ETANERCEPT RISK MANAGEMENT PLAN

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number: 7.9

Data lock point for this RMP: 15 August 2024

Date of final sign off: 12 June 2025

Rationale for submitting an updated RMP:

The primary purpose of this RMP revision is to remove the following text (in strikethrough format) from the patient card:

Traceability of etanercept ~~drug product manufactured using drug substance (DS) derived from the SFPHC process for detection of any new safety signals or reported trends associated with product manufactured using the new process.~~

Summary of significant changes in this RMP (version 7.8):

- Part V.2
  - Updates to the patient card
    - Removal of the following text (in strikethrough format)

  Traceability of etanercept ~~drug product manufactured using drug substance (DS) derived from the SFPHC process for detection of any new safety signals or reported trends associated with product manufactured using the new process.~~

- Part VII, Annex 8: Updated to reflect changes in version 7.9.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP:

Version number: 7.6

Approved with procedure: EMEA/H/C/000262/II/0246

Date of approval (opinion date): 05 May 2022

QPPV name: Barbara De Bernardi, MD

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

LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Event
aRMM	Additional Risk Minimisation Measure
ANA	Antinuclear Antibody
ANCA	Antineutrophil Cytoplasmic Antibodies
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ATV	Anatomical Therapeutic Chemical
AUC	Area Under Concentration Time Curve
AxSpA	Axial Spondyloarthritis
BADBIR	British Association of Dermatologists Biologics Interventions Registry
BIW	Twice Weekly
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
BM	Bone Marrow
BMI	Body Mass Index
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CNS	Central Nervous System
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CRP	C-Reactive Protein
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
CV	Cardiovascular
CVD	Cardiovascular Disease
DAS	Disease Activity Score
DCA	Data Capture Aid
DILI	Drug Induced Liver Injury
DM	Diabetes Mellitus
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
DS	Drug Substance
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EMR	Electronic Medical Record
eoJIA	Extended Oligoarticular Juvenile Idiopathic Arthritis
ERA	Enthesitis-Related Arthritis
EU	European Union
EULAR	European League Against Rheumatism

Abbreviation	Term
F	Fatal
GBS	Guillain-Barré Syndrome
GDPR	General Practice Research Database
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
H	Hospitalisation
HBV	Hepatitis B Virus
HBcAg	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IBD	International Birth Date
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IMS	Intercontinental Medical Statistics
INN	International Nonproprietary Name
IQR	Interquartile Range
IR	Incidence Rate
IV	Intravenous
JAK	Janus Kinase
JCA	Juvenile Chronic Arthritis
JIA	Juvenile Idiopathic Arthritis
JRA	Juvenile Rheumatoid Arthritis
LT	Life-threatening
MAH	Marketing Authorisation Holder
MAS	Macrophage Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MN	Minnesota
MOA	Mechanism of Action
MOD	Moderate
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NA	North America
NR	Not Resolved
Nr-AxSpA	Non-Radiographic Axial Spondyloarthritis
NSAID	Nonsteroidal Anti-Inflammatory Drug
NTEL	No-Toxic-Effect-Level
OR	Odds Ratio
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PDE	Phosphodiesterase
PFP	Pre-filled Pen

Abbreviation	Term
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PURPOSE	Paediatric Registry of Psoriasis and Enbrel
PUVA	Psoralen and Ultraviolet-A Light
PY	Patient/Person Year
QPPV	Qualified Person for Pharmacovigilance
QW	Once Weekly
R	Resolved/Resolving
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RMP	Risk Management Plan
ROW	Rest of World
RS	Resolved with Sequelae
RSI	Reference Safety Information
SAE	Serious Adverse Event
SC	Subcutaneous
SFPHC	Serum Free Process High Capacity
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMR	Standardized Mortality Ratio
TB	Tuberculosis
TEN	Toxic Epidermal Necrolysis
THIN	The Health Improvement Network
TNF	Tumour Necrosis Factor
TNFR	Tumour Necrosis Factor Receptor
U	Unknown
UK	United Kingdom
US	United States
UV	Ultraviolet
VS	Very Severe
VZV	Varicella Zoster Virus

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (International Nonproprietary Name [INN] or common name)	Etanercept
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors (L04AB01)
Marketing Authorisation Holder	Pfizer Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Enbrel
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class
	Summary of mode of action: Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface tumour necrosis factor receptor (TNFR), preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.
	Important information about its composition: Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH_2 and CH_3 regions, but not the CH_1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7×10^6 units/mg.

Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Rheumatoid arthritis (RA): Etanercept in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adults when the response to disease-modifying antirheumatic drugs (DMARDs), including MTX (unless contraindicated), has been inadequate. Etanercept can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Etanercept is also indicated in the treatment of severe, active and progressive RA in adults not previously treated with MTX. Psoriatic arthritis (PsA): Treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. Etanercept has been shown to improve physical function in patients with PsA, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. Ankylosing spondylitis (AS): Treatment of adults with severe active AS who have had an inadequate response to conventional therapy. Non-radiographic axial spondyloarthritis (nr-AxSpA): Treatment of adults with severe nr-AxSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs). Plaque psoriasis (PsO): Treatment of adults with moderate to severe plaque PsO who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, MTX or psoralen and ultraviolet-A light (PUVA). *Paediatric population* Juvenile idiopathic arthritis (JIA): Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, MTX. Treatment of psoriatic arthritis (PsA) in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, MTX. Treatment of enthesitis-related arthritis (ERA) in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

	Paediatric plaque PsO: Treatment of chronic severe plaque PsO in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
Dosage in the EEA	RA: 25 mg etanercept administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective. PsA, AS, and nr-AxSpA: The recommended dose is 25 mg etanercept administered twice weekly, or 50 mg administered once weekly. Plaque PsO: The recommended dose of etanercept is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with etanercept should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with etanercept is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly. *Paediatric population* JIA: The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months. The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg. No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously. Paediatric plaque PsO (age 6 years and above): The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with etanercept is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

	Method of administration: Enbrel is administered by subcutaneous injection.
Pharmaceutical form(s) and strengths	Enbrel® is available in strengths of 10, 25, and 50 mg vials of lyophilized powder for reconstitution with solvent for solution for injection; 25 mg and 50 mg solution for injection in pre-filled syringes; and 25 mg and 50 mg solution for injection in a pre-filled pen.
Is/will the product be subject to additional monitoring in the EU?	No

AS = ankylosing spondylitis; ATC = anatomical therapeutic chemical; CHO = Chinese hamster ovary; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; DNA = deoxyribonucleic acid; ERA = enthesitis-related arthritis; INN = international nonproprietary name; JIA = juvenile idiopathic arthritis; MRI = magnetic resonance imaging; MTX = methotrexate; nr-AxSpA = non-radiographic axial spondyloarthritis; NSAID = nonsteroidal anti-inflammatory drug; PsA = psoriatic arthritis; PsO = plaque psoriasis; PUVA = psoralen and ultraviolet-A light; RA = rheumatoid arthritis; TNF = tumour necrosis factor; TNFR = tumour necrosis factor receptor

PART II. SAFETY SPECIFICATION

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

Etanercept (invented name: Enbrel ®) is indicated for the following conditions:

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PsA)
- Ankylosing spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-AxSpA)
- Juvenile idiopathic arthritis (JIA): including polyarthritis (rheumatoid factor [RF] positive or negative) and extended oligoarthritis (ages 2-17 years), adolescent PsA (ages 12-17 years), adolescent enthesitis-related arthritis (ERA) (ages 12-17 years)
- Adult plaque psoriasis (PsO)
- Paediatric plaque PsO (ages 6-17 years)

SI.1. Epidemiology of the Disease

Indication: Rheumatoid Arthritis

Incidence: Studies of various European populations suggest the incidence rate (IR) of RA to be approximately 2.5 per 10,000 person-years (PYs).[1] Population-based studies of RA in various regions of the United States (US) demonstrate somewhat higher age adjusted IRs ranging from 4 to 7 per 10,000 PYs. One study in the US demonstrated an annual IR of 7.3 per 10,000 population with the incidence in females and males as 10 and 4.4 per 10,000 population, respectively.[2] Much of this variability is likely due to differences in ascertainment.

In Swedish and Italian studies, the IR of RA was 4.05 (95% confidence interval [CI] 3.97, 4.14) and 3.5 (95% CI 2.9, 4.2) per 10,000 PYs, respectively. Incidence increased with age, from 1.0 (95% CI 1.0, 1.1) and 1.7 (95% CI 1.5, 2.1) per 10,000 PYs in those age 18-29 years, to 8.6 (95% CI 8.2, 9.0) and 6.2 (95% CI 5.8-6.6) per 10,000 PYs in those age 70-79 years. Incidence was twice as high for women (5.57 [95% CI 5.43, 5.71] and 4.8 [95% CI 4.0, 5.7] per 10,000 PYs) than for men (2.50 [95% CI 2.40, 2.59] and 2.0 [95% CI 1.0, 3.0] per 10,000 PYs).[3,4]

Prevalence: RA has worldwide distribution, and with few exceptions, has relatively consistent prevalence rates across geographic regions.[1] Prevalence estimates for RA among adults of European ancestry, including those in North America, range from 0.5% to 1.0%.[5] Studies of Asian populations reveal a lower prevalence of about 0.2% to 0.3%.[5] RA has been shown to have increased prevalence with increasing age. Regardless of age, there is a consistent female predilection.[6]

In Italy, among women, 47 per 10,000 have active RA, increasing from 14 per 10,000 among those aged 18-39 to 95 per 10,000 in those aged 70-79 years. Among men, 15 per 10,000 have active RA, increasing from 4 per 10,000 among those aged 18-39 to 37 per 10,000 in those aged 70-79 years.[4]

In Estonia, the crude prevalence is 46 per 10,000; prevalence in women is 70 (95% CI 66.8, 73.7) per 10,000 and in men is 16 (95% CI 14.2, 17.9) per 10,000. Prevalence is low in younger adults (6 per 10,000 in age 20-29 years) and increases with age (121 per 10,000 in age 70-79 years).[7]

In Poland, a cross-sectional population-based study determined a prevalence of RA as 90 per 10,000 population, with a prevalence in males and females as 74 and 106 per 10,000 population, respectively.[8]

An analysis of a United Kingdom (UK) electronic medical record (EMR) database found that, annually, 40 (95% CI 36.0, 44.0) per 10,000 of the population consult primary and secondary care physicians for RA, and 25 (95% CI 22.0, 28.0) per 10,000 consult a primary care physician for RA.[9] An analysis of a Sweden EMR database found that, annually, 59 (95% CI 58.0-61.0) per 10,000 consult primary and secondary care physicians for RA, and 26 (95% CI 25.0, 28.0) per 10,000 consult a primary care physician for RA.[9]

Prevalence in the US ranged from 53 – 63 per 10,000 according to two studies.[2,10] Also, based on one of these studies, prevalence in males ranged from 29 to 31 per 10,000 while prevalence in females ranged from 73 to 78 per 10,000 population.[10]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: For all studies, incidence among female subjects ranged from 2 to 3 times higher than that in male subjects. The difference for both incidence and prevalence is highest among younger adults (female:male ratio is 3:6 for incidence and 3:5 for prevalence in 18-39 year olds), and decreases with age (2:0 for both incidence and prevalence among those >79 years old).[4]

Most studies find a mean age of onset in the early-to-mid-fifties[11,12,13] and a mean age of diagnosis in the late fifties.[14]

Risk for RA is increased in women and with age, such that prevalence is highest in women older than 65 years. This suggests that hormonal factors may have a pathogenic role. Prevalence also varies geographically, being common (affecting 0.5–1.0% of adults, with 5–50 new cases per 100,000 annually) in Northern Europe and North America compared with other parts of the developing world. These variations are indicative of different genetic risks and environmental exposures. Smoking is the dominant environmental risk factor and doubles the risk of developing RA.[15] Other risk factors include pregnancy complications (such as preeclampsia, pregnancy-associated hypertension, hyperemesis, self-rated poor or very poor pregnancy course),[16,17] obesity,[11] having a first degree relative with RA or lupus,[14] and lower testosterone levels in men.[18] Presence of RF also increases risk for diagnosis of RA. With each doubling of RF level, RA diagnosis risk increases by hazard ratio (HR)=3.3 (95% CI 2.7, 4.0), and higher levels of RF increases risk of hospitalization for RA.[19]

The main existing treatment options: Twenty-first century treatment of RA is often referred to as a reversal of a twentieth century pyramid that begins at the bottom with nonsteroidal anti-inflammatory drugs (NSAIDs), progressing upward with steroids, then disease modifying antirheumatic drugs (DMARDs) of increasing potency, culminating at the top in treatment with biologics. Early, aggressive treatment with non-biologic/and or biologic DMARDs (bDMARDs) has been shown in multiple studies to reduce the progression of irreversible joint damage. Non-biologic DMARDs, along with an increasing combination of biologic DMARDs are becoming the standard of care in moderate to severe active RA, with occasional oral and intra-articular steroids and NSAIDs used as adjunct therapy. Commonly used non-biologic DMARDs include methotrexate (MTX), sulfasalazine, chloroquine, hydroxychloroquine, and leflunomide. Less commonly used DMARDs include cyclosporine, and azathioprine. These therapies carry increased risk of infection, liver, renal, bone marrow, and lung toxicities. Oral gold and gold injections, while once commonly used, are currently very seldom used.

Alternative biologic treatments approved for RA include the TNF inhibitors adalimumab, golimumab, infliximab, certolizumab, the interleukin-6 (IL-6) inhibitors tocilizumab and sarilumab, the B cell depleter rituximab, the T cell costimulating inhibitory agent abatacept, and the interleukin-1 receptor antagonist anakinra. Common to all these biologics is increased risk of infection.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Key outcomes in RA are persistent joint inflammation, progressive joint damage, and continuing functional decline. Other important outcomes include extra-articular features (e.g., vasculitis), comorbidities (e.g., cardiac disease and infections), and patient-related factors (e.g., fatigue).[15]

The key treatment goal in RA is remission with no active joint inflammation and no erosive or functional deterioration. 10-50% of patients with early RA achieve remission. Other important goals are reduced disease activity and pain, maintenance of function, and preservation of work and recreational activities.[15]

Epidemiologic studies have generally found that compared to the general population, RA is associated with a 1.5 to 2-fold increased risk of mortality.[20,21] Additionally, studies have demonstrated that the greater the severity of RA, the greater the increased risk of death.[20] In an analysis of adults in a UK EMR database from 1994-2010, the mortality rate was 31.71 deaths per 1000 PYs of follow-up: 24.50 for those on DMARDs and 38.33 for those not on DMARDs.[22] However, a study of RA patients treated with an anti-TNF biologic using a US claims database did not show a mortality rate different from the general population (all-cause mortality 5.34 [95% CI 4.20-6.69] per 1000 PYs; standardized mortality ratio [SMR] [vs. the US general population] was 0.95 [95% CI 0.73, 1.17]).[23]

Indication: Psoriatic Arthritis

Incidence: Epidemiologic estimates (e.g., incidence, prevalence, mortality rates) of PsA may vary as a result of lack of a standard case definition, differences in genetics across different geographic and ethnic groups, and exposure to environmental factors and study methods. For example, a population-based study carried out in 2006–2008 in Norway found an IR of

41.3 (95% CI 35.8, 47.6) per 100,000 PYs.[24] Yet, a study using the European Spondylarthropathy Study Group (ESSG) criteria for PsA found the reported age-adjusted IR in northwest Greece to be 3.02 (95% CI 1.55, 4.49) per 100,000 PYs (2.87 among men and 3.14 among women).[25] In addition, a recent systematic review reported an incidence of PsA that varies from 0.1 per 100,000 PYs in Japan to 23.1 per 100,000 PYs in Finland.[26] Also, a study in Canada found an annual IR of 15.3 per 100,000 population.[27]

Prevalence: The prevalence of PsA was evaluated in multiple population-based studies in geographic locations such as Europe (UK, Sweden, Denmark, and Norway) and the US. For example, in the UK, among 4.8 million patients in The Health Improvement Network (THIN) database (aged 18-90 years), 9045 patients had at least one medical code for PsA, giving an overall prevalence of 0.19% (95% CI 0.19, 0.19). Among the 4064 confirmed PsO patients, the prevalence of PsA was 8.6% (95% CI 7.7, 9.5). PsA was more prevalent among patients with severe PsO (odds ratio [OR] 3.34; 95% CI 2.40, 4.65), obesity (OR 1.77; 95% CI 1.30, 2.41) and duration of PsO over 10 years (OR 7.42; 95% CI 3.86, 14.25) in the fully adjusted model.[28] The prevalence of PsA in THIN is consistent with previous population-based estimates; however, in the Nord-Trøndelag Health Study 3 in Norway, the prevalence of PsA was 6.7 per 1000 inhabitants (95% CI 5.9, 7.4) in patients older than 20 years old with no significant difference between men and women.[24] The prevalence of PsA in central Norway appears to be higher than previously reported. The reason for this is unknown and may include environmental factors, life style factors and genetic differences.[24]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: Most cases of PsA occur when subjects are in their early to mid-forties, with the majority of cases occurring in subjects aged 45 to 64 years old. With the exception of a single Finnish study, which found a slightly increased risk in men, most European and US studies have identified no gender predilection in the risk of developing PsA.[29]

The main existing treatment options: NSAIDs are considered first-line therapy for the management of joint pain in combination with topical antipsoriatic agents. Therapy is typically escalated in patients who fail to respond adequately to NSAIDs. Intra-articular corticosteroid injections are effective if joint involvement is limited. MTX, sulfasalazine, and cyclosporine may be employed as immunomodulators and are effective in managing the skin and joint manifestations of the disease. These agents do require monitoring to avoid or minimize safety complications (e.g., liver and/or lung fibrosis, renal dysfunction, bone marrow suppression).

Biologic DMARDs for treatment of PsA have until recently consisted only of TNF inhibitors (e.g., etanercept, infliximab, adalimumab, golimumab and certolizumab pegol). bDMARDs with new mechanisms of action (MOA), such as rituximab (a B cell depleter), ustekinumab (a human interleukin [IL] -12 and IL-23 antagonist that binds the P40 subunit shared by these 2 cytokines), and secukinumab and ixekizumab (human IL-17A antagonists), have recently been approved. In addition, alternative nonbiologic oral therapies, such as tofacitinib (a Janus Kinase [JAK] inhibitor) and apremilast (a phosphodiesterase 4 [PDE4] inhibitor) have been approved for the treatment of PsA. Common to all these therapies is the increased risk of infection.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Data are limited regarding mortality in subjects with PsA; the most frequently reported cause of mortality was due to diseases of the circulatory and respiratory systems, followed by malignancies and injury or poisoning.[29] In a population-based medical record review study in Olmsted County, Minnesota (MN), US, Shbeeb et al. reported that the survival of subjects with PsA was not significantly different from that of the local general population (p=0.546). [30] In contrast, others have shown an increased death rate with a SMR of 1.6 (95% CI 1.2, 2.1) in a study of 428 subjects with PsA seen at a tertiary care centre over 11.4 years of follow-up.[31] The discrepant results between these 2 studies may be attributable to referral bias (ie, subjects with greater disease severity being seen at specialized centres of care). [30] In a more recent longitudinal retrospective cohort study using THIN (general practitioner [GP] EMR database) in the UK, Ogdie et al reported that the death rate of subjects with PsA was 10.37 deaths per 1000 PYs (7.80 for those on DMARDs, 12.46 for those without DMARDs).[22]

Indication: Ankylosing Spondylitis

Incidence: The reported incidence of AS ranges from 0.5 to 14 cases per 100,000 people per year in studies conducted throughout different countries.[32] Several clinical and methodological factors likely contribute to this inconsistency in rates. Among these factors is the selection of the target population and its ethnicity. Because susceptibility is strongly associated with human leukocyte antigen (HLA) B27 and its specific subtypes, the incidence of AS often closely parallels the background rate of this genetic polymorphism in different ethnic groups. Additionally, methods of ascertainment and case definition, i.e., screening and diagnosis, may also vary despite the fact that AS is the prototypical spondyloarthropathy characterized by sacroiliitis and ankylosis of the spine, resulting in a wide range of incidence.

Data from a 50-year study conducted in Olmsted County MN, US from 1935-1989, based on hospital attendance over a 50-year period (1935 to 1989) showed the age-and-sex adjusted IR of AS was 7.3 (95% CI: 6.1, 8.4) per 100,000 PYs. The age-adjusted IRs were 11.7 per 100,000 PYs for males and 2.9 per 100,000 PYs for females.[33] Another study from Finland reported an incidence of 7 per 100,000 PYs based on subjects having been registered as having AS from studies of individuals eligible to receive free medication.[34]

Prevalence: Based primarily on European data, several population based-studies have shown that the prevalence of AS ranges from 0.1% to 1.4%.[32] In Olmsted County, MN (a population primarily of northern European extraction), Carter et al, reported an overall prevalence of AS of 12.9 per 10,000 inhabitants, with 19.7 per 10,000 males and 7.3 per 10,000 females.[35] An analysis of a UK EMR database found that, annually, 5 (95% CI 3, 6) per 10,000 of the population consult primary and secondary care physicians for AS, and 3 (95% CI 2, 4) per 10,000 consult a primary care physician.[9] An analysis of a Sweden EMR database found that, annually, 6 (95% CI 5, 6) per 10,000 consult primary and secondary care physicians for AS, and 0.2 (95% CI 0.1, 0.3) per 10,000 consult a primary care physician for AS.[9]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: Peak age of onset of AS is reportedly between 25 and 34 years of age for both men and women, with increasing rarity of incidence after 55. In a cohort of 2356 AS patients across Spain, Belgium, and Portugal, the mean age at symptom onset was 27 years, and the mean age at diagnosis was 34 years.[36]

The age-adjusted IR for men was approximately 4 times greater than that in women. More recent prevalence studies in the general population reported a male to female prevalence ratio of 3.0 - 4.0.[33] Studies in Spain, Belgium, Portugal,[36] and Denmark[37] suggest a male:female prevalence ratio of approximately 2:5.

Ankylosing spondylitis is a disease that affects young people, with the majority experiencing their first symptoms prior to age 30. Men are more often affected than women, with a ratio of approximately 2 to 1. There is a rough correlation between prevalence of HLA B27 and the incidence and prevalence of AS in a specific population.[32] There is evidence that there may be increased risk with chronic periodontitis.[38]

The main existing treatment options: Therapeutic measures are largely aimed at alleviation of symptoms of inflammation and pain as well as maintenance of range of motion and muscle strength. These measures do not alter disease progression, however. As with the other inflammatory arthritides, treatment regimens are individualized according to gender, age, and comorbid conditions.

NSAIDs are typically first-line therapy in AS.[39] Brief courses of low to medium dose oral corticosteroids may be used to control severe episodes of arthritis. Intra-articular corticosteroid injections are effective in relieving persistent arthritis refractory to NSAIDs. Sulfasalazine is also beneficial particularly if peripheral symptoms are dominant.

Alternative biologics approved for AS are the TNF inhibitors adalimumab, golimumab, and infliximab, and the B cell depleter, rituximab. Common to all these biologics is increased risk of infection.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Earlier studies conducted over 20 to 30 years in the 1970s and 1980s showed that the mortality of subjects with AS was 1.6-1.9 times higher than that of the general population. However, 2 more recent population-based studies in the US showed no increase in mortality associated with AS.[33,35]

Lehtinen investigated the mortality among 398 AS subjects hospitalized in Finland between 1961 and 1969 and reported a mortality of 38% during the 25.7 years of follow-up.[40] The observed mortality was 1.5 times higher in subjects with AS than in the general population. The mean decrease in survival was 15 years among males and 6 years among females. Excess mortality was noted as the underlying cause of death in 27 of the subjects; circulatory, gastrointestinal and renal diseases, accidents and violence also caused more deaths than expected.[40]

Indication: Non-Radiographic Axial Spondyloarthritis

Incidence: Review of the published literature did not identify any studies of the incidence of non-radiographic axial spondyloarthritis.

Prevalence: The true prevalence of non-radiographic axial spondyloarthritis has not been well studied. Based on the currently available epidemiological studies, the proportion of patients identified as truly having non-radiographic axial spondyloarthritis among newly diagnosed axial spondyloarthritis patients ranged from 23% to 80%. A global study involving 19 countries in Latin America, Europe, Africa, and Asia reported a prevalence of 19.23%, 29.53%, 16.02% and 36.46% among patients with inflammatory back pain in these respective regions. Sex-specific prevalence was similar at 28.74% in males and 29.75% in females.[41] In treatment trials, the proportion of patients with non-radiographic axial spondyloarthritis was 49%.[42] This wide range of frequencies reflects differences in patient populations and methodologies (e.g., eligibility criteria) within the studies.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: Demographic and disease characteristics data for patients with non-radiographic axial spondyloarthritis are available only from non-interventional cohorts and anti-TNF treatment trials, which allow just an informal comparison of demographic and disease characteristics in patients with non-radiographic axial spondyloarthritis vs radiographic axial spondyloarthritis. Because patients participating in treatment trials were required to satisfy restrictive inclusion criteria, findings from these populations cannot be generalizable to patients in the "real world". In some studies, a significant difference was seen in the male to female ratio by approximately doubling the risk for males compared to females.[42]

Review of the published literature did not identify any study on the risk factors of non-radiographic axial spondyloarthritis.

The main existing treatment options: Therapeutic measures are largely aimed at alleviating symptoms of inflammation and pain as well as maintenance of range of motion and muscle strength. These measures do not alter disease progression, however, NSAIDs are typically first-line therapy in nr-AxSpA.[43,44] MTX and sulfasalazine are also used, but are largely ineffective.[44,45,46,47]

Little data exist on the role of anti-tumor necrosis factor (TNF) agents in the treatment nr-AxSpA, including the effect on prevention of anatomical progression in this early disease stage before significant X-ray abnormalities develop.[48] In patients with AS, there is no convincing evidence that TNF inhibitors can prevent progressive structural damage. In clinical trials conducted to date, anti-TNF agents have demonstrated similar efficacy in AxSpA patients with and without radiographic sacroiliitis.[49,50,51,52] In addition to etanercept, adalimumab, [52] certolizumab pegol[53] and golimumab have also been approved in the European Union (EU) for the treatment of adults with nr-AxSpA.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Review of the published literature did not identify any study of the morbidity and mortality of non-radiographic axial spondyloarthritis.

Indication: Juvenile Idiopathic Arthritis

Incidence: JIA is the newest classification system used to describe a heterogeneous group of inflammatory arthritides diagnosed in persons aged 16 or younger. This system is intended to replace the earlier classification systems used by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (Juvenile Rheumatoid Arthritis [JRA] and Juvenile Chronic Arthritis [JCA], respectively), with the intent of unifying diagnostic criteria and standardizing research definitions. Each of the 3 systems differs slightly in its approach to classifying subtypes of juvenile arthritis. Therefore, any evaluation of epidemiologic data must consider the classification system used in the study.

A published review of the epidemiologic literature of JIA from 1966 to 1998 found an annual incidence range of 0.8 to 23 per 100,000 children.[54] Studies specific to Northern Europe and the US suggest an incidence between 7 and 21 cases per 100,000 children per year.[55] Incidence studies are limited in precision due to the small number of new subjects who present with juvenile arthritis each year, which results in large confidence intervals (CI) for individual studies, as well as large differences in estimates across studies. A study conducted in Finland found variation in estimates of the incidence of juvenile arthritis within one country.[56] In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (International League of Associations for Rheumatology [ILAR] and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 1.5 (95% CI 1.3, 1.7) per 10,000 children/year according to the ILAR criteria.

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, the mean annual IR of JIA was 6.9 (95% CI 5.8, 8.1) per 100,000 children.[58]

In a study using Kaiser Permanente Northern California data for those age ≤15 years, the incidence of JIA was 11.9 (95% CI 10.9, 12.9) per 100,000 PYs in 1996-2009, with incidence lowest for the youngest (8.8 [95% CI 3.5, 14.2] per 100,000 PYs for age 0-5) and increasing with age (12.1 [95% CI 5.8, 18.4] per 100,000 PYs for age 6-10, and 15.1 [95% CI 8.2, 22.4] per 100,000 PYs for age 11-15). Incidence was more than twice as high for girls (16.4 [95% CI 14.6, 18.1] per 100,000 PYs) than for boys (7.7 [95% CI 6.5, 8.9] per 100,000 PYs).[59]

Among all live born infants delivered in Denmark 1980-2009, JIA occurred in 16.73 (95% CI 16.28, 17.20) per 100,000 PYs. This study also found an increasing incidence with age (from 2.40 [95% CI 1.80-3.12] per 100,000 PYs for age <1, increasing to 20.03 [95% CI 19.20, 20.89] per 100,000 PYs for age 10-17), and a higher incidence for girls (20.40 [95% CI 19.69, 21.13] per 100,000 PYs) than boys (13.23 [95% CI 12.67, 13.81] per 100,000 PYs).[60]

The ILAR 2001 criteria define 8 subtypes of JIA which include systemic JIA, persistent oligoarthritis, extended oligoarticular JIA (eoJIA), RF positive polyarticular JIA, RF negative polyarticular JIA, ERA, PsA, and undifferentiated JIA. In North America and Europe, the relative frequencies of JIA subtypes are 5 to 10% RF positive polyarticular, 10 to 30% RF negative polyarticular, and 30 to 60% oligoarticular, with approximately 50% of these progressing to the extended form.[61] The 5 ILAR subtypes (RF positive polyarthritis, RF

negative polyarthritis, eoJIA, ERA, and PsA), which are proposed for inclusion in the etanercept Summary of Product Characteristics (SmPC), are presented below.

Polyarthritis (Rheumatoid Factor Positive): In a population-based study (utilizing the ILAR criteria) of 248,625 children in Estonia conducted from January 1998 through December 2000, Pruunsild et al. identified 162 cases of new-onset JIA. Seven (7) of these cases were diagnosed as RF positive polyarthritis, for a mean annual IR of 0.9 (95% CI 0, 2.1) per 100,000 children.[62]

In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (ILAR and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 15 (95% CI 13, 17) per 100,000 children/year according to the ILAR criteria. Among 314 children diagnosed with JIA, 6 (2%) patients qualified as having RF positive polyarthritis (no information is provided which would allow a calculation of incidence or prevalence).

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 145 new cases of JIA according to the ILAR criteria, with a mean annual IR of 6.9 (95% CI 5.8, 8.1) per 100,000 children. Three (2%) of these cases were diagnosed as RF positive polyarthritis, for a mean annual IR of 0.1 (95% CI 0, 0.4) per 100,000 children.[58]

In a study using Kaiser Permanente Northern California data for those age ≤15 years, the incidence of JIA was 11.9 (95% CI 10.9, 12.9) per 100,000 PYs in 1996-2009; 31% was polyarthritis (RF status not provided).[61]

In summary, the annual IR of RF positive polyarthritis in these studies ranges from 0.1 to 0.9 per 100,000 children.

Polyarthritis (Rheumatoid Factor Negative): In a population-based study (utilizing the ILAR criteria) of 248,625 children in Estonia conducted from January 1998 through December 2000, Pruunsild et al identified 162 cases of new-onset JIA. Thirty-three (33) of these cases were diagnosed as RF negative polyarthritis, for a mean annual IR of 4.4 (95% CI 1.8, 7.0) per 100,000 children.[62]

In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (ILAR and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 15 (95% CI 13, 17) per 100,000 children/year according to the ILAR criteria. Among 314 children diagnosed with JIA, 22 (7%) patients qualified as having RF negative polyarthritis (no information is provided which would allow a calculation of incidence or prevalence).

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 145 new cases of JIA according to the ILAR criteria, with a mean annual IR of 6.9 (95% CI 5.8, 8.1) per 100,000 children.

Fifteen (10%) of these cases were diagnosed as RF negative polyarthritis, for a mean annual IR of 0.7 (95% CI 0.4, 1.2) per 100,000 children.[58]

In summary, the annual IR of RF negative polyarthritis in these studies ranges from 0.7 to 4.4 per 100,000 children.

Extended Oligoarthritis: In a population-based study (utilizing the ILAR criteria) of 248,625 children in Estonia conducted from January 1998 through December 2000, Pruunsild et al. identified 162 cases of new-onset JIA. Seventeen (17) of these cases were diagnosed as extended oligoarthritis, for a mean annual IR of 2.3 (95% CI 0.4, 4.2) per 100,000 children.[62]

In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (ILAR and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 15 (95% CI 13, 17) per 100,000 children/year according to the ILAR criteria. Among 314 children diagnosed with JIA, 17 (5%) patients qualified as having extended oligoarthritis (no information is provided which would allow a calculation of incidence or prevalence).

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 145 new cases of JIA according to the ILAR criteria, with a mean annual IR of 6.9 (95% CI 5.8, 8.1) per 100,000 children. Eight (6%) of these cases were diagnosed as extended oligoarthritis, for a mean annual IR of 0.4 (95% CI 0.2, 0.7) per 100,000 children.[58]

In summary, the annual IR of extended oligoarthritis in these studies ranges from 0.4 to 2.3 per 100,000 children.

Enthesitis-related Arthritis: In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (ILAR and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 15 (95% CI 13, 17) per 100,000 children/year according to the ILAR criteria. Among 314 children diagnosed with JIA, 12 (4%) patients qualified as having juvenile AS (no information is provided which would allow a calculation of incidence or prevalence).

In a study conducted in Finland, the overall annual incidence of JIA was 22.7 cases per 100,000 based on 87 incident cases.[56] Of these 87 cases, 3 were attributed to juvenile AS and ERA, yielding an annual incidence of 0.8 cases per 100,000.

In a population-based study (utilizing the ILAR criteria) of 248,625 children in Estonia conducted from January 1998 through December 2000, Pruunsild et al. identified 162 cases of new-onset JIA. Eleven (11) of these cases were diagnosed as ERA, for a mean annual IR of 1.5 (95% CI 0, 3.0) per 100,000 children.[62]

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 145 new cases of JIA according to the ILAR criteria, with a mean annual IR of 6.9 (95% CI 5.8, 8.1) per 100,000 children.

Eighteen (12%) of these cases were diagnosed as ERA, for a mean annual IR of 0.8 (95% CI 0.5, 1.3) per 100,000 children.[58]

In summary, the annual IR of ERA in these studies ranges from 0.8 to 1.5 per 100,000 children.

Juvenile Psoriatic Arthritis: In a study conducted in Finland, the overall annual IR of JIA was 22.7 per 100,000 based on 87 incident cases.[56] Of these 87 cases, 2 were associated with PsO, yielding an annual IR of 0.5 cases of juvenile PsA per 100,000.

In a population-based study (utilizing the ILAR criteria) of 248,625 children in Estonia between January 1998 and December 2000, Pruunsild et al. identified 162 cases of new-onset JIA. Of these, 5 were diagnosed as associated with PsO, with a mean annual IR for PsA of 0.7 (95% CI 0, 1.7) per 100,000 children.[62]

In a study of the overall incidence of JIA in the Nordic countries, the authors applied different classification criteria (ILAR and EULAR) to determine incidence of juvenile arthritis over an 18-month period from July 1997 through December 1998.[57] The IR of JIA was 15 (95% CI 13, 17) per 100,000 children/year according to the ILAR criteria. Among 314 children diagnosed with JIA, 9 (3%) patients qualified as having juvenile PsA (no information is provided which would allow a calculation of incidence or prevalence).

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 145 new cases of JIA according to the ILAR criteria, with a mean annual IR of 6.9 (95% CI 5.8, 8.1) per 100,000 children. Nine (6%) of these cases were diagnosed as juvenile PsA, for a mean annual IR of 0.4 (95% CI 0.2, 0.8) per 100,000 children.[58]

In a study using Kaiser Permanente Northern California data for those age ≤15 years, the incidence of JIA was 11.9 (95% CI 10.9, 12.9) per 100,000 PYs in 1996-2009; 8% were psoriatic arthritis.[59]

In summary, the annual IR of juvenile PsA in these studies ranges from 0.4 to 0.7 per 100,000 children.

Prevalence: The 3 major subtypes of juvenile arthritis are systemic, oligoarthritis (also called pauciarthritis) and polyarthritis (RF positive or negative). Estimates for the proportion of these subtypes among all juvenile arthritis cases are as follows: 2-17% systemic, 12-29% oligoarthritis, and 2-28% polyarthritis.[55,63] A published review of the epidemiologic literature of JIA from 1966 to 1998 found a prevalence range of 7 to 400 cases per 100,000 children.[54] One difficulty in estimating prevalence is that studies may either include children who are currently symptomatic or they may include children who have ever had a diagnosis, regardless of current symptoms. Based on the estimated incidence and age of diagnosis, Silman suggests that prevalence should range from 40 to 160 per 100,000 children.[63] Estimates are influenced by study design, and especially setting, where clinic-based studies often suggest lower prevalence estimates than community-based studies. Although some subjects achieve complete remission post-adolescence, many children remain symptomatic throughout life and will always be considered juvenile arthritis subjects, even as adults.

Prevalence studies often do not include adult-aged subjects with JIA;[64] this should be considered when using prevalence estimates to extrapolate the total number of cases in a population.

Polyarthritis (Rheumatoid Factor Positive): In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 432 cases of JIA according to the ILAR criteria, yielding a prevalence of 39.7 (95% CI 36.1, 43.7) per 100,000 children. Three (0.7%) of these cases were diagnosed as RF positive polyarthritis, for a prevalence of 0.7 (95% CI 0.1, 0.8) per 100,000 children.[58]

Polyarthritis (Rheumatoid Factor Negative): In a population-based study conducted by Danner et al.[65] in the Alsace region of France, 67 children were diagnosed with JIA among 339,095 children under the age of 16 years, resulting in an overall prevalence of JIA of 19.8 cases per 100,000 children. Of these 67 cases of JIA, 15 cases were due to RF negative polyarthritis, for a prevalence of 4.4 cases per 100,000 children.

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 432 cases of JIA according to the ILAR criteria, yielding a prevalence of 39.7 (95% CI 36.1, 43.7) per 100,000 children. Forty (9%) of these cases were diagnosed as RF negative polyarthritis, for a prevalence of 3.7 (95% CI 2.6, 5.0) per 100,000 children.[58]

In summary, the prevalence of RF negative polyarthritis in these studies ranges from 3.7 to 4.4 per 100,000 children.

Extended Oligoarthritis: In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 432 cases of JIA according to the ILAR criteria, yielding a prevalence of 39.7 (95% CI 36.1, 43.7) per 100,000 children. Thirty-eight (9%) of these cases were diagnosed as extended oligoarthritis, for a prevalence of 3.5 (95% CI 2.5, 4.8) per 100,000 children.[58]

Enthesitis-related Arthritis: In a review paper, the authors cited the prevalence of ERA (characterized by involvement of the entheses and the axial skeleton in addition to the peripheral joints)[66] including juvenile AS to range from 11 to 86 per 100,000 children and that it contributed consistently across geographic populations to 20% to 30% of all cases of JIA worldwide.[67] Proportions of juvenile AS differ between the Caucasian population (21%) and Mexican mestizos (50%) which are believed to be a consequence of the high frequency of HLA-B27 in the latter population.

In a population-based study conducted by Danner et al.[65] in the Alsace region of France, 67 children were diagnosed with JIA among 339,095 children under the age of 16 years, resulting in an overall prevalence of JIA of 19.8 cases per 100,000 children. Of these 67 cases of JIA, 12 cases were due to ERA, for a prevalence of 3.5 cases per 100,000 children.

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 432 cases of JIA according to the ILAR criteria, yielding a prevalence of 39.7 (95% CI 36.1, 43.7) per 100,000 children.

Thirty-seven (9%) of these cases were diagnosed as ERA, for a prevalence of 3.4 (95% CI 2.4, 4.7) per 100,000 children.[58]

In summary, the prevalence of ERA in these studies ranges from 3.4 to 86 per 100,000 children.

Juvenile Psoriatic Arthritis: In a population-based study conducted by Danner et al.[65] in the Alsace region of France, of 67 children diagnosed with JIA (out of 339,095 children under the age of 16), 3 were ultimately attributed to juvenile PsA for a prevalence of 0.9 cases per 100,000 children.

In a prospective, population-based study of 2,119,382 children in Catalonia (Spain) conducted from 2004 through 2006, Modesto et al. identified 432 cases of JIA according to the ILAR criteria, yielding a prevalence of 39.7 (95% CI 36.1, 43.7) per 100,000 children. Twenty (5%) of these cases were diagnosed as juvenile PsA, for a prevalence of 1.8 (95% CI 1.1, 2.8) per 100,000 children.[58]

In summary, the prevalence of juvenile PsA in these studies ranges from 0.9 to 1.8 per 100,000 children.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: By definition, JIA is limited to persons whose symptoms begin at or before the age of 16 years. As noted previously, if the disease does not go into remission, the diagnosis carries into adulthood and is considered juvenile arthritis at any age. Because there is limited information available on patient demographic characteristics for each JIA subtype, demographic characteristics are presented for JIA patients overall.

The age and gender distribution for JIA varies greatly by subtype; however, across all subtypes, JIA is more prevalent in females than males, with an overall female to male ratio of 1.5-2 to 1.0.[63] The gender difference is greatest for polyarticular and oligoarticular disease, while systemic disease affects boys and girls at roughly the same rate.[54,63] Among 488 incident JIA cases from Kaiser Permanente Northern California (US), the female:male gender ratio is 2:5.[59] Estimates of the female to male gender ratio range from 3-4 to 1, depending on the study. In a study of 1104 JIA cases in Canada, 64.0% were female across all of JIA; the proportion of female were 69.5% for oligoarthritis, 76.9% for RF-negative polyarthritis, 95.5% for RF-positive polyarthritis, 66.1% for juvenile PsA, and 26.5% for ERA.[68]

In general, systemic and oligoarthritis tend to present in younger aged children (average age 1-6 years and 1-5 years, respectively), whereas polyarthritis generally presents in children who are at least 8 years of age.[54] In a study of 1104 JIA cases in Canada, the median age at diagnosis overall was 9.3 years (interquartile range 3.9-13.0). For oligoarthritis, median age of onset was 6.4 (interquartile range [IQR] 2.9, 11.4); for RF-negative polyarthritis 8.8 (IQR 3.4, 12.5); for RF-positive polyarthritis 13.2 (IQR 10, 15.3), for juvenile PsA 11.3 (IQR 4.9, 13.6), and for ERA 11.3 (IQR 10.8, 14.5).[68]

A Canadian study of ethnicity in subjects with JIA found that subjects of European descent were more likely to develop any of the JIA subtypes, except RF positive polyarticular JIA, than were subjects of Indian, Asian, or African descent, and they were especially more likely to develop the extended oligoarticular and psoriatic subtypes; the ethnic distribution varied by subtype of JIA.[69] However, a US study suggested that Caucasian and African American children had similar rates of JIA.[64] Further, studies have reported geographic differences in the epidemiology of JIA, even within a single country. It is unclear whether these differences are due to environmental factors, genetic differences, or a combination of the two.

Like other autoimmune diseases, risk of developing JIA is thought to be determined by a complex combination of genetic and environmental risk factors.[70] Girls and older children are at increased risk.[58,59] There may be genetic susceptibility, and several candidate genes are under study. [70,71] Some authors have hypothesised vaccinations may trigger the disease in those genetically predisposed, but studies have not supported a link to vaccines.[71] Some infections can lead to transient post-infectious arthritis, usually lasting only a few weeks; however this can occasionally become chronic, resembling JIA.[70] Early-life risk factors include not having been breastfed and maternal smoking.[70]

The main existing treatment options: No treatment guidelines exist for JIA. Therapy is largely based on evidence extrapolated from clinical trials in adult RA. However, data suggest that patients with JIA do not always respond to treatment in a similar fashion as patients with adult RA. For several of the more conventional therapies used in adult RA (D-penicillamine, hydroxychloroquine), efficacy has not been demonstrated in children.[72] In contrast, the anti-TNF-alpha therapies have demonstrated efficacy in both adult RA and JIA.

It should be noted, however, that reports suggest that MTX is less effective in ERA than in other JIA subtypes. Management of JIA is based on a combination of pharmacologic interventions, and physical and occupational therapy. NSAIDs are a mainstay of therapy for all JIA subtypes. Agents approved for use in children include naproxen, ibuprofen, and indomethacin. For patients who fail to respond to NSAIDs, intra-articular steroid injections are often effective, particularly in the setting of oligoarticular disease.[73] Failure to respond to these therapies warrants escalation to immunomodulatory therapy such as MTX.[74] For patients who are refractory to, or intolerant of MTX, the anti-TNF biologic therapy etanercept is approved for use in JIA. ERA is treated similarly to adult AS and paediatric PsA is treated similarly to adult PsA.

Alternative biologics approved for polyarticular JIA include the TNF inhibitor adalimumab, the IL-6 inhibitor tocilizumab, and the T cell costimulation inhibitor abatacept. Common to all these biologics is increased risk of infection. There are currently no biologics other than etanercept approved specifically for eoJIA, ERA, or paediatric PsA.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Relevant information could not be identified in the literature for each JIA subtype; therefore, information on morbidity and mortality is presented for JIA overall.

A prospective cohort study of 132 JIA patients identified in 1984-1986 found that, among the 128 followed up for 5 years after diagnosis, disease was still active in 12%, stable in 28%, inactive in 25%, and in remission in 34%.[75] After 17 years of follow-up (n=86), 2% had active disease, 40% were stable, 19% had inactive disease, and 40% were in remission. In the subset with polyarthritis, 6% had active disease, 48% stable, 6% inactive, and 39% in remission. Both the 2 JIA cases that were still active after 17 years were in the polyarthritis group.[75]

Among 1086 JIA cases in Canada who were enrolled in a prospective observational study within 6 months of diagnosis and had at least 1 follow-up visit, 95% were able to achieve inactive disease at some point during 5 years of follow-up. Among those with oligoarthritis, the corresponding proportion was 96%; RF-negative polyarthritis 97%, RF-positive polyarthritis 93%, juvenile psoriatic arthritis 100%, ERA 92.5%.[68] In the same cohort, among 1146 patients with at least 1 study visit with inactive disease, the median time from diagnosis to inactive disease was 10.9 months. After attaining inactive disease, however, 54.7% had at least 1 flare during follow-up (35% had 1, 13.2% had 2, 6.5% had >2), 42.5% had at least 1 flare within 1 year, and 26.6% had at least 1 significant flare within 1 year. The risk of a flare was highest for the RF-positive polyarthritis patients.[68]

One of the most significant complications of JIA is anterior uveitis. The risk of uveitis is based on the JIA subtype, age at disease onset, and ANA (antinuclear antibody) status. The highest risk group of patients is oligoarticular JIA, especially if the patient is female, ANA-positive, and less than 4 years of age.[76]

JIA may be complicated by linear or localized growth disturbance. Linear growth abnormalities are particularly observed in patients with chronic active disease and are therefore most common in children with polyarthritis or systemic JIA. [76]

Using subject hospitalization records in Scotland, findings of a study of children with JIA suggested that the overall mortality was elevated 3-5-fold over the general population.[77] The Rochester Epidemiology Project database tracked 57 subjects with a history of JIA into adulthood. Four deaths occurred among these subjects (compared to one expected death). Although this finding is statistically significant, the small sample size limits the generalizability of this finding in JIA subjects overall. Of note, all deaths were attributable to complications from other autoimmune diseases.[78] Studies of mortality among subjects with JIA have estimated that the standardized mortality rate is 3 to 14 times greater than that of the general age-matched US population.[55]

Indication: Adult Plaque Psoriasis

Incidence: Recent systematic reviews reported a range of incidence estimate from 78.9 (US) to 230 per 100,000 PYs (Italy).[79] The age-and sex-adjusted IR of PsO has been estimated to be 60.4 per 100,000 PYs in a study performed in Olmsted County, MN, US in 1980. According to this study, the crude average annual IR was 54.4/100,000 PYs for men and 60.2/100,000 PYs for women.[80] Also, a study conducted in Ontario, Canada estimated the annual incidence of psoriasis to be 69.9 per 100,000 population.[27]

Prevalence: According to available population-based studies, the prevalence of PsO in subjects of all ages ranged from 0.91% to 8.5% of the general population.[79] The highest prevalence (8.5% [95% CI: 8.03, 8.97]) (Norway) was obtained by subject questionnaire without validation of positive responses. The lowest reported European prevalence came from the UK (1.30% [95% CI 1.21, 1.39]). A study from Croatia in the late 1980s reported a PsO prevalence (1.21% [95% CI 0.95, 1.47]) similar to that of the UK. However, other countries, in Northeastern and Southern Europe, reported higher values than the UK, specifically 3.73% (95% CI 3.13, 4.32) in Denmark, 4.82% (95% CI 4.47, 5.17) in Norway, 3.10% (95% CI 2.54, 3.66) in Italy, and 5.20% (95% CI 4.68, 5.72) in France. Population-based studies in the US have yielded prevalence rates ranging from 2.2% (95% CI 2.0, 2.4) to 3.15% (95% CI 2.60, 3.70) with approximately 150,000 newly diagnosed cases per year.[79]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: Psoriasis may first present at any age. Some reports describe a bimodal distribution of age at onset. Initial presentation of PsO is most commonly between the ages of 15 and 30 years but ranges from birth to the eighth or ninth decade. Median age at onset is approximately 40 years. Earlier age of onset is associated with a positive family history and specific HLA class I antigens, particularly HLA-Cw6.[27] Psoriasis is equally common in male and female subjects.[81]

The causes of PsO are not fully understood, but a number of risk factors are recognized, including family history and environmental risk factors, such as smoking, stress, obesity, and alcohol consumption.[79]

Huerta et al. in a prospective cohort study with nested case-control analysis evaluated the clinical spectrum of PsO and the incidence in the general population using the General Practice Research Database (GPRD) database and identified the risk factors associated with the occurrence of PsO. The study found that patients with antecedents of skin disorders and skin infection within the last year carried the highest risk of developing PsO (OR, 3.6 [95% CI, 3.2-4.1], and OR, 2.1 [95% CI, 1.8-2.4], respectively). Also, smoking was found to be an independent risk factors for PsO (OR, 1.4 [95% CI, 1.3-1.6]). The study did not find an association between risk of PsO and antecedents of stress, diabetes, hypertension, hyperlipidemia, cardiovascular disease (CVD), or RA.[82]

In a more recent study, Khalid et al. in a nationwide cohort in Denmark found that PsO was associated with increased IRs of new-onset diabetes mellitus (DM). The association remained statistically significant after adjustment for confounding factors.[83]

The main existing treatment options: Topical agents are often used as a first-line therapy in the treatment of PsO, but generally only in mild cases. These include steroids, vitamin-D analogues (such as calcipotriol), tazarotene, dithranol, coal tar extracts, and combinations of any of these agents. In PsO cases where large body surface areas are involved, absorption of vitamin D and topical steroids can be substantial and thus lead to systemic side effects. Steroids are the mainstay of topical therapy, and while they are generally well tolerated, they can induce skin atrophy and striae, and when absorbed systemically, can cause suppression of the hypothalamic-pituitary-adrenal axis. The other topical agents have few side effects

other than skin irritation. However, topical treatments are inconvenient to use, particularly when large areas of skin need to be treated, and also tend to soil/stain clothing.

Phototherapy and systemic therapies are usually reserved for patients with extensive disease and those refractory to topical treatments because they have significant potential liabilities, particularly long-term cumulative toxicities.[84] Phototherapy (broad or narrow band ultraviolet B [UVB] or psoralen plus ultraviolet A [PUVA]) requires frequent sessions at a treatment center and is therefore relatively inconvenient and disruptive to the patient's schedule. Risks associated with phototherapy include photoaging of treated skin and an increased incidence of cutaneous malignancies, particularly for PUVA. In addition, PUVA causes nausea and photosensitivity necessitating sun avoidance and protective eyewear on treatment days. Fumaric acid esters are an older therapy; while they are generally regarded as effective and safe in PsO, there is relatively little well-controlled clinical trial evidence in the published literature.[85] Adverse events (AEs) associated with fumaric acid esters include diarrhoea, stomach ache, flushing, eosinophilia, and reductions in relative lymphocyte counts. All other currently available systemic treatments are associated with significant long-term toxicities, including teratogenic effects and abnormalities of lipid metabolism with retinoids; cumulative liver toxicity and the risk of bone marrow suppression with MTX; hypertension, renal dysfunction, and risk of malignancies with Cyclosporine A. Careful follow-up and laboratory monitoring are required for patients treated with these drugs. Due to the dose-dependent, cumulative nature of the toxicities, intermittent or rotational treatment with different agents, with a goal of controlling the disease with the lowest total dose of the systemic agent, is a common clinical practice to lessen the risk of serious adverse effects (SAEs).[86]

Other approved therapies include the biologic agents etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), ustekinumab (Stelara), golimumab (Simponi), secukinumab (Cosentyx), ixekizumab (Taltz), brodalumab (Kyntheum), and the nonbiologic, apremilast (Otezla).

Common to all these biologics is increased risk of infection.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: While PsO causes significant morbidity, most studies suggest it is generally not directly associated with mortality. However, as several comorbid conditions found commonly in PsO subjects are themselves associated with excess mortality, there may be an indirect association with mortality.[87] Severe but not mild PsO may be associated with an increased risk of death. For example, Pearce et al. reported a mortality rate of 1.5% among subjects hospitalized for PsO exacerbations.[88] Subjects with severe PsO demonstrated an increased overall mortality risk (HR 1.4; 95% CI 1.3, 1.6) after adjustment for other risk factors. A large longitudinal retrospective cohort study using THIN (GP EMR database) identified cases with age 18-89 years between 1994-2010, and found death rate of 12.12 deaths per 1000 PYs (22.19 for those on DMARDs, 11.92 for those without DMARDs) across all PsO severities.[22] Additionally, both male and female subjects with severe PsO died 3.5 (95% CI 1.2, 5.8) and 4.4 (95% CI 2.2, 6.6) years younger, respectively, than subjects without PsO ($p<0.001$).[89]

Indication: Paediatric Plaque Psoriasis

Incidence: A single study was identified from the review of published literature of the incidence of PsO in children. The study was conducted in the US over a 30-year period and found the IR of PsO to be 40.8 (95% CI 36.6, 45.1) per 100,000 PYs between 1970 and 1999. The IR of PsO was slightly higher in girls than in boys (43.9 [95% CI 37.6, 50.2] vs 37.9 [95% CI 32.2, 43.6] per 100,000 PYs), although the difference was not statistically significant. The data showed a rise in the incidence of PsO between 1970 and 2000.[79]

Prevalence: A systematic review identified 14 studies that examined the prevalence (mostly lifetime prevalence) of PsO by age. Psoriasis was rare before 9 years of age, and prevalence for PsO in children (defined as those aged <18 years) varied from 0% (Norway) to 0.55% (UK).[79]

Overall, the true prevalence of PsO in the paediatric population is unknown due to the small number of reported studies. However, it is estimated that 30% to 45% of affected subjects develop signs of disease before adolescence.[90] Psoriasis represents 4.1% of all dermatoses seen in children under the age of 16 in Europe and North America.[91] In affected cases, 10% experience disease onset prior to 10 years of age, 6.5% before age 5, and 2% at less than 2 years of age, with a small but significant number of cases developing during infancy.[92]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease: The reported age distribution of PsO in children varies considerably between studies partly due to the inclusion or exclusion of psoriatic diaper rash. Nanda et al. excluded diaper rash and reported a peak age of onset for paediatric PsO to be between 2 and 8 years.[93] Another study found 27% of children to be less than 2 years old at disease onset.[94]

Several studies have reported that the number of females affected with childhood PsO (birth to 12 years) is higher than that of males.[90] In a study of 190 cases of childhood PsO subjects in Kuwait, the female to male ratio was 1.5:1.0. However, another large study by the US Psoriasis Research Institute found an equal gender distribution in the paediatric PsO population.

The incidence of PsO for children is highest among whites, less common among blacks, and even less so among East Asians and Native Americans.[95]

The role of environmental factors in the pathogenesis of PsO remains largely unknown. Several environmental factors, such as high body mass index (BMI), environmental tobacco smoke exposure at home, and stressful life events may influence the development of paediatric psoriasis.[96] Studies have demonstrated percentages of PsO in family members with children with PsO of up to 71%.[96] Özden at al. found a genetic predisposition in children with PsO, a familial distribution with an average of 28% was described. In addition, this study also showed that environmental tobacco smoke exposure was associated with paediatric PsO, a risk that has been well demonstrated in adults.[96]

Boccardi et al. demonstrated a positive association between paediatric PsO and overweight (OR 3.38; 95% CI 1.5, 7.30). They concluded that PsO should be accepted as a consequence

of childhood obesity. However, this study was conducted with a limited number of paediatric patients (n = 96).[97]

The main existing treatment options: No treatment guidelines exist for paediatric PsO. Treatment options include topical agents, phototherapy, and systemic agents (including biologic therapies), which may be used alone, in combination, or on a rotating basis. For the majority of topical agents, safety and efficacy has not been established in paediatric patients. Notable exceptions include Elocon® (mometasone furoate) and Aclovate® (alclometasone dipropionate), both of which are topical corticosteroids.

Topical corticosteroids are the most common therapy for plaque PsO among children of all age groups, and may be used in combination with other agents. Steroid-sparing agents such as calcipotriene (vitamin D analog) are also effective, as are topical retinoids, although skin irritation may result with the latter. Other agents include anthralin and coal tar, both of which have limitations in terms of tolerability and convenience.

Phototherapy (UVB, PUVA) is generally considered second-line therapy in children. Narrow-band UVB in children with widespread disease is often effective when topical agents alone have failed. PUVA is used with caution in children because of safety concerns, namely long-term risk of carcinogenesis. Access to phototherapy (particularly narrow-band UVB) outside of academic centers varies by region and may influence treatment decisions.

Systemic agents are typically reserved for patients who fail to respond to less aggressive measures. Acitretin is the only systemic drug approved in certain European countries for the treatment of severe plaque PsO in children, and it is associated with numerous safety concerns (hepatotoxicity, birth defects, potential effects on growth, and skeletal development). Acitretin is therefore recommended for use only in patients who are refractory to less aggressive measures. Immunomodulators such as cyclosporine and MTX, which can be effective in adult PsO, are also used in children who have failed conventional therapy.[98]

Recently the following treatments have been approved for treatment of psoriasis in children: a topical combination corticosteroid-vitamin D3 analog (calcipotriene and betamethasone dipropionate 0.005%/0.064%, Taclonex), and the biologics ustekinumab (Stelara), adalimumab (Humira), and etanercept (Enbrel), but the topical product and ustekinumab are only approved in adolescents aged 12 years and older.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Review of the published literature did not identify any epidemiologic studies of paediatric PsO and mortality.

SI.2. Important co-morbidities Found in the Target Population

Important co-morbidities associated with various indications of etanercept are summarized in Table 1.

Table 1. Summary of Co-morbid Conditions Associated with the Various Indications for Etanercept

Indication	Co-morbidities
Rheumatoid arthritis	Septic arthritis[99,100]
	Interstitial lung disease[5,101,102]
	Eye inflammation (scleritis) [103]
	Osteoporosis and fractures[99,102,104,105]
	Anaemia[102,106,107]
	Cardiovascular disease[102,108,109]
	Depression[110]
	Malignancies[111,112,113]
Juvenile idiopathic arthritis	Growth retardation[114,115,116]
	Osteopenia[117,118,119]
	Uveitis[120,121,122]
	Diabetes[123,124]
Adult psoriasis	Cardiovascular disease[125,126,127,128]
	Metabolic syndrome[126,129]
	Cutaneous malignancies[130,131,132,133,134]
	Inflammatory bowel disease (Crohn's and ulcerative colitis)[135,136,137]
	Non-alcoholic fatty liver disease[138,139,140]
	Psoriatic arthritis[141,142,143]
Paediatric psoriasis	Hypertension[144,145]
	Diabetes[146,147]
	Inflammatory bowel disease[146]
Psoriatic arthritis	Cardiovascular disease[148,149,150,151]
	Inflammatory bowel disease[152,153]
	Uveitis[154,155]
	Diabetes mellitus[156,157]
Ankylosis spondylitis	Cardiovascular disease[158,159,160]
	Osteoporosis and fractures[161,162]
	Lung disease[163,164]
	Uveitis[165,166]
	Inflammatory bowel disease[167,168]
Non-radiographic axial spondyloarthritis	Depression[169]

Module SII. Non-Clinical Part of the Safety Specification

A summary of key safety findings with implications for the risk profile of etanercept is presented below. These data were generated using etanercept manufactured via serum-containing processes.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Single dose toxicity studies Acute toxicology was evaluated in single-dose subcutaneous (SC) and intravenous (IV) studies in mice and rats. The estimated median lethal dose in mice and rats was >2000 mg/kg for SC administration and >1000 mg/kg for IV administration.	No relevance to human usage: these are single dose studies to determine actual doses for more relevant repeated dosing studies.
Repeat-dose toxicity Toxicity was evaluated in multiple-dose SC, IV, and inhaled studies in cynomolgus monkey for up to 26 weeks. Conclusions from the 26-week SC study were that twice weekly (BIW) SC administration of etanercept to cynomolgus monkeys did not elicit dose-limiting or systemic toxicity at dosages up to and including 15 mg/kg. This no-toxic-effect-level (NTEL; 15 mg/kg) was associated with a week 26 serum etanercept area under concentration-time curve from 0 to 96 hours (AUC(0 96)) value of 9328 µg•h/mL; this value was approximately 40-fold higher than the mean area under concentration time curve from time 0 extrapolated to infinite time (AUC(0 oo)) value in humans (235 µg•h/mL) after a single SC dose of 25 mg. In the 26-week SC study, anti-etanercept antibodies were first detected at week 5 (12 of 12 animals in the 1 mg/kg group and 11 of 12 animals in the 5 and 15 mg/kg groups) and were evident in all etanercept-treated cynomolgus monkeys at week 9 and thereafter. Neutralizing antibodies were detected at week 5 in 1 of 12 cynomolgus monkeys in the 1 mg/kg group and in 1 to 3 cynomolgus monkeys in each of the compound-treated groups during subsequent treatment weeks. There is no explanation for the apparent formation of anti-etanercept antibodies in 2 control animals.	Etanercept is not expected to pose a risk of systemic toxicity in humans. Antibodies to protein components of the etanercept drug product have been detected in the sera of adult patients; these antibodies were all non-neutralizing and were generally transient.
Reproductive Developmental and perinatal/postnatal toxicity studies were conducted in rats and rabbits. Daily SC administration of etanercept to pregnant rats did not elicit maternal, foetal, or perinatal/early postnatal toxicity at dosages up to and including 30 mg/kg, which was associated with a maternal area under concentration-time curve from 0 to 24 hours (AUC (0 24)) of 2026 µg•h/mL. This value was approximately 26 times higher than the projected human exposure adjusted for daily dosing (78.3 µg•h/mL). Daily SC administration of etanercept to pregnant rabbits did not elicit maternal or foetal toxicity at dosages up to and including 40 mg/kg, which was associated with a maternal AUC (0 24) of 2446 µg•h/mL. This value was approximately 31 times higher than the projected human exposure adjusted for daily dosing (78.3 µg•h/mL).	Etanercept is not expected to pose a risk to the foetus; however, animal reproduction studies are not always predictive of human response.
Genotoxicity Etanercept was not genotoxic in 3 in vitro assays (the *Salmonella typhimurium/Escherichia coli* reverse mutation assay, the mammalian cell forward mutation assay in mouse lymphoma cells, and the chromosome aberration assay in cultured human peripheral blood lymphocytes) and 1 in vivo assay (the mouse micronucleus test).	Etanercept is not expected to pose a risk of genotoxicity in humans.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Effects of general activity and behaviour, mice Etanercept was administered to male mice (3/group) at single SC dosages of 0, 15, 50, or 150 mg/kg. There was no mortality and no effects on general activity and behaviour.	Etanercept is not expected to pose a risk on general activity and behaviour in humans.
Effects on smooth muscle, isolated guinea pig ileum Etanercept at a concentration of 100 µg/mL had no effect on the contractile responses to acetylcholine chloride, histamine dihydrochloride, and barium chloride, or on spontaneous motility of isolated guinea pig ileum.	Etanercept is not expected to pose a risk on smooth muscle function in humans.
Effects on water and electrolyte metabolism, rats Etanercept was administered to male rats (5/group) at single SC dosages of 0, 5, 15, or 50 mg/kg. There were no effects on urine volume, urinary pH, or excretion of electrolytes.	Etanercept is not expected to pose a risk on electrolytes in humans.
Central nervous system (CNS) pharmacology Etanercept was administered to mice (5 or 10/group) at single SC dosages of 0, 5, 15, or 50 mg/kg. There were no effects on the central nervous system (CNS) as assessed by evaluation of mortality, spontaneous motor activity, thiopental induced sleeping time, electroshock-induced convulsions, pentylenetetrazole induced convulsions, and analgesic activity. Etanercept was administered to male rats (6/group) at single SC dosages of 0, 5, 15, or 50 mg/kg. There were no effects on the CNS as assessed by rectal temperature.	Etanercept is not expected to pose a risk of CNS toxicity in humans.
Digestive system safety pharmacology, mice Etanercept was administered to male mice (5/group) at single SC dosages of 0, 5, 15, or 50 mg/kg. There were no effects on the digestive system as assessed by evaluation of gastrointestinal transit time.	Etanercept is not expected to pose a risk on the digestive system in humans.
Respiratory safety pharmacology, rabbits Etanercept was administered to 4 male rabbits as an IV infusion (30 minutes) at ascending dosages of 0, 1, 3, and 10 mg/kg. There were no effects on respiratory rate.	Etanercept is not expected to pose a risk on the respiratory system in humans.
Cardiovascular safety pharmacology *Rats:* Etanercept was administered to conscious rats (3/sex) at a single SC dosage of 0 or 30 mg/kg. There were no mortalities or changes in heart rate, blood pressure, or gross spontaneous motor activity. *Rabbits:* Etanercept was administered to 4 male rabbits as an IV infusion (30 minutes) at ascending dosages of 0, 1, 3, and 10 mg/kg. There were no effects on arterial blood pressure, heart rate, femoral arterial blood flow, or electrocardiogram (ECG). *Monkeys:* Etanercept was administered to conscious cynomolgus monkeys (3/sex) at a single SC dosage of 0 or 15 mg/kg. There were no mortalities or consistent pattern of statistically significant changes in heart rate, blood pressure, or ECGs.	Etanercept is not expected to pose a direct risk on the cardiovascular system in humans via immediate changes in cardiac function.

AUC = area under concentration time curve; BIW = twice weekly; CNS = central nervous system; ECG = electrocardiogram; IV = intravenous; NTEL = no-toxic-effect-level; SC = subcutaneous

Module SIII. Clinical Trial Exposure

Cumulatively through 15 August 2024, it is estimated that 29,726 participants have participated in the Sponsor initiated (Pfizer and Amgen) etanercept clinical development

program with 26,958 participants exposed to etanercept, either as a monotherapy or in combination with comparators.

A total of 23,146 subjects were included in the analysis for this RMP as only centrally managed studies for which clinical databases were available are included in this analysis. The following tables provide details on exposure in patients treated with etanercept for the approved indications (RA, JIA, PsA, AS, nr-AxSpA, and adult and paediatric PsO).

The exposures in Table 3, Table 4, Table 5 and Table 6 were calculated from all completed clinical studies conducted by the MAH and Amgen that had a completed database available as of 31 August 2019 for the approved indications. Exposure data from studies B1801023 and B1801381 include data through 12 July 2019 and 12 June 2019, respectively.

Exposure is presented for the overall population, as well as by indication (Table 3), by duration of exposure (Table 4), by age group (Table 5), by gender (Table 6), and by race (Table 7). Exposure is not presented by dose since there is only one tested dosage of etanercept in adults. Special populations (e.g., pregnant women, lactating women, renal impairment, hepatic impairment, cardiac impairment, immunocompromised) have been excluded from clinical studies.

Table 3. Etanercept Exposure in Double-blind and Open-label Studies by Indication and Overall

Indication	Etanercept Exposure (PYs)	Number of Patients
Rheumatoid Arthritis[a]	16948.47	9926
Juvenile Idiopathic Arthritis[b,c]	1944.27	642
eoJIA[d]	300.79	60
ERA[d]	198.65	38
Paediatric PsA[d]	150.98	29
Psoriatic Arthritis	1722.09	2891
Axial Spondyloarthritis[e]	1639.49	1651
Psoriasis	6410.01	7826
Paediatric Psoriasis	840.03	210
All Indications	29504.36	23146

a. Etanercept exposure during the double-blind treatment phase for study 0881A1-4423 was excluded from the calculation for patients who were randomised to placebo.
b. The sum of JIA subtypes does not equal the total in the JIA row.
c. Data from studies 0881A1-3338, B1801023, 16.0016, 16.0018.
d. Data from studies 0881A1-3338, B1801023.
e. Axial spondyloarthritis includes ankylosing spondyloarthritis and non-radiographic axial spondyloarthritis.

Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient years
Source: exp4_rmp_indic – 24OCT19 – 14:42

Table 4. Etanercept Exposure in Double-blind and Open-label Studies by Time Interval for Each Indication and Overall

Indication	Time Interval	Etanercept Exposure (PYs) per Time Interval	Number of Patients Exposed per Time Interval
Rheumatoid arthritis[a]	0-6 months	3912.25	9926
	6-12 months	2216.91	5114
	12-18 months	1592.74	3882
	18-24 months	1360.37	3116
	24-30 months	994.50	2429
	30-36 months	802.44	1719
	36-42 months	731.84	1568
	42-48 months	669.51	1413
	48-54 months	588.74	1315
	54-60 months	529.90	1117
	60-66 months	453.43	1029
	66-72 months	337.71	744
	72-78 months	323.37	665
	78-84 months	312.73	647
	84-90 months	302.86	622
	90-96 months	292.33	608
	96-102 months	277.91	582
	102-108 months	262.77	549
	108-114 months	236.64	509
	114-120 months	215.07	454
	120-132 months	382.60	424
	132-144 months	135.90	301
	> 144 months	15.95	52
	Total	16948.47	9926
Juvenile Idiopathic Arthritis[b,c]	0-6 months	299.30	642
	6-12 months	263.69	564
	12-18 months	240.21	510
	18-24 months	213.48	463
	24-30 months	186.85	405
	30-36 months	163.38	356
	36-42 months	84.07	264
	42-48 months	61.19	134
	48-54 months	53.85	114
	54-60 months	50.44	106
	60-66 months	47.74	100
	66-72 months	44.73	95
	72-78 months	40.16	85
	78-84 months	37.35	78
	84-90 months	34.49	72
	90-96 months	33.18	69
	96-102 months	28.11	64
	102-108 months	22.55	51
	108-114 months	14.38	40
	114-120 months	8.87	18
	120-132 months	14.83	18
	132-144 months	1.41	8

Table 4. Etanercept Exposure in Double-blind and Open-label Studies by Time Interval for Each Indication and Overall

Indication	Time Interval	Etanercept Exposure (PYs) per Time Interval	Number of Patients Exposed per Time Interval
	Total	1944.27	642
eoJIA[d]	0-6 months	28.44	60
	6-12 months	28.09	57
	12-18 months	27.42	57
	18-24 months	26.26	55
	24-30 months	23.24	50
	30-36 months	20.56	45
	36-42 months	18.30	39
	42-48 months	17.22	36
	48-54 months	16.38	34
	54-60 months	14.52	32
	60-66 months	12.77	28
	66-72 months	11.61	25
	72-78 months	10.35	21
	78-84 months	10.35	21
	84-90 months	9.36	21
	90-96 months	8.87	18
	96-102 months	8.42	18
	102-108 months	6.32	15
	108-114 months	2.31	9
	Total	300.79	60
ERA[d]	0-6 months	17.75	38
	6-12 months	16.75	35
	12-18 months	15.94	33
	18-24 months	14.91	31
	24-30 months	14.30	30
	30-36 months	14.16	29
	36-42 months	31.21	28
	42-48 months	11.57	24
	48-54 months	10.48	22
	54-60 months	10.23	21
	60-66 months	9.86	20
	66-72 months	9.39	20
	72-78 months	8.19	18
	78-84 months	6.50	14
	84-90 months	5.91	12
	90-96 months	5.91	12
	96-102 months	5.42	11
	102-108 months	5.42	11
	108-114 months	2.75	11
	Total	198.65	38
Paediatric PsA[d]	0-6 months	13.97	29
	6-12 months	13.72	28
	12-18 months	13.31	27
	18-24 months	11.92	27
	24-30 months	9.36	19

Table 4. Etanercept Exposure in Double-blind and Open-label Studies by Time Interval for Each Indication and Overall

Indication	Time Interval	Etanercept Exposure (PYs) per Time Interval	Number of Patients Exposed per Time Interval
	30-36 months	9.36	19
	36-42 months	9.13	19
	42-48 months	8.38	17
	48-54 months	8.24	17
	54-60 months	7.89	16
	60-66 months	7.89	16
	66-72 months	7.00	16
	72-78 months	6.41	13
	78-84 months	6.32	13
	84-90 months	5.91	12
	90-96 months	5.60	12
	96-102 months	4.30	11
	102-108 months	1.85	6
	108-114 months	0.45	2
	Total	150.98	29
Psoriatic Arthritis	0-6 months	1256.33	2891
	6-12 months	321.66	820
	12-18 months	79.53	170
	18-24 months	62.08	154
	24-30 months	2.50	55
	Total	1722.09	2891
Axial Spondyloarthritis[e]	0-6 months	574.97	1651
	6-12 months	283.25	627
	12-18 months	233.43	511
	18-24 months	186.55	435
	24-30 months	108.85	284
	30-36 months	97.67	209
	36-42 months	75.92	185
	42-48 months	38.82	119
	48-54 months	20.24	45
	54-60 months	17.15	39
	60-66 months	2.64	21
	Total	1639.49	1651
Psoriasis	0-6 months	3244.97	7826
	6-12 months	1142.75	2509
	12-18 months	709.42	2051
	18-24 months	582.09	1296
	24-30 months	435.83	1071
	30-36 months	165.16	664
	36-42 months	65.46	143
	42-48 months	53.33	119
	48-54 months	11.00	72
	Total	6410.01	7826
Paediatric Psoriasis	0-6 months	100.67	210
	6-12 months	94.15	199
	12-18 months	85.40	178

Table 4. Etanercept Exposure in Double-blind and Open-label Studies by Time Interval for Each Indication and Overall

Indication	Time Interval	Etanercept Exposure (PYs) per Time Interval	Number of Patients Exposed per Time Interval
	18-24 months	79.47	168
	24-30 months	72.94	153
	30-36 months	64.40	142
	36-42 months	59.05	124
	42-48 months	53.77	116
	48-54 months	46.21	101
	54-60 months	40.98	88
	60-66 months	37.19	79
	66-72 months	29.02	72
	72-78 months	15.01	42
	78-84 months	12.65	28
	84-90 months	10.45	24
	90-96 months	8.83	19
	96-102 months	7.61	16
	102-108 months	6.56	14
	108-114 months	4.50	12
	114-120 months	3.43	7
	120-132 months	4.87	6
	132-144 months	2.31	4
	> 144 months	0.56	1
	Total	840.03	210
All Indications	0-6 months	9388.44	23146
	6-12 months	4322.40	9833
	12-18 months	2940.74	7302
	18-24 months	2484.03	5632
	24-30 months	1801.48	4397
	30-36 months	1293.06	3090
	36-42 months	1016.34	2284
	42-48 months	876.62	1901
	48-54 months	720.03	1647
	54-60 months	638.48	1350
	60-66 months	541.00	1229
	66-72 months	411.46	911
	72-78 months	378.54	792
	78-84 months	362.74	753
	84-90 months	347.80	718
	90-96 months	334.33	696
	96-102 months	313.63	662
	102-108 months	291.89	614
	108-114 months	255.52	561
	114-120 months	227.37	479
	120-132 months	402.30	448
	132-144 months	139.62	313
	> 144 months	16.51	53
	Total	29504.39	23146

Table 4. Etanercept Exposure in Double-blind and Open-label Studies by Time Interval for Each Indication and Overall

Indication	Time Interval	Etanercept Exposure (PYs) per Time Interval	Number of Patients Exposed per Time Interval

a. Etanercept exposure during the double-blind treatment phase for study 0881A1-4423 was excluded from the calculation for patients who were randomised to placebo.
b. The sum of JIA subtypes does not equal the total in the JIA row.
c. Data from studies 0881A1-3338, B1801023, 16.0016, 16.008.
d. Data from studies 0881A1-3338, B1801023.
e. Axial Spondyloarthritis includes ankylosing spondyloarthritis and non-radiographic axial spondyloarthritis.
Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient year.
Source: exp4_rmp_indic_dur – 24OCT19 – 14:43

Table 5. Etanercept Exposure in Double-blind and Open-label Studies by Age Category for Each Indication and Overall

Indication	Age Interval (years)	Etanercept Exposure (PY) per Time Interval	Number of Patients Exposed per Time Interval
Rheumatoid Arthritis[a]	≥18 to <65	14440.53	8212
	≥65	2507.95	1714
	Total	16948.47	9926
Juvenile Idiopathic Arthritis[b,c]	<5	197.14	74
	≥5 to <12	712.99	244
	≥12 to <18	1007.71	311
	≥18 to <65	26.43	13
	Total	1944.27	642
eoJIA[d]	<5 yrs	49.39	10
	≥5 to <12 yrs	130.35	23
	≥12 to <18 yrs	106.71	22
	≥18 to <65	14.33	5
	Total	300.79	60
ERA[d]	≥12 to <18 yrs	198.65	38
	Total	198.65	38
Paediatric PsA[d]	≥12 to <18 yrs	150.98	29
	Total	150.98	29
Psoriatic Arthritis	≥18 to <65 yrs	1568.58	2609
	≥65 yrs	153.51	282
	Total	1722.09	2891
Axial Spondyloarthritis[e]	≥18 to <65 yrs	1630.62	1629
	≥65 yrs	8.87	22
	Total	1639.49	1651
Psoriasis	≥18 to <65 yrs	5971.21	7225
	≥65 yrs	438.80	601
	Total	6410.01	7826
Paediatric Psoriasis	<5 yrs	11.66	5
	≥5 to <12 yrs	360.57	71
	≥12 to <18 yrs	467.80	134

Table 5. Etanercept Exposure in Double-blind and Open-label Studies by Age Category for Each Indication and Overall

Indication	Age Interval (years)	Etanercept Exposure (PY) per Time Interval	Number of Patients Exposed per Time Interval
	Total	840.03	210
All Indications	<5 yrs	208.79	79
	≥5 to <12 yrs	1073.56	315
	≥12 to <18 yrs	1475.51	445
	≥18 to <65 yrs	23637.37	19688
	≥65 yrs	3109.13	2619
	Total	29504.36	23146

a. Etanercept exposure during the double-blind treatment phase for study 0881A1-4423 was excluded from the calculation for patients who were randomised to placebo.
b. The sum of JIA subtypes does not equal the total in the JIA row.
c. Data from studies 0881A1-3338, B1801023, 16.0016, 16.0018.
d. Data from studies 0881A1-3338, B1801023.
e. Axial Spondyloarthritis includes ankylosing spondyloarthritis and non-radiographic axial spondyloarthritis.
Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient years
Source: exp4_rmp_indic_age - 24OCT19 – 14:43

Table 6. Etanercept Exposure in Double-blind and Open-label Studies by Gender for Each Indication and Overall

Indication	Gender	Etanercept Exposure (PY)	Number of Patients
Rheumatoid Arthritis[a]	Male	3617.63	2050
	Female	13330.84	7876
	Total	16948.47	9926
Juvenile Idiopathic Arthritis[b,c]	Male	630.40	190
	Female	1313.87	452
	Total	1944.27	642
eoJIA[d]	Male	111.75	19
	Female	189.04	41
	Total	300.79	60
ERA[d]	Male	163.55	30
	Female	35.11	8
	Total	198.65	38
Paediatric PsA[d]	Male	31.84	6
	Female	119.15	23
	Total	150.98	29
Psoriatic Arthritis	Male	947.67	1604
	Female	774.42	1287
	Total	1722.09	2891
Axial Spondyloarthritis[e]	Male	1153.64	1167
	Female	485.85	484
	Total	1639.49	1651
Psoriasis	Male	4310.76	5086
	Female	2099.24	2740

Table 6. Etanercept Exposure in Double-blind and Open-label Studies by Gender for Each Indication and Overall

Indication	Gender	Etanercept Exposure (PY)	Number of Patients
	Total	6410.01	7826
Paediatric Psoriasis	Male	413.51	108
	Female	426.52	102
	Total	840.03	210
All Indications	Male	11073.62	10205
	Female	18430.74	12941
	Total	29504.36	23146

a. Etanercept exposure during the double-blind treatment phase for study 0881A1-4423 was excluded from the calculation for patients who were randomised to placebo.
b. The sum of JIA subtypes does not equal the total in the JIA row.
c. Data from studies 0881A1-3338, B1801023, 16.0016, 16.0018.
d. Data from studies 0881A1-3338, B1801023.
e. Axial Spondyloarthritis includes ankylosing spondyloarthritis and non-radiographic axial spondyloarthritis.
Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient years
Source: exp4_rmp_indic_sex - 24OCT19 – 14:41

Table 7. Etanercept Exposure in Double-blind and Open-label Studies by Race for Each Indication and Overall

Indication	Race	Etanercept Exposure (PY)	Number of Patients Exposed
Rheumatoid Arthritis[a]	White	14124.86	7438
	Black	380.79	263
	Asian	1199.10	1349
	Other	1243.73	876
	Total	16948.47	9926
Juvenile Idiopathic Arthritis[b,c]	White	1567.96	472
	Black	68.98	40
	Asian	78.10	47
	Other	229.23	83
	Total	1944.27	642
eoJIA[d]	White	282.05	55
	Other	18.74	5
	Total	300.79	60
ERA[d]	White	172.37	32
	Asian	3.33	1
	Other	22.96	5
	Total	198.65	38
Paediatric PsA[d]	White	149.14	28
	Other	1.84	1
	Total	150.98	29
Psoriatic Arthritis	White	1534.37	2547
	Black	27.25	47
	Asian	39.74	83
	Other	120.73	214

Table 7. Etanercept Exposure in Double-blind and Open-label Studies by Race for Each Indication and Overall

Indication	Race	Etanercept Exposure (PY)	Number of Patients Exposed
	Total	1722.09	2891
Axial Spondyloarthritis[e]	White	1443.70	1327
	Black	3.23	6
	Asian	124.02	247
	Other	68.54	71
	Total	1639.49	1651
Psoriasis	White	5657.39	6710
	Black	131.05	215
	Asian	223.78	328
	Other	387.78	560
	Missing	10.00	13
	Total	6410.01	7826
Paediatric Psoriasis	White	633.49	157
	Black	46.50	11
	Asian	61.11	15
	Other	98.92	27
	Total	840.03	210
All Indications	White	24961.78	18651
	Black	657.79	582
	Asian	1725.85	2069
	Other	2148.94	1831
	Missing	10.00	13
	Total	29504.36	23146

a. Etanercept exposure during the double-blind treatment phase for study 0881A1-4423 was excluded from the calculation for patients who were randomised to placebo.
b. The sum of JIA subtypes does not equal the total in the JIA row.
c. Data from studies 0881A1-3338, B1801023, 16.0016, 16.0018.
d. Data from studies 0881A1-3338, B1801023.
e. Axial Spondyloarthritis includes ankylosing spondyloarthritis and non-radiographic axial spondyloarthritis.
Abbreviations: eoJIA=extended oligoarticular juvenile idiopathic arthritis; ERA=enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient years
Source: exp4_rmp_indic_race - 24OCT19 - 14:45

Module SIV. Populations Not Studied in Clinical Trials

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

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Hypersensitivity to the active substance or to any of the excipients	Patients cannot be treated with etanercept if they have a known or suspected allergy or intolerance to etanercept or any components of the investigational product.	Not considered missing information. Hypersensitivity to the active substance or to any of the excipients is listed as a contraindication for etanercept in section 4.3 of the SmPC.
Sepsis or risk of sepsis	Patients cannot be treated with etanercept if they have sepsis or at risk of acquiring sepsis.	Not considered missing information. Sepsis or risk of sepsis is listed as a contraindication for etanercept in section 4.3 of the SmPC.
Active infections, including chronic or localized infections	Patients cannot be treated with etanercept if they have an active infection, including chronic or localized infection.	Not considered missing information. The SmPC states in section 4.3 that treatment with etanercept should not be initiated in patients with active infections, including chronic or localized infections.
Any major illness/condition or any serious disorder that would increase the risks associated with the studies	This exclusion criterion was included with the caveat that, in the investigator's judgment, the condition would increase the risk associated with the subject's participation in and completion of the study, or could preclude the evaluation of the subject's response or interfere with the subject's ability to give informed consent.	Not considered missing information. Cases seen in the post-marketing setting, where patients with other illnesses/conditions or serious disorders were treated with etanercept did not suggest a difference in the safety profile of etanercept.
Pregnant or breastfeeding female subjects	This exclusion criterion was included to ensure uniformity of the clinical trial population and because the safe use of etanercept had not been definitively established in this population.	Not considered missing information. The SmPC states in section 4.6 that the effects of etanercept on pregnancy outcomes have been investigated in 2 observational cohort studies. It also states that etanercept should only be used during pregnancy if clearly needed, and that a decision must be made whether to discontinue breast-feeding or to discontinue etanercept therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Active uveitis	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results. To reduce the potential risk of worsening of the active uveitis.	Not considered missing information. Uveitis is listed as an adverse reaction in section 4.8 of the SmPC.

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
Receipt within 2 months before the baseline visit of any live (attenuated) vaccines	This exclusion criterion is included because of a desire to take special precautions with live vaccination because the safe use of etanercept together with live vaccination has not been established.	Not considered missing information, as no data exist to suggest a negative benefit-risk profile for etanercept in patients who receive any live (attenuated vaccines). The SmPC has language in section 4.4 stating that live vaccines should not be given concurrently with etanercept.
Cancer or history of cancer	To ensure uniformity of clinical trial population and eliminate interference from or possible recurrence of second primary malignancy during ongoing trial participation.	Not considered missing information. Various malignancies are described in section 4.4 of the SmPC and listed as adverse reactions in section 4.8 of the SmPC. In addition, malignancy (including lymphoma and leukaemia) is an important identified risk for etanercept.
History of blood dyscrasias	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information. Various blood dyscrasias are described in section 4.4 of the SmPC and listed as adverse reactions in section 4.8 of the SmPC.
History of macrophage activation syndrome (MAS)	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information. Histiocytosis haematophagic (MAS) is listed as an adverse reaction in section 4.8 of the SmPC.
History of demyelinating diseases (e.g., multiple sclerosis or optic neuritis)	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information. Demyelinating events are described in section 4.4 of the SmPC and listed as adverse reactions in section 4.8 of the SmPC. In addition, demyelinating disorders is considered an important identified risk for etanercept.
Documented immunodeficiency disease, including subjects with known human immunodeficiency virus (HIV)	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information. The SmPC states in section 4.4 that the possibility exists for TNF-antagonists, including etanercept, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.
Positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and/or hepatitis C virus (HCV)	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information. Serious and opportunistic infections (including hepatitis) are considered an important identified risk for etanercept.

Table 8. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale
History of clinically significant drug induced liver injury (DILI), liver cirrhosis or fibrosis	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information, as no data exist to suggest a negative benefit-risk profile for etanercept in patients with a history of DILI, liver cirrhosis or fibrosis.
Clinically significant laboratory or vital sign abnormalities at screening	To ensure uniformity of clinical trial population and to avoid exposure to study drug in patients that may be at increased risk due to certain laboratory abnormalities.	Not considered missing information, as no data exist to suggest a negative benefit-risk profile for etanercept in patients with significant laboratory or vital sign abnormalities.
Active tuberculosis (TB), history of tuberculosis or evidence of latent tuberculosis without initiating prophylaxis treatment.	To ensure uniformity of clinical trial population and exclude patients with active TB and those with a history of TB or evidence of latent TB without initiating prophylaxis treatment, which could potentially adversely impact clinical trial results.	Not considered missing information. Serious and opportunistic infections (including tuberculosis) are considered an important identified risk for etanercept.
History of clinically significant finding(s) on a prior chest radiograph or electrocardiogram (ECG) within 6 months before the baseline visit	To ensure uniformity of clinical trial population and exclude patients with significant co-morbidities potentially adversely impacting clinical trial results.	Not considered missing information, as no data exist to suggest a negative benefit-risk profile for etanercept in patients with a history of clinically significant finding(s) on a prior chest radiograph or ECG.

DILI = drug induced liver injury; ECG = electrocardiogram; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MAS = macrophage activation syndrome; SmPC = Summary of Product Characteristics; TNF = tumor necrosis factor; TB = tuberculosis

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions (i.e. ≥1/10,1000 to <1/1000) or very rare, adverse reactions with a long latency, or those caused by prolonged exposure and cumulative effects.

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

Table 9. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There are no adequate and well-controlled studies on the use of etanercept in pregnant and breastfeeding women. Due to very limited information, calculation of exposure is not possible.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular disease	For subjects with renal impairment, a small pharmacokinetic study (n=6) was performed in subjects with end-stage renal disease requiring dialysis. The pharmacokinetics in these subjects were similar to subjects with psoriasis not requiring dialysis.[170] No formal pharmacokinetic study has been conducted to examine the effects of hepatic impairment on etanercept disposition; however, the pharmacokinetic results from a study of 9 subjects with septic shock complicated by hepatic impairment and 14 others with septic shock complicated by both hepatic and renal failure showed similar AUC, to patients with septic shock, but no evidence of hepatic impairment. For patients with cardiovascular disease, the pharmacokinetics of etanercept in subjects with CHF (n=11) were found to be similar to those observed in healthy subjects and in subjects with RA.[171]
Population with relevant different ethnic origin	The clinical development program included multiple racial groups and geographic regions as well as different ethnicities and has not shown any differences between the groups.[172]
Subpopulations carrying relevant genetic polymorphisms	This subpopulation is not included in the clinical development program.

AUC = area under concentration time curve; CHF = congestive heart failure; RA = rheumatoid arthritis

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Worldwide patient exposure to etanercept for the cumulative period since the International Birth Date (IBD) through to the data lock-point for this RMP (15 August 2024) is estimated to be 8,601,385 patient-years (PYs).

Unit sales data for the US and Canada are provided by Amgen. The source of unit sales data outside of the US and Canada is Pfizer Global Logistics and Supply. The methodology for calculating exposure remains the same as in previous RMPs (i.e., vials and syringes sold are divided by the weekly average dose for the respective strengths to obtain patient weeks. The patient weeks are divided by 48 to obtain PYs).

Using data from Amgen and Pfizer as described, the combined exposure was estimated using the average dose of 2 vials/syringes for the 25 mg strength and 1 vial/syringe for the 50 mg strength in North America, and the 2 vials/syringes of 10 mg and 25 mg strengths and 1 vial/syringe for the 50 mg strength in markets outside North America.

Amgen and Pfizer sales data were used to determine region-wise split across indications based on the percentages of individual indication prescription to the total prescription for each region. The indication wise sum of all the totals was taken as the base data to split PYs for gender and age based on the percentages of IQVIA Health Prescription Data.

The recommended dose varies by indication and may vary by market. For most indications of etanercept, the adult dosage is 25 mg given twice weekly (BIW) or 50 mg given once weekly (QW) as an SC injection. In Japan, the 10 mg vial was launched in December 2009 and is given BIW to JIA patients and low body weight RA patients. The recommended dose of etanercept for paediatric patients aged 2 to 17 years with juvenile rheumatoid arthritis (JRA) is 0.4 mg/kg (up to a maximum of 25 mg per dose) given BIW or 0.8 mg/kg (up to a maximum of 50 mg per dose) given QW as an SC injection. In some markets, paediatric patients may dose QW. In markets outside of North America, the recommended dose of 2 vials per week for adults, containing 10 mg per vial or 25 mg per vial, is used to estimate market exposure. For North America patients who are dosing BIW, the weekly dose is 2 vials per week, containing 25 mg per vial. For PY calculations, the assumed dosage is 25 mg given BIW or 50 mg given QW as an SC injection.

Reporting cumulative estimated exposure by dose, indication, region was also obtained based on split for each indication using the region share from IQVIA data for the cumulative period. The cumulative exposure was calculated by adding the previous PYs from IBD to 10 July 2023 to the balance interval PYs from 11 July 2023 to 15 August 2024 and are presented in Table 10. Exposure estimates are prorated for the reporting period. The split for each region was multiplied by the patient days factored by dosages to obtain category wise PYs.

In the US and Canada, it is estimated that 13,742,176 vials/syringes of 25 mg and 98,993,427 vials of 50 mg etanercept have been distributed commercially during the cumulative period of IBD to 15 August 2024.

SV.1.2. Exposure

Table 10. Cumulative Estimated Exposure for Etanercept (Patient-years) (IBD to 15 August 2024)

Indication	Sex			Age (years)				Region			
	Female	Male	UNK	0-16	17-65	>65	UNK	EU	Japan	NA	ROW
RA	4,050,403	967,847	17,659	18,472	2,372,056	2,627,722	17,659	982,249	473,641	3,352,953	227,066
PsO/PsA	1,263,634	1,060,876	-	27,007	2,021,233	276,270	0	576,018	1,610	1,708,235	38,645
AS	185,924	627,909	-	78	752,407	61,348	0	392,270	-	347,041	74,522
All others	233,342	193,791	-	73,586	302,148	51,400	0	324,277	13,643	65,706	23,508
Total	5,733,303	2,850,424	17,659	119,143	5,447,844	3,016,740	17,659	2,274,814	488,894	5,473,935	363,743

Note: Patient-year data in table is rounded to the nearest whole number.
AS = ankylosing spondylitis; EU = European Union; IBD = International Birth Date; NA = North America; RA = rheumatoid arthritis; PsA; psoriatic arthritis; PsO = psoriasis; ROW = rest of world; UNK = unknown

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Given the lack of reported abuse potential due to no known mechanism associated with physiological or psychological dependency, misuse for illegal purposes are not expected to occur with this medicinal product. Etanercept has no known attributes that make it attractive for intentional overdose or illegal use.

Module SVII. Identified and Potential Risks

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

Not applicable as this is not an initial submission.

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

Not applicable.

Reason for not including an identified or potential risk 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

The following important identified risks have been removed from the RMP.

- Congestive heart failure in adult subjects
- Aplastic anaemia and pancytopenia

Rationale for the removal: No significantly increased rates of congestive heart failure in adult subjects or aplastic anaemia for etanercept have emerged during the BADBIR study, the extension study of BSR Register of Anti-TNF Treated Patients and Prospective Surveillance Study for Adverse Events Enbrel study, or within the post marketing experience. The product labelling and standards of medical care provide adequate risk mitigation.

The following important potential risk has been removed from the RMP.

- Acute ischemic CV events in adult subjects

Rationale for the removal: No new safety concerns regarding acute ischemic CV events in adult subjects for Enbrel have emerged during the BADBIR study, the extension study of BSR Register of Anti-TNF Treated Patients and Prospective Surveillance Study for Adverse

Events Enbrel study, or within the post marketing experience. The product labelling and standards of medical care provide adequate risk mitigation.

The following missing information has been removed from the RMP.

- Immunogenicity Profile and Related Clinical Outcomes of Etanercept Manufactured using the SFPHC Process in a Real-life Post-marketing Setting

Rationale for the removal: No new safety information regarding immunogenicity for etanercept using the SFPHC Process have emerged during the extension study of BSR Register of Anti-TNF Treated Patients and Prospective Surveillance Study for Adverse Events Enbrel study. Also, in the post-marketing experience, no new safety trends were observed during routine pharmacovigilance for etanercept due to SFPHC changes. The product labelling and standards of medical care provide adequate risk mitigation.

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

The risk analyses associated with clinical data presented in the following sections are based on etanercept clinical studies across the approved indications conducted by the MAH and Amgen as of 31 August 2019 (except for studies B1801381 and B1801023 that have data lock points of 12 June 2019 and 12 July 2019, respectively). Data provided from the post-marketing safety database has a data lock point of 15 August 2024. A pivotal registration study (Registry study 20021626 [formerly 16.0026]) in patients with JIA was also included in the analyses as requested by a Health Authority. The clinical and safety databases were searched using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and version 27.0, respectively. All events identified in the clinical database that occurred in subjects who had received at least 1 dose of etanercept to date of last dose in the study plus 30 days were included. In addition, the safety database was searched to ensure that all fatal cases originating from clinical trials including after the 30-day period are included in this update.

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

SVII.3.1.1. Important Identified Risks

SVII.3.1.1.1. Important Identified Risk: Malignancy (Including Lymphoma and Leukaemia)

SVII.3.1.1.1.1. Potential Mechanisms

There may be an increased rate of malignancy in some of the conditions for which etanercept is indicated (such as RA), but the potential role of TNF-alpha inhibition in malignancies is not well understood.

SVII.3.1.1.1.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.1.1.3. Characterisation of the Risk

Frequency

In the clinical database, 340 (1.47%) subjects experienced 413 malignancy-related events. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- RA: 1.530 (1.348, 1.730)
- JIA: 0.051 (0.001, 0.287)
  eoJIA: 0.333 (0.008, 1.853)
- Adult PsA: 1.046 (0.620, 1.653)
- Axial Spondyloarthritis (AxSpA): 0.736 (0.380, 1.286)
- Adult PsO: 1.998 (1.666, 2.377)
- All Indications: 1.417 (1.283, 1.560)

Seriousness/Outcomes

Clinical Trials:

In the clinical database, there were 413 malignancy-related events reported. Of these events, 285 (69.01%) were serious, 102 (24.70%) were resolved, 79 (19.13%) were not resolved, and 232 (56.17%) had unknown outcome. The most common (≥2%) events are summarized in the table below.

Table 11. Reported Events, Seriousness, and Outcomes from Clinical Trials – Malignancies

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Basal cell carcinoma	86	29	22	1	63
Breast cancer	31	30	10	9	12
Prostate cancer	31	28	4	14	13
Squamous cell carcinoma	28	11	4	2	22
Squamous cell carcinoma of skin	18	7	3	0	15
Malignant melanoma	12	11	5	2	5
Lung neoplasm malignant	11	11	2	6	3
Colon cancer	10	10	4	2	4

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were 38 serious malignancy-related events with a fatal outcome involving 34 subjects originating from clinical trials in the safety database. The fatal events reported more than once coded to PTs Lung neoplasm malignant (5), Neoplasm malignant, Metastasis, Lung cancer metastatic, and Ovarian cancer (2 each).

Post-Marketing:

In the post-marketing experience, since first approval through 15 August 2024, there have been 19,045 cases received by the MAH reporting 21,132 relevant malignancy-related AEs.

Table 12. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Malignancies

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Breast cancer	1374	1374	343	14	308	0	297	735
Neoplasm malignant	1229	1228	121	104	76	2	172	875
Basal cell carcinoma	968	967	92	0	354	15	123	481
Lung neoplasm malignant	886	886	262	157	90	6	195	438
Skin cancer	893	892	51	1	187	2	119	584
Lymphoma	861	861	169	58	114	0	186	503
Malignant melanoma	780	780	89	11	204	14	92	461
Prostate cancer	735	735	141	9	117	9	204	396
Breast cancer female	712	712	165	3	102	9	112	486
Colon cancer	444	444	172	25	98	7	72	242
Squamous cell carcinoma	410	409	63	5	122	3	64	216
All others	11,840	11,355	3757	1139	2118	186	2930	5488
Total	21,132	20,643	5425	1526	3890	253	4566	10,905

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

Of the 413 malignancies in the clinical database, 88 (21.31%) events were mild, 93 (22.52%) were moderate, 94 (22.76%) were severe, 1 (0.24%) was very severe, 34 (8.23%) were life-threatening, 1 (0.24%) was fatal, and 102 (24.70%) had unknown severity. The severity of the most common events (≥2%) is summarized in the table below.

Table 13. Severity of Malignancies from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Basal cell carcinoma	39	34	6	0	0	0	7	86
Breast cancer	1	2	16	0	1	0	11	31
Prostate cancer	3	4	14	0	0	0	10	31
Squamous cell carcinoma	7	16	3	0	0	0	2	28
Squamous cell carcinoma of skin	7	7	1	0	0	0	3	18
Malignant melanoma	1	1	6	0	1	0	3	12
Lung neoplasm malignant	0	1	2	0	1	0	7	11
Colon cancer	0	2	4	0	2	0	2	10

F = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

SVII.3.1.1.1.4. Risk Factors and Risk Groups

Overall risk of malignancy including cutaneous and non-cutaneous cancers in subjects with RA and PsO has been reported to be higher than that observed in healthy subjects.

SVII.3.1.1.1.5. Preventability

The potential role of TNF-blocking therapy in the development of malignancies is not known. There are no known preventable actions.

SVII.3.1.1.1.6. Impact on the Risk-Benefit Balance of the Product

Malignancy can severely impact a patient's quality of life. While specific potential effects on an individual patient depend upon a variety of factors including site of malignancy, tolerance of therapy, and degree of social and emotional support, malignancy can cause psychological distress due to the gravity of the diagnosis and fear about its effects and possible recurrence. In addition, it can directly impact a patient's physical functioning and lifespan.

SVII.3.1.1.1.7. Public Health Impact

Autoimmune diseases, such as RA, are known to be associated with an increased risk of malignancy. In the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) study (protocol B1801311), there was a significantly increased risk of malignant events (adjusted hazard ratio 1.49; 95% confidence interval 1.13, 1.95) for psoriasis patients currently or previously receiving etanercept, compared with patients treated with conventional systemic therapy. Additionally, etanercept-treated patients were at a significantly increased risk of skin cancer (adjusted hazard ratio 1.75; 95% confidence interval 1.15, 2.66) and solid tumours (adjusted hazard ratio 1.52; 95% confidence interval 1.06, 2.19). There were no malignancies reported in the PURPOSE study (a long-term, prospective observational cohort study of the safety and effectiveness of etanercept in the treatment of paediatric psoriasis patients in Germany, France, Italy, Greece, Spain, Austria, Netherlands, Portugal, and Hungary [protocol 0881X1-4654]). In the British Society for Rheumatology Biologics Register (BSRBR) registry protocol B1801309, the incidence rate of malignancy in etanercept treated patients was 1.51 per 100 PYs, which was lower than the rate observed in patients treated with csDMARDs (2.45 per 100 PYs). As of 15 August 2024, there have been 19,045 cases of malignancy received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 patient-years (estimated reporting rate of 0.22 per 100 patient-years). Although there is an increased background risk of malignancy and a lower incidence rate in patients treated with etanercept as compared to other treatments, such as csDMARDs, considering the potentially serious outcomes (such as hospitalizations and death) and number of cases observed in post-marketing, the risk of malignancy may have significant impact on public health.

SVII.3.1.1.2. Important Identified Risk: Serious and Opportunistic Infections (Including Tuberculosis, Legionella, Listeria, and Parasitic Infections)

SVII.3.1.1.2.1. Potential Mechanisms

There are several proposed mechanisms of immune deficiency in patients receiving anti-TNF therapy. TNF-α is essential for the formation and maintenance of granulomas, therefore its inhibition can lead to increased risk of new tuberculosis infection, reactivation of latent tuberculosis, and can predispose to other granulomatous infections, such as Histoplasma capsulatum. TNF-α plays a role in macrophage activation and differentiation and phagosome formation and is critical for the clearance of intracellular pathogens (e.g., *Listeria, Legionella, Salmonella*). Neutropenia can occur after anti-TNF administration, predisposing to opportunistic infections such as Candida or Aspergillus. TNF-α is also important for immune responses against viral pathogens, and its inhibition could cause complications in

patients infected with hepatitis B virus (HBV) or varicella zoster virus (VZV), for example.[173]

SVII.3.1.1.2.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.1.2.3. Characterisation of the Risk

Frequency

Serious Infections:
In the clinical database, 603 (2.61%) subjects experienced 878 serious infections. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- RA: 4.207 (3.897, 4.535)
- JIA: 2.805 (2.095, 3.678)
  - eoJIA: 2.503 (1.007, 5.158)
  - ERA: 2.237 (0.610, 5.728)
  - Paediatric PsA: 3.459 (1.123, 8.072)
- Adult PsA: 1.926 (1.326, 2.705)
- AxSpA: 1.481 (0.949, 2.204)
- Adult PsO: 1.300 (1.035, 1.611)
- Pediatric PsO: 0.484 (0.132, 1.240)
- All Indications: 3.069 (2.869, 3.278)

Opportunistic Infections[1]

In the clinical database, 377 (1.63%) subjects experienced 450 opportunistic-related infections. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- RA: 2.003 (1.791, 2.232)
- JIA: 0.314 (0.115, 0.682)
  - eoJIA: 0.334 (0.008, 1.860)
  - ERA: 0.527 (0.013, 2.939)
  - Paediatric PsA: 0.698 (0.018, 3.886)
- Adult PsA: 0.757 (0.403, 1.294)
- AxSpA: 1.297 (0.803, 1.983)
- Adult PsO: 1.195 (0.942, 1.496)
- Paediatric PsO: 0.844 (0.339, 1.739)
- All Indications: 1.564 (1.423, 1.716)

[1] Note that all cases reporting an opportunistic infection PT are included.

Tuberculosis
In the clinical database, 12 (0.05%) subjects experienced 12 tuberculosis-related events. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- RA: 0.030 (0.010, 0.069)
- Adult PsA: 0.058 (0.001, 0.324)
- AxSpA: 0.183 (0.038, 0.535)
- Adult PsO: 0.047 (0.010, 0.137)
- All Indications: 0.041 (0.021, 0.071)

Legionella
In the clinical database, 1 (0.01%) subject with indication of psoriasis experienced *legionella*. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- Adult PsO: 0.016 (0.000, 0.087)
- All Indications: 0.003 (0.000, 0.019)

Listeria

In the clinical database, there were no subjects who experienced *listeria*.

Parasitic Infections

In the clinical database, 35 (0.15%) of subjects experienced 38 parasitic infections. The exposure-adjusted event rates per 100 patient-years (95% CI) by indication are presented below:

- RA: 0.112 (0.068, 0.175)
- JIA: 0.103 (0.013, 0.373)
  eoJIA: 0.684 (0.083, 2.473)
- Adult PsA: 0.233 (0.063, 0.596)
- AxSpA: 0.244 (0.067, 0.625)
- Adult PsO: 0.062 (0.017, 0.160)
- Paediatric PsO: 0.603 (0.196, 1.407)
- All Indications: 0.129 (0.091, 0.177)

Seriousness/Outcomes

Clinical Trials:

Serious Infections
In the clinical database, there were 878 serious infection-related events. Of these events, 625 (71.18%) were resolved, 83 (9.45%) were not resolved, and 170 (19.36%) had unknown outcome. The most common events (≥2%) are summarized in the table below.

Table 14. Reported Events, Seriousness, and Outcomes from Clinical Trials – Serious Infections

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Pneumonia	141	141	104	12	25
Cellulitis	83	83	55	3	25
Bronchitis	35	35	30	0	5
Gastroenteritis	33	33	26	0	7
Sepsis	31	31	15	9	7
Arthritis bacterial	30	30	24	2	4
Diverticulitis	25	25	15	0	10
Urinary tract infection	23	23	20	0	3
Pyelonephritis	20	20	16	1	3
Appendicitis	19	19	10	0	9
Skin infection	19	19	19	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were 82 serious infection-related events with a fatal outcome involving 63 subjects originating from clinical trials in the safety database. The fatal events reported more than once coded to the PTs Pneumonia (23), Sepsis (15), Septic shock (8), Infection, Staphylococcal sepsis, Disseminated tuberculosis, Staphylococcal bacteraemia, and Fungal sepsis (2 each).

Opportunistic Infections[2]

In the clinical database, there were 450 opportunistic-related infections. Of these events, 23 (5.11%) were considered serious, 308 (68.44.%) events were resolved, 35 (7.78%) were not resolved, and 107 (23.78%) had unknown outcome. The most common events (≥2%) are summarized in the table below.

Table 15. Reported Events, Seriousness, and Outcomes from Clinical Trials – Opportunistic Infections

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Herpes zoster	228	14	154	16	58
Vulvovaginal candidiasis	95	0	66	9	20
Oral candidiasis	63	1	46	4	13
Candida infection	20	0	14	1	5
Skin candida	14	0	6	1	7

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were 8 opportunistic infection-related events with a fatal outcome involving 8 subjects originating from clinical trials in the safety database. The fatal events reported coded to the PTs Disseminated tuberculosis (2), Pneumocystis jirovecii pneumonia, Cytomegalovirus

[2] Note that all cases reporting an opportunistic infection PT are included.

infection, Bronchopulmonary aspergillosis, Aspergillus infection, Human herpes virus 6 infection, and Mucormycosis (1 each).

Tuberculosis

In the clinical database, there were 12 tuberculosis-related events. Of these events, 4 (33.33%) were serious, 1 (8.33%) was resolved, 7 (58.33%) were not resolved, and 4 (33.33%) had an unknown outcome. The events are summarized in the table below.

Table 16. Reported Events, Seriousness, and Outcomes from Clinical Trials – Tuberculosis

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Tuberculin test positive	4	0	0	2	2
Tuberculosis	3	2	1	1	1
Latent tuberculosis	2	1	0	1	1
Pulmonary tuberculosis	2	0	0	2	0
Lymph node tuberculosis	1	1	0	1	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were 2 tuberculosis infection-related events with a fatal outcome involving 2 subjects originating from clinical trials in the safety database. The fatal events reported coded to the PT Disseminated tuberculosis (2).

Legionella

In the clinical database, there was 1 event of legionella (PT Pneumonia legionella). The event was serious and had unknown outcome.

There were no fatal cases of *legionella* originating from clinical trials in the safety database.

Parasitic Infections

In the clinical database, there were 38 parasitic infection-related events. None of the events were serious, 22 (57.89%) events were resolved, 4 (10.53%) were not resolved, and 12 (31.58%) had unknown outcome. The most common events (≥2 events) are summarized in the table below.

Table 17. Reported Events, Seriousness, and Outcomes from Clinical Trials – Parasitic Infections

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Lice infestation	6	0	0	0	6
Acarodermatitis	5	0	3	0	2
Infection parasitic	5	0	4	1	0
Enterobiasis	4	0	2	0	2
Amoebiasis	3	0	2	1	0
Arthropod infestation	2	0	2	0	0
Giardiasis	2	0	1	0	1

Table 17. Reported Events, Seriousness, and Outcomes from Clinical Trials – Parasitic Infections

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Helminthic infection	2	0	2	0	0
Urethritis trichomonal	2	0	2	0	0
Vulvovaginitis trichomonal	2	0	2	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were no fatal cases of parasitic infection-related events originating from clinical trials in the safety database.

Post-Marketing:

Serious Infections (all serious events)

In the post-marketing experience, since first approval through 15 August 2024, there have been 56,811 cases received by the MAH reporting 69,364 relevant infection-related SAEs.

Table 18. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Serious Infections (all serious events)

MedDRA PT	No. Events	H	F	R	RS	NR	U
Pneumonia	11,887	5539	767	4593	56	1355	5141
Lower respiratory tract infection	5010	449	36	841	9	544	3583
Urinary tract infection	3269	1246	44	1301	8	673	1246
Cellulitis	2985	1470	26	1185	15	443	1319
Sepsis	2182	1479	508	607	33	132	902
Staphylococcal infection	2101	1020	27	879	11	262	922
Infection	1932	1255	95	484	4	243	1107
All others	39,998	16,872	1353	14976	391	6451	16,836
Total	69,364	29,330	2856	24,866	527	10,103	31,056

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Opportunistic Infections (all serious events)

In the post-marketing experience, since first approval through 15 August 2024, there have been 5027 cases received by the MAH reporting 5212 relevant opportunistic infection-related SAEs.

Table 19. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Opportunistic Infections (all serious events)

MedDRA PT	No. Events	H	F	R	RS	NR	U
Tuberculosis	1288	209	21	219	4	251	793
Herpes zoster	1061	352	5	499	11	212	334
Pulmonary tuberculosis	289	150	11	107	2	63	106
Pneumocystis jirovecii pneumonia	277	216	42	146	4	16	69
Latent tuberculosis	174	10	0	43	0	54	77
Candida infection	171	49	3	53	2	33	80

Table 19. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Opportunistic Infections (all serious events)

MedDRA PT	No. Events	H	F	R	RS	NR	U
Pseudomonas infection	112	66	8	38	1	15	50
Coccidioidomycosis	110	17	6	26	1	19	58
Mycobacterium avium complex infection	108	37	3	23	0	24	58
All Others	1622	748	112	636	27	243	604
Total	5212	1854	211	1790	52	930	2229
Subgroup of Serious Opportunistic Infections							
Tuberculosis-related PTs	2055	508	54	486	13	417	1085
Listeria-related PTs	62	46	5	35	5	3	14
Legionella-related PTs	63	46	4	29	5	1	24
Parasitic infections	146	42	7	57	1	26	55

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

Serious Infections

Of the 878 serious infections in the clinical database, 34 (3.87%) events were mild, 190 (21.64%) were moderate, 324 (36.90%) were severe, 24 (2.73%) were life-threatening, 7 (0.80%) were fatal, and 299 (34.05%) had unknown severity. The severity of the most common events (≥2%) is summarized in the table below.

Table 20. Severity of Serious Infections from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Pneumonia	4	24	51	0	4	1	57	141
Cellulitis	0	11	30	0	0	0	42	83
Bronchitis	0	10	13	0	1	0	11	35
Gastroenteritis	3	8	16	0	1	0	5	33
Sepsis	0	1	7	0	1	2	20	31
Arthritis bacterial	0	4	14	0	0	0	12	30
Diverticulitis	1	7	10	0	0	0	7	25
Urinary tract infection	4	9	4	0	0	0	6	23
Pyelonephritis	0	3	5	0	3	0	9	20
Appendicitis	0	3	13	0	1	0	2	19
Skin infection	0	8	11	0	0	0	0	19

Fatal = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

Opportunistic Infections[3]

Of the 450 events of opportunistic-related infections in the clinical database, 235 (52.22%) events were mild, 181 (40.22%) were moderate, 13 (2.89%) were severe, 1 (0.22%) was life-

[3] Note that all cases reporting an opportunistic infection PT are included.

threatening, and 20 (4.44%) had unknown severity. The severity of the most common events (≥2%) is summarized in the table below.

Table 21. Severity of Opportunistic Infections from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Herpes zoster	86	120	8	0	0	0	14	228
Vulvovaginal candidiasis	68	26	0	0	0	0	1	95
Oral candidiasis	38	23	1	0	0	0	1	63
Candida infection	18	2	0	0	0	0	0	20
Skin candida	10	4	0	0	0	0	0	14

Fatal = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

Tuberculosis

Of the 12 events of TB in the clinical database, 7 (58.33%) events were mild, 4 (33.33%) were moderate, and 1 (8.33%) was severe. The severity of the events is summarized in the table below.

Table 22. Severity of Tuberculosis Infections from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Tuberculin test positive	3	1	0	0	0	0	0	4
Tuberculosis	1	1	1	0	0	0	0	3
Latent tuberculosis	2	0	0	0	0	0	0	2
Pulmonary tuberculosis	1	1	0	0	0	0	0	2
Lymph node tuberculosis	0	1	0	0	0	0	0	1

Fatal = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

Legionella

The 1 *legionella* event in the clinical data base coded to the PT Pneumonia legionella and was considered life-threatening.

Parasitic Infections

Of the 38 parasitic infections in the clinical database, 27 (71.05%) events were mild and 11 (28.95%) were moderate. The severity of the most common events (≥5%) is summarized in the table below.

Table 23. Severity of Parasitic Infections from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Lice infestation	3	3	0	0	0	0	0	6
Acarodermatitis	5	0	0	0	0	0	0	5
Infection parasitic	4	1	0	0	0	0	0	5
Enterobiasis	3	1	0	0	0	0	0	4
Amoebiasis	1	2	0	0	0	0	0	3

Table 23. Severity of Parasitic Infections from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Arthropod infestation	2	0	0	0	0	0	0	2
Giardiasis	1	1	0	0	0	0	0	2
Helminthic infection	2	0	0	0	0	0	0	2
Urethritis trichomonal	2	0	0	0	0	0	0	2
Vulvovaginitis trichomonal	2	0	0	0	0	0	0	2

Fatal = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

SVII.3.1.1.2.4. Risk Factors and Risk Groups

Subjects on concomitant immunosuppressive therapy, in addition to their underlying disease, could be predisposed to infections.

Treatment of moderate to severe PsO has typically involved conventional systemic therapies such as MTX, cyclosporine, and oral retinoids, or phototherapy,[174] which may increase the incidence of infections. Studies have shown that cyclosporine can be associated with influenza-like symptoms (9.9%) and upper respiratory tract infections (7.7%) when administered to subjects with PsO.[175]

SVII.3.1.1.2.5. Preventability

No data are available to identify specific measures that can be used to prevent serious infections. At the initiation of TNF blocker therapy, the subjects should review the subject leaflet for information about the risk of infections. Subjects should be evaluated for infections, before, during, and after treatment with etanercept.

SVII.3.1.1.2.6. Impact on the Risk-Benefit Balance of the Product

Serious and opportunistic infections can have a significant impact on a patient's quality of life and overall health. Serious and opportunistic infections can often necessitate hospitalization, requiring prolonged antimicrobial therapy, and result in severe consequences including death. If such infections are identified early, and appropriate therapy instituted, a full recovery is often possible. However, sometimes in an immunocompromised patient these infections can be difficult to identify and to treat.

SVII.3.1.1.2.7. Public Health Impact

In the BADBIR study, the incidence rate of total serious infections (includes serious and opportunistic infections) among patients treated with etanercept was 1.903 per 100 PYs, compared with an incidence rate of 0.803 per 100 PYs among patients treated with conventional therapy, indicating a significantly increased risk of serious infection (adjusted hazard ratio 1.79; 95% CI 1.37, 2.33) in the etanercept treated cohort. Specifically, psoriasis patients currently or previously receiving etanercept had a significantly increased risk of pneumonia (adjusted hazard ratio 1.68; 95% confidence interval 1.02, 2.77), septicaemia (adjusted hazard ratio 2.78; 95% confidence interval 1.21, 6.39), cellulitis (adjusted hazard ratio 2.28; 95% confidence interval 1.19, 4.37), and other serious infection (adjusted hazard ratio 1.93; 95% confidence interval 1.33, 2.79), compared with patients treated with

conventional therapy. There were no serious or opportunistic infections reported in the PURPOSE study. In the BSRBR registry protocol B1801309, the incidence rate of serious infections in etanercept treated patients was 3.87 per 100 PYs, which was slightly higher than the rate observed in patients treated with csDMARDs (3.29 per 100 PYs). As of 15 August 2024, there have been 56,811 cases of serious infections received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 PYs (estimated reporting rate of 0.66 per 100 PYs). Considering the potentially serious outcomes (such as hospitalizations and death) and number of cases observed in post-marketing, the risk of serious infections may have significant impact on public health.

SVII.3.1.1.3. Important Identified Risk: Demyelinating Disorders

SVII.3.1.1.3.1. Potential Mechanisms

Chronic inflammatory demyelinating polyneuropathy is an acquired demyelinating disease of the peripheral nerves in which myelin is presumably the target of the immune attack. Cases could be the result of a specific autoimmune response induced by anti-TNFα. Accordingly, inflammatory demyelinating neuropathy has previously been described as occurring with other immunotherapies such as interferon-α, tacrolimus (FK506), cyclosporine A, and suramin. All these therapies might be involved in the disequilibrium of the immune system and could exacerbate the deleterious pro-inflammatory and tissue-damaging activities of the immune system.[176] The potential mechanism for central demyelinating disorders is currently not well understood.

SVII.3.1.1.3.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.1.3.3. Characterisation of the Risk

Frequency

In the clinical database, 13 (0.06%) subjects experienced 14 events of demyelinating disorders. The exposure-adjusted event rates per 100 patient-years by indication are presented below. There were no events in the paediatric indications (JIA, eoJIA, ERA, PsA, PsO).

- RA: 0.047 (0.020, 0.093)
- PsA: 0.174 (0.036, 0.509)
- AxSpA: 0.061 (0.002, 0.340)
- Adult PsO: 0.031 (0.004, 0.113)
- All Indications: 0.047 (0.026, 0.080)

Seriousness/Outcomes

Clinical Trials:

In the clinical database, there were 14 events of demyelinating disorders. Of these events, 10 (71.43%) were considered serious, 4 (28.57%) were resolved, 6 (42.86%) were not resolved, and 4 (28.57%) had an unknown outcome. The reported events are summarized in the table below.

Table 24. Reported Events, Seriousness, and Outcomes from Clinical Trials – Demyelinating Disorders

MedDRA PT	No. Events	Serious	Resolved	Not Resolved	Unknown
Multiple sclerosis	5	5	2	2	1
Demyelinating polyneuropathy	3	1	1	1	1
Demyelination	3	2	0	2	1
Myelitis	2	1	0	1	1
Optic neuritis	1	1	1	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

There were no demyelinating disorder events with a fatal outcome originating from clinical trials in the safety database.

Post-Marketing:

In the post-marketing experience, since first approval through 15 August 2024, there have been 1876 cases received by the MAH reporting 2019 relevant demyelinating disorder AEs.

Table 25. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Demyelinating Disorders

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Multiple sclerosis	758	757	131	3	98	7	243	407
Demyelination	500	497	126	2	109	13	136	240
Optic neuritis	355	354	78	1	116	10	91	138
Guillain-Barre syndrome	127	127	78	2	33	2	24	66
Myelitis transverse	90	90	44	0	31	4	21	34
Myelitis	68	68	38	1	20	4	15	28
Demyelinating polyneuropathy	52	52	10	0	13	1	15	23
All others	69	69	19	0	18	1	22	28
Total	2019	2014	524	9	438	42	567	964

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

Of the 14 demyelinating disorders in the clinical database, 3 (21.43%) events were mild, 4 (28.57%) were moderate, 5 (35.71%) were severe, and 2 (14.29%) had unknown severity. The severity of the reported events is summarized in the table below.

Table 26. Severity of Demyelinating Disorders from Clinical Trials

MedDRA PT	Mild	Mod	Severe	VS	LT	F	U	Total
Multiple sclerosis	0	2	2	0	0	0	1	5
Demyelinating polyneuropathy	1	1	1	0	0	0	0	3
Demyelination	1	1	1	0	0	0	0	3
Myelitis	1	0	1	0	0	0	0	2
Optic neuritis	0	0	0	0	0	0	1	1

F = fatal; LT = life-threatening; MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; PT = preferred term; U = unknown; VS = very severe

SVII.3.1.1.3.4. Risk Factors and Risk Groups

In RA, the primary autoimmune condition may be a contributing factor to the development of demyelinating disorders, other inflammatory rheumatic disorders, particularly SpAs, are not classically associated with immune neurological disorders. Potential risk factors for central demyelinating disorders include vitamin D deficiency and certain childhood infections including Epstein-Barr virus.[177,178]

SVII.3.1.1.3.5. Preventability

Prescribers should exercise caution in considering the use of etanercept in subjects with pre-existing or recent-onset central nervous system or peripheral demyelinating disorders.

SVII.3.1.1.3.6. Impact on the Risk-Benefit Balance of the Product

Central and peripheral demyelinating disorders can have significant impact on a patient's quality of life and a negative impact on a patient's physical functioning, including increased morbidity and mortality, given the severe nature of the symptoms of these conditions (e.g., GBS, multiple sclerosis, etc.).

SVII.3.1.1.3.7. Public Health Impact

In the BADBIR study, there were no confirmed events of central or peripheral demyelination