innovator and Pfizer), registries as describe below, and from Innovator post-marketing data. **Data from Innovator 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 adalimumab. Patients who have severe, long-standing rheumatoid arthritis are at higher than average risk of getting lymphoma or leukaemia. This risk is independent of adalimumab usage. When taking adalimumab, the risk of getting lymphoma, leukaemia, or other cancers may increase. The risk can increase if a patient takes AZA or 6-MP. No reports of HSTCL were received from any clinical trial, OL or controlled. **Information from Innovator post-marketing 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.

Table 11. Important Identified Risk: Malignancies

Characterisation of the risk	Frequency by Incidence In controlled trials, the rate of malignancy in subjects treated with adalimumab was 1.2/100 PY. 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 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]).[22] Compared to malignancy rates in the general population, the RR for NHL and 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.[23] 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.[24] 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.[25] 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.[26] 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.[27] A study using inpatient records for patients with RA from California hospitals linked to the California Cancer Registry reported the 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 S 6 months after initial hospitalization.[28]

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	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.[29] 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).[22] 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).[22] 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).[8] **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]).[30] **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.[31] 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 IRR of lymphoma for CD patients compared to individuals without IBD was 2.40 (95% CI: 1.17 - 4.97).[32] United Kingdom 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.[43] 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.[33] 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).[34] 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.[35] 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).[36] **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.[32] In this study, the IRR of lymphoma for UC patients compared to individuals without IBD was 1.03 (95% CI: 0.47 - 2.24).[32] 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).[33] Similarly, analyses of

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	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).[37] 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).[38] 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.[39] 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.[40] 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.[41] 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]).[42] **HSTCL:** The frequency of this aggressive form of lymphoma is exceedingly rare. Accurate incidence rates are not available. For adalimumab-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 from 1999 to 2005. The SIR was 8.8 (95% CI: 2.4 - 22.6)[22] 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.[26] 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.[24] 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.[24] **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).[31] 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.[31] 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.[43] 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

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	hospitalization of 0.97 (95% CI: 0.12 - 3.53).[33] The adjusted RR of myeloid leukaemia was 2.0 (95% CI: 0.73 - 4.41).[33] 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 leukaemia as 1.2 (95% CI: 0.2 - 3.4).[34] 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.[35] 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.[32] 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).[32] **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.[44] 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).[45] 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).[36] **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.[32] 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).[32] 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.[33] The adjusted RR of myeloid leukaemia was 2.15 (95% CI: 1.02 - 4.03).[33] 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.[40] 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.[41] For adalimumab-indicated populations, the background prevalence of leukaemia is not well described. **NMSC:** **RA**

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	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.[25] 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.[26] 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.[23] 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.[24] 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.[22] **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).[46] **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.[43] 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.[34] 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.[35] **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).[48] 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).[45] 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).[44] **UC** Results from the Danish cancer registry data (1977 - 1989) found a slight increase in NMSC in UC patients compared to the general Danish population (RR = 1.4 [95% CI: 1.0 - 1.9]).[47] 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.[40]

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	For adalimumab-indicated populations, the background mortality from NMSC is not well described. **Melanoma:** **RA** The incidence rate of melanoma per 10,000 PYs as shown in a cohort of 789 Spanish RA patients was 4.0 (95% CI: 1.0 - 31.0).[22] Compared to the general Danish population, the relative risk 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.[23] 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.[25] 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.[26] 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).[24] A study using inpatient records from California hospitals linked to the California Cancer Registry reported the 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.[28] 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.[29] 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).[22] **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.[32] 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).[32] 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.[43] 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.[33]

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	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).[34] 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.[35] **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.[44] 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.[48] 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).[45] 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).[36] **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).[32] 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).[32] 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.[33] 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.[40] For adalimumab-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,[49,50,51,52] and increases dramatically with age (18.3 to 56.2 per 1,000,000 for those aged 65 - 69 years and 85+ years, respectively).[51] RA and other autoimmune diseases may increase the risk of MCC in elderly patients.[53] In a case-control study using SEER Medicare-linked data, RA was associated with an increased risk of MCC [OR = 1.39 (1.10 - 1.75)].[53] 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.[53] The study findings are limited to elderly patients (~ 65 years) and did not adjust for immunosuppressive therapy.[53] In Europe, the prevalence of MCC is estimated to be 0.86 per 100,000.[52] In Europe, the 5-year survival of MCC is estimated to be 39.1 %.[52]

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Pfizer-sponsored clinical trials.

For the safety population *All Subjects that Received PF-06410293* (N=904), the incidence, seriousness, severity, and outcome of treatment-emergent adverse events (all causalities) for malignancies - safety population are presented below. There were no events reported as moderate (grade 3), and no fatalities in this dataset. There were also no reported outcomes of resolved with sequelae or unknown.

			Seriousness	Severity		Outcome	
Reported PTs (MedDRA v21.1)	**Number of Subjects**	**Incidence (95% CI) (%)**	**SAEs (n)**	**Mild (Grade 1-2) (n)**	**Severe (Grade 4-5) (n)**	**Resolved (n)**	**Present (n)**
Basal cell carcinoma	2	0.22	0	2	0	2	0
Breast cancer stage II	1	0.11	1	0	1	0	1
Endometrial adenocarcinoma	1	0.11	1	0	1	1	0
Human chorionic gonadotropin positive	1	0.11	0	1	0	1	0
Squamous cell carcinoma	2	0.22	0	2	0	2	0
Total	6	0.66 (0.27,1.48)	2 (33.3%)	4 (66.7%)	2 (33.3%)	5 (83.3%)	1 (16.7%)

MedDRA version 16.1, 19, 18 and 20.1 were used for coding AEs to PTs included in CSRs for studies B5381001, B5381005, B5381007 and B5381002 respectively, and the most recent MedDRA version 21.1 was used for coding AEs to PTs included within Important identified risks and Important Potential risks.

For the safety population *Humira (Adalimumab-EU)-Naïve Subjects Treated with PF-06410293* (N=651), incidence, seriousness, severity, and outcome of treatment-emergent adverse events (all causalities) for malignancies - safety population are presented below. There were no events reported as moderate (grade 3) or severe (grade 4-5), and no fatalities in this dataset. There were also no reported outcomes of present, resolved with sequelae or unknown.

			Seriousness	Severity	Outcome
Reported PTs (MedDRA v21.1)	**Number of Subjects**	**Incidence (95% CI) (%)**	**SAEs (n)**	**Mild (Grade 1-2) (n)**	**Resolved (n)**
Basal cell carcinoma	2	0.31	0	2	2
Human chorionic gonadotropin positive	1	0.15	0	1	1
Squamous cell carcinoma	2	0.31	0	2	2
Total	4	0.61 (0.18, 1.63)	0	4 (100%)	4 (100%)

MedDRA version 16.1, 19, 18 and 20.1 were used for coding AEs to PTs included in CSRs for studies B5381001, B5381005, B5381007 and B5381002 respectively, and the most recent MedDRA version 21.1 was used for coding AEs to PTs included within Important identified risks and Important Potential risks.

Pfizer Post-Marketing Data

In the post-marketing experience, since first approval through 28 February 2025, there have been 119 cases received by the MAH reporting 133 relevant AEs, including 131 that were reported as serious and 2 that were reported as non-serious. Frequently reported (≥3) relevant malignancy-related events were Breast cancer, Breast cancer stage III, Malignant melanoma (10 each), Lung neoplasm malignant, Lymphoma, Skin cancer (9 each), Intestinal resection (7), Breast cancer stage II (5), B-cell lymphoma, Colectomy (4 each), Ileocolectomy, Squamous cell carcinoma, Squamous cell carcinoma of skin, and Thyroid cancer (3 each). Event outcomes were reported as

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	resolved/resolving (12), resolved with sequelae (2) not resolved (35), fatal (20), or not reported (64).
Risk factors and risk groups	**Lymphoma:** Factors associated with an increased risk of NHL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), infection (eg, HIV, Epstein-Barr virus, H. pylori, HTLV-I, and hepatitis C), and age (over 60 years).[54] Factors associated with an increased risk of HL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), viral infection (eg, HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older).[54] 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]).[55] **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.[56, 57] **Leukaemia:** Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia 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 leukaemia.[54] **NMSC:** Factors associated with an increased risk of skin cancer include radiation (eg, sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (eg, antibiotics, hormones, antidepressants, thiopurines[58]) medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic.[59] Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis.[59] **Melanoma**: Factors associated with an increased risk of melanoma include UV radiation (eg, sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (eg, 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.[59] **MCC:** Factors associated with an increased risk of MCC include advanced age, immunosuppression (eg, organ transplant, HIV), other cancers (eg, squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure.[60]
Preventability	For all malignancies, patients are instructed to do the following: The doctor should be told if symptoms including but not limited to fevers, weight loss, swelling of the lymph nodes, fatigue, easy bruising, or bleeding develop. These may be early signs and symptoms of cancer. Further testing may be needed to determine if this is the case. Any doctor seen by the patient should be told that adalimumab is being taken.

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	The Patient Reminder Card should be shown to any healthcare professional that is consulted. The doctor should be told if AZA or 6-MP is being given in addition to adalimumab. 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, the doctor should be told. Skin examinations by a physician should be performed before starting adalimumab 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. The physician should educate the 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.

SVII.3.1.4. Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

Demyelinating disorders are an important identified risk based on clinical data (summarised below). For this RMP, AEs indicative of demyelinating disorders are defined as TEAEs with a PT search including terms from the Demyelination SMQ (narrow and broad scope). For a full list of the PTs in this search, see Annex 7. Table 12 summarises information relevant to the important identified risk of demyelinating disorders.

Table 12. Important Identified Risk: 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 source and strength of evidence	Data from adalimumab trials as described below.
Characterisation of the risk	**Frequency by Incidence** In controlled trials, the rate of demyelinating disorders in subjects treated with adalimumab was between <0.1/100 PYs in the JIA, PSA, AS, CD, Ps, pedPs, UC, 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**

Table 12. Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

	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]).[61] **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]).[62] 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).[63] 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).[64] 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.[65] 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]).[62] **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]).[62] 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]).[63] 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]).[64] 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]).[65] 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

Table 12. Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

	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]).[62] **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) 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) (Innovator reports 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.[66] Among 2,617 uveitis patients treated at a single center in Vienna, Austria between 1995 and 2009, the prevalence of MS equalled 1.0%. MS was one of the most common comorbidities associated with intermediate uveitis with a prevalence rate of 4.9% among this group.[67] 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.[68] A single-center Spanish study including 1,022 uveitis patients treated between 2009 and 2012 reported that the overall prevalence of MS equalled 0.8%. MS had the highest prevalence among patients with intermediate uveitis (7%), while the prevalence among patients with pan uveitis equalled 0.6%.[72] A retrospective cohort study including 1,450 uveitis patients treated between 1985 and 2000 at a single center in the USA reported that the prevalence of MS and ON equalled 1.0% and 0.5%, respectively.[69] No studies/analyses with incidence or prevalence data for demyelinating disorders in pedUV patients are available. For adalimumab-indicated populations, the background mortality from demyelinating disorders is not well described. **Frequency, seriousness, severity and outcomes:** **Pfizer-sponsored clinical trials:** There were no reports of demyelinating disorders in subjects receiving PF-06410293 in Pfizer-sponsored clinical trials. **Pfizer Post-Marketing Data** In the post-marketing experience, since first approval through 28 February 2025, there have been 13 cases received by the MAH reporting 14 relevant AEs, 13 of which were reported as serious. Relevant reported AEs were Multiple sclerosis (3), Guillain-Barre syndrome, Optic neuritis (2 each), Acute disseminated encephalomyelitis, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelination, Leukoencephalopathy, Multiple sclerosis relapse, Subacute inflammatory demyelinating polyneuropathy, and Trigeminal neuralgia (1 each). AE outcomes were reported as resolved or resolving (8), not resolved (2), or not reported (4).
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition [eg, HLA-DR2 (HLA-DRBl *15), ethnic origin (being white), female sex, Epstein-Barr

Table 12. Important Identified Risk: Demyelinating Disorders (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis)

	infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors].[70] Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age.[71] Subjects with intermediate uveitis have a high prevalence of demyelination.[66,72,73]
Preventability	Screening and evaluation by a physician for demyelinating disorders in patients with intermediate uveitis. Patients are instructed of the following: If the patient has a demyelinating disease such as MS, the doctor will decide if adalimumab should be given. The Patient Reminder Card should be given to any healthcare professional that is consulted.
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.3.1.5. Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to adalimumab is an important potential risk based on clinical data (summarised below). There have been no cases of exposure to adalimumab *in utero* in Pfizer -sponsored clinical trials. Table 13 summarises information relevant to the important potential risk of Infections in infants exposed to adalimumab in utero.

Table 13. Important Identified Risk: Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to Adalimumab

Potential mechanisms	Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.
Evidence source and strength of evidence	Data from adalimumab trials and registries as described below and from the Innovator's post-marketing safety database.
Characterisation of the risk	Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses. It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. Administration of live vaccines (eg, BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. There have been no cases of exposure to adalimumab in utero in Pfizer -sponsored clinical trials. **Pfizer Post-Marketing Data** Cumulatively there have been no PM cases reporting Disseminated Bacillus Calmette-Guérin infection.
Risk factors and risk groups	Infants exposed to adalimumab in utero.

Table 13. Important Identified Risk: Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to Adalimumab

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

SVII.3.1.6. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is an important potential risk based on clinical data (summarised below). For this RMP, AEs indicative of PML are defined as TEAEs with a customized PT search (see Annex 7). Table 14 summarises information relevant to the important identified risk of PML.

Table 14. Important Potential Risk: Progressive Multifocal Leukoencephalopathy

Potential mechanisms	Reactivation of Polyomavirus JC (often called JCV).
Evidence source and strength of evidence	Potential source data from adalimumab trials and from the Innovator's post-marketing safety database.
Characterisation 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-naive patients, and 2.3 (0.1 - 71) per 100,000 person-years among RA biologic-treated patients.[74] The mortality of PML in the USA (estimated from analysis of national mortality and AIDS surveillance data) rose from 0.15 cases per million before the AIDS pandemic to 0.61 cases per million during the HIV/AIDS era.[75, 76] **Pfizer clinical trials:** There were no reports of PML in subjects receiving PF-06410293 in Pfizer-sponsored clinical trials. **Pfizer Post-Marketing Data** There have been no reports of PML in the post-marketing experience.
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.[75] Prior to the era of HIV

Table 14. Important Potential Risk: Progressive Multifocal Leukoencephalopathy

	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.[77] Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, SLE and other rheumatic diseases. [77, 78, 79, 80, 81] 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.

SVII.3.1.7. Reversible Posterior Leukoencephalopathy Syndrome

Progressive multifocal leukoencephalopathy (PML) is an important potential risk based on clinical data (summarised below). For this RMP, AEs indicative of PML are defined as TEAEs with a customized PT search (see Annex 7). Table 15 summarises information relevant to the important identified risk of PML.

Table 15. Important Potential Risk: Reversible Posterior Leukoencephalopathy Syndrome

Potential mechanisms	Unknown.
Evidence source and strength of evidence	Potential source data from adalimumab trials and from the Innovator post-marketing safety database.
Characterisation 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 adalimumab-indicated populations, the background incidence and prevalence of and the mortality from RPLS are not well described. **Pfizer clinical trials:** There were no reports of RPLS in subjects receiving PF-06410293 in Pfizer-sponsored clinical trials. There were 2 cases reporting the relevant event Hypertensive crisis,

Table 15. Important Potential Risk: Reversible Posterior Leukoencephalopathy Syndrome

	which is potentially indicative of RPLS. In 1 case the event was reported as serious. Severity was reported as mild in 1 case and as moderate in the other. In both cases the outcome was resolved. The frequency of this event in the safety population *All Subjects that Received PF-06410293* (N=904) was 0.22% (95% CI = 0.01, 0.86). In the safety population *Humira (Adalimumab-EU)-Naïve Subjects Treated with PF-06410293* (N=651) the incidence rate was reported as 0.31% (95% CI = 0.01, 1.19). **Pfizer Post-Marketing Data** In the post-marketing experience, since first approval through 28 February 2025, there have been 2 cases received by the MAH reporting 2 relevant AEs, both of which were reported as serious. Relevant reported AEs were Leukoencephalopathy and Posterior reversible encephalopathy syndrome (1 each). AE outcomes were reported as not resolved and resolving respectively.
Risk factors and risk groups	Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Co-morbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%).[82] 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.

SVII.3.1.8. Adenocarcinoma of Colon in Ulcerative Colitis Patients

Adenocarcinoma of colon in ulcerative colitis patients is an important potential risk based on clinical data (summarised below). There have been no Pfizer studies in UC patients. Table 16 summarises information relevant to the important potential risk of adenocarcinoma of colon in ulcerative colitis patients.

Table 16. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis Patients

Potential mechanisms	Unknown
Evidence source and strength of evidence	Potential source data from adalimumab trials as described below.
Characterisation 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.

Table 16. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis Patients

	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).[32] 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).[32] 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.[33] 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).[32] 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).[32] 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.[33] For adalimumab-indicated populations, the background prevalence of colorectal cancer in the UC population is not well described. The SMR for colon cancer was 0.75 (95% CI: 0.01 - 4.2) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996.[41] 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.[83] 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.[41] **Pfizer clinical trials:** There have been no Pfizer studies in UC patients. **Pfizer Post-Marketing Data** There have been no reports of adenocarcinoma of the colon in UC patients in the post-marketing experience.

Table 16. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis Patients

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, co-morbid PSC,[84] diet, and cigarette smoking.[85] 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

The Innovator reports the estimated total patient exposure to Humira in clinical trials (through 31 December 2021) is 48,262.4 PYs. Additionally, 65,813.2 PYs exposure to adalimumab have accumulated in AbbVie conducted registries. The estimated cumulative post-marketing patient exposure since the International Birth Date (31 December 2002) through 28 February 2025 is 9,827,466 PYs. Pfizer experience includes 1124 clinical trial participants exposed to Pfizer's adalimumab as well as an estimated 16,532 PY of post-marketing exposure, through 28 February 2025. 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
- Identification of AEs due to cumulative effects, if any

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

Table 17. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD.

Evidence source and strength of evidence	The safety of adalimumab in paediatric patients has not been established. An Innovator registry for pedCD patients is ongoing.
Anticipated risk/consequence of the missing information	Information is unknown at this time.

Missing Information: Episodic treatment in UC

Table 18. Missing Information: Episodic treatment in UC

Evidence source and strength of evidence	The safety of adalimumab in episodic treatment in UC has not been established. Treatment interruptions in registry studies are being evaluated by the Innovator.
Anticipated risk/consequence of the missing information	Information is unknown at this time.

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

Table 19. Missing Information: Long-term safety information in the treatment of children aged 6 years to less than 18 years with ulcerative colitis.

Evidence source and strength of evidence	The safety of adalimumab as long-term treatment in patients aged 6 years to less than 18 years of age with UC has not been studied. Long-term pedUC data is being collected though an extension study by the Innovator.
Anticipated risk/consequence of the missing information	Information is unknown at this time.

Module SVIII. Summary of the Safety Concerns

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

Table 20. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including MS, GBS and ON) • Bacillus Calmette-Guérin disease following live BCG vaccination in infants with *in utero* exposure to adalimumab
Important potential risks	• Progressive multifocal leukoencephalopathy • Reversible posterior leukoencephalopathy syndrome • Adenocarcinoma of colon in UC patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Episodic treatment in UC • Long-term safety information in the treatment of children from 6 years to less than 18 years with UC

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

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

There are no other forms of routine pharmacovigilance activities with adalimumab.

III.2. Additional Pharmacovigilance Activities

Additional PV Activities to Assess Effectiveness of Risk Minimisation Measures

There are none.

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are none.

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

V.1. Routine Risk Minimisation Measures

The product information is sufficient to mitigate the current identified and potential risks of adalimumab. The necessary information to ensure appropriate use of the product is included in the relevant sections of the SmPC to minimise the risk of severe and life-threatening consequences. No additional measures for risk minimisation are considered necessary by the Marketing Authorisation Holder at this time. The proposed minimisation measures are summarised in Table 21 for each safety concern.

Table 21. Description of routine risk minimisation measures by safety concern

Safety Concerns	Routine risk minimisation activities
Important Identified Risks	
Serious Infections	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use Proposed SmPC Section 4.8, Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.3 Contraindications: Contraindication for patients with active tuberculosis or other severe infections such as sepsis, and opportunistic infections SmPC Section 4.4, Special warnings and precautions for use: this section includes information regarding increased susceptibility for infections in patients receiving TNF agonists. This section also includes a warning that patients with active infections including chronic or localised infections should not take adalimumab until infections are controlled. Further information includes a warning that patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Additional information focuses on specific categories of infections and is very comprehensive. SmPC Section 4.8, Undesirable effects: This section includes a comprehensive list of infections for which adalimumab patients may be at increased risk. Other routine risk minimisation measures: Prescription only medicine.
Tuberculosis	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk:

Table 21. Description of routine risk minimisation measures by safety concern

Safety Concerns	Routine risk minimisation activities
	SmPC Section 4.3 Contraindications: Contraindication for patients with active tuberculosis or other severe infections such as sepsis, and opportunistic infections SmPC Section 4.4, Special warnings and precautions for use: *Tuberculosis* *Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.* *Before initiation of therapy with Amsparity, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.* *If active tuberculosis is diagnosed, Amsparity therapy must not be initiated.* *In all situations described below, the benefit/risk balance of therapy should be very carefully considered.* *If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.* *If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Amsparity and in accordance with local recommendations.* *Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Amsparity in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.* *Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab.* *Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Amsparity.* SmPC Section 4.8, Undesirable effects: Tuberculosis is listed as an undesirable effect. <u>Other routine risk minimisation measures</u>: Prescription only medicine.

Table 21. Description of routine risk minimisation measures by safety concern

Safety Concerns	Routine risk minimisation activities
Malignancies	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use Proposed SmPC Section 4.8, Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4, Special warnings and precautions for use: The risk of various malignancies is discussed at length under the heading *Malignancies and lymphoproliferative disorders*. The following text is included under Undesirable effects in proposed SmPC Section 4.8. various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of adalimumab. The following events are also included in Section 4.8 of the proposed SmPC: • Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm • Lymphoma • solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), • Melanoma • Leukaemia • Hepatosplenic T-cell lymphoma • Merkel cell carcinoma (neuroendocrine carcinoma of the skin) Other routine risk minimisation measures: Prescription only medicine.
Demyelinating Disorders (including MS, GBS and ON)	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use Proposed SmPC Section 4.8, Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4, Special warnings and precautions for use: the following text regarding the risk of demyelinating disorders is included under *Neurological events*. TNF-antagonists including adalimumab have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the

Table 21. Description of routine risk minimisation measures by safety concern

Safety Concerns	Routine risk minimisation activities
	initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. The terms *Multiple sclerosis* and *demyelinating disorders (eg optic neuritis, Guillain-Barré syndrome)* are included in Undesirable effects section (Section 4.8) of the proposed SmPC. Other routine risk minimisation measures: Prescription only medicine.
Bacillus Calmette–Guérin (BCG) disease following live BCG vaccination in infants with *in utero* exposure to adalimumab.	Routine risk communication SmPC Section 4.6 Fertility, pregnancy, and lactation
	Routine risk minimisation activities recommending specific clinical measures to address the risk: The following text on pregnancy is included in section 4.6, Fertility, pregnancy, and lactation, of the proposed SmPC. Women of child bearing potential Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last adalimumab treatment. Pregnancy For adalimumab, limited clinical data on exposed pregnancies are available In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available (see section 5.3). Due to its inhibition of TNF-α, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. 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. Other routine risk minimisation measures: Prescription only medicine.
Important Potential Risks	
PML	Routine risk communication: Text in SmPC: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures: Prescription only medicine.
RPLS	Routine risk communication: Text in SmPC: None.

Table 21. Description of routine risk minimisation measures by safety concern

Safety Concerns	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures: Prescription only medicine.
Adenocarcinoma of colon in ulcerative colitis patients	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Proposed SmPC Section 4.4, Special warnings and precautions for use: The risk of various malignancies is discussed at length under the heading *Malignancies and lymphoproliferative disorders*. Other routine risk minimisation measures: Prescription only medicine.
Missing Information	
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 minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures: Prescription only medicine.
Episodic treatment in UC	Routine risk communication: Text in SmPC: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures: Prescription only medicine.
Long-term safety information in the treatment of children from 6 years to less than 18 years with UC	Routine risk communication: Proposed Text in SmPC: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

The MAH has an additional risk minimisation program to remind patients about key risks associated with the use of adalimumab. The additional risk minimisation measures are outlined below.

Patient Material

Additional risk minimisation measure: Patient (including pediatric) Reminder Card

Safety topic: Serious infections

Risk minimisation measures:

- Patient Reminder Card

Objectives and rationale for the additional risk minimisation activity: To educate prescribers and patients about the risks of serious infections associated with the use of adalimumab. Patients need to be aware of signs/symptoms that may be used to help patients recognize when they should seek medical advice.

Target audience and planned distribution path: All patients receiving adalimumab.

Plans to evaluate the effectiveness of the interventions and criteria for success: Not applicable.

Safety topic: Tuberculosis

Risk minimisation measures:

- Patient Reminder Card

Objectives and rationale for the additional risk minimisation activity: To educate prescribers and patients about the risks of tuberculosis associated with the use of adalimumab. Patients need to be aware of signs/symptoms that may be used to help patients recognize when they should seek medical advice.

Target audience and planned distribution path: All patients receiving adalimumab.

Plans to evaluate the effectiveness of the interventions and criteria for success: Not applicable

Safety topic: Malignancies

Risk minimisation measure:

- Patient Reminder Card

Objectives and rationale for the additional risk minimisation activity: To educate prescribers and patients about the risk of malignancies associated with the use of adalimumab. Patients need to be aware of signs/symptoms that may be used to help patients recognize when they should seek medical advice.

Target audience and planned distribution path: All patients receiving adalimumab.

Plans to evaluate the effectiveness of the interventions and criteria for success: Not applicable.

Safety topic: Demyelinating disorders (including MS, GBS and ON)

Risk minimisation measure:

- Patient Reminder Card

Objectives and rationale for the additional risk minimisation activity: To educate prescribers and patients about the risk of demyelinating disorders associated with the use of adalimumab. Patients need to be aware of signs/symptoms that may be used to help patients recognize when they should seek medical advice.

Target audience and planned distribution path: All patients receiving adalimumab.

Plans to evaluate the effectiveness of the interventions and criteria for success: Not applicable.

Safety topic: BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Risk minimisation measure:

- Patient Reminder Card

Objectives and rationale for the additional risk minimisation activity: To educate prescribers and patients about the risk of malignancies associated with the use of adalimumab. Patients need to be aware of signs/symptoms that may be used to help patients recognize when they should seek medical advice.

Target audience and planned distribution path: All patients receiving adalimumab.

Plans to evaluate the effectiveness of the interventions and criteria for success: Not applicable.

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

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

V.3. Summary of Additional Risk Minimisation Measures

Table 22. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious infections	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.

Table 22. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Tuberculosis	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.
Malignancies	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.
Demyelinating disorders (including MS, GBS and ON)	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.
Bacillus Calmette-Guérin disease following live BCG vaccination in infants *with in* utero exposure to adalimumab	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.
Important Potential Risks		
Progressive multifocal leukoencephalopathy	Routine risk minimisation measures: Text in SmPC: None Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.
Reversible posterior leukoencephalopathy syndrome	Routine risk minimisation measures: Text in SmPC: None Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.

Table 22. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Adenocarcinoma of colon in ulcerative colitis patients	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use Additional risk minimisation measures: There are none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: There are none. Additional pharmacovigilance activities: There are none.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for adalimumab[3]

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

Amsparity's SmPC and its PL give essential information to HCPs and patients on how adalimumab should be used.

This summary of the RMP for Amsparity should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

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

I. The Medicine and What It Is Used For

Amsparity is being developed as a biosimilar to the Innovator's product Humira (adalimumab). Humira was developed and is currently marketed by AbbVie. Humira is authorised in adults for indications RA, PsA, AxSpA, CD, Ps, UC and HS. Humira is authorised in paediatric patients for the treatment of JIA, pedERA, pedCD, pedPs, HS, Uveitis, and UC. Adalimumab is the active substance and it is given by the SC route of administration. Indications for Amsparity are all indications approved for Humira.

Further information about the evaluation of Amsparity benefits can be found in Amsparity's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's link to product's EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of adalimumab, together with measures to minimise such risks and the proposed studies for learning more about adalimumab'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 to ensure that the medicine is used correctly

[3] Changes are considered important if they relate to the following: new safety concerns or important changes/removal to a known safety concerns, major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies), any 'additional risk minimisation measure' which is added or removed, routine risk minimisation activities recommending specific clinical measures to address the risk.

- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

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

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

Patient reminder cards for the following important risks:

- Serious infections
- Tuberculosis
- Demyelinating disorders (including MS, GBS, and ON)
- Bacillus Calmette-Guérin disease following live BCG vaccination in infants with *in utero* exposure to Amsparity

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

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

II.A. List of Important Risks and Missing Information

Important risks of adalimumab are risks that need special risk management activities to further investigate or minimise 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 adalimumab. 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 (eg on the long-term use of the medicine).

Table 23. List of important risks and missing information

Important identified risks	• Serious infections • Tuberculosis • Malignancies • Demyelinating disorders (including MS, GBS and ON) • Bacillus Calmette-Guérin disease following live BCG vaccination in infants with *in utero* exposure to Amsparity.
Important potential risks	• Progressive multifocal leukoencephalopathy • Reversible posterior leukoencephalopathy syndrome • Adenocarcinoma of colon in ulcerative colitis 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

Table 23. List of important risks and missing information

	• Long-term safety information in the treatment of children from 6 years to less than 18 years with UC

II.B. Summary of Important Risks

Table 24. Important Identified Risk: Serious infections

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), registries and from the Innovator's post-marketing data.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of co-morbidities, 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 (eg, pneumonia, influenza, and TB), bacteraemia, UTIs, salmonellosis, hepatitis, and nosocomial infections.[18] While taking adalimumab, the risk for infection might increase, particularly if you are over 65 years of age, taking immunosuppressive treatment (eg, 6-MP, AZA), a heavy smoker, or have a history of decreased lung function. Infections may be serious and, in rare cases, life threatening.
Risk minimisation measures	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 25. Important Identified Risk: Tuberculosis (TB)

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), registries and from the Innovator's post-marketing data.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of co-morbidities, 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 (eg, pneumonia, influenza, and TB), bacteraemia, UTIs, salmonellosis, hepatitis, and nosocomial infections.[18]

Table 25. Important Identified Risk: Tuberculosis (TB)

Risk minimisation measures	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 26. Important Identified Risk: Malignancies

Evidence for linking the risk to the medicine	Data from clinical trials (Innovator and Pfizer), and from the Innovator's post-marketing data.
Risk factors and risk groups	Factors associated with an increased risk of NHL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), infection (eg, HIV, Epstein-Barr virus, H. pylori, HTLV-I, and hepatitis C), and age (over 60 years). [54] Factors associated with an increased risk of HL include weakened immune system (eg, heritable disease, certain drugs used after an organ transplant), viral infection (eg, HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older).[54] 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]).[55] 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.[56,57] Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia 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 leukaemia.[54] Factors associated with an increased risk of skin cancer include radiation (eg, sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (eg, antibiotics, hormones, antidepressants[58]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic.[59] Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis.[59] Factors associated with an increased risk of melanoma include UV radiation (eg, sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (eg, antibiotics, hormones, antidepressants), medical

Table 26. Important Identified Risk: Malignancies

	conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles.[59] Factors associated with an increased risk of MCC include advanced age, immunosuppression (eg, organ transplant, HIV), other cancers (eg, squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and UV light exposure.[60]
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 27. Important Identified Risk: Demyelinating disorders (including multiple sclerosis, Guillain-Barré syndrome, and optic neuritis)

Evidence for linking the risk to the medicine	Data from Innovator clinical trials.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (eg, HLA-DR2 (HLA-DRBl *15), ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors.[70] Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age.[71] Subjects with intermediate uveitis have a high prevalence of demyelination.[66,72,73]
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk management measures Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 28. Important Identified Risk: Bacillus Calmette–Guérin disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Evidence for linking the risk to the medicine	Data from Innovator clinical trials.
Risk factors and risk groups	Infants exposed to adalimumab in utero.
Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings are precautions for use SmPC Section 4.6 Fertility, pregnancy, and lactation In order to inform patients of this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient Reminder Card
Additional pharmacovigilance activities	There are none.

Table 29. Important Potential Risk: Progressive multifocal leukoencephalopathy

Evidence for linking the risk to the medicine	Data from Innovator clinical trials and post-marketing data.
Risk factors and risk	PML occurs predominantly among severely immunosuppressed patients. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS.[75] 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. [77] Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, SLE, and other rheumatic diseases.[78,77, 79, 80, 81] 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.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 30. Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Evidence for linking the risk to the medicine	Data from Innovator clinical trials and post-marketing data.

Table 30. Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Risk factors and risk groups	Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Co-morbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%).[82] 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.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 31. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis patients

Evidence for linking the risk to the medicine	Data from Innovator clinical 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, co-morbid PSC,[84] diet, and cigarette smoking.[85] 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.

Table 31. Important Potential Risk: Adenocarcinoma of Colon in Ulcerative Colitis patients

Risk minimisation measures	Routine risk communication SmPC Section 4.4, Special warnings and precautions for use. 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 minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 32. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Risk minimisation measures	Routine risk communication SmPC Section 4.2 Posology and method of administration Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 33. Missing Information: Episodic treatment in UC

Risk minimisation measures	Routine risk communication Prescription only medicine Additional risk minimisation measures: There are none.
Additional pharmacovigilance activities	There are none.

Table 34. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Risk minimisation measures	Routine risk communication Prescription only medicine Additional risk minimisation measures: There are none.

Table 34. Missing Information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Additional pharmacovigilance activities	There are none.

II.C. Post-Authorisation Development Plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of adalimumab.

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

There are none.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 – Protocols for proposed and on-going studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (Including Referenced Material)

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

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Additional risk minimization measures are planned for the important identified risks listed below, in the form of a patient information card.

- Serious infections
- Tuberculosis
- Malignancies
- Demyelinating disorders (multiple sclerosis, Guillain-Barre syndrome, optic neuritis)
- Bacillus Calmette-Guérin (BCG) disease following live BCG vaccination in infants with in utero exposure to adalimumab

The patient information card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using adalimumab.
- That adalimumab treatment may increase the potential risks of serious infections, sepsis, tuberculosis and opportunistic infections; demyelinating disorders; malignancies.
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the prescriber

The patient information pack should contain:

Patient information leaflet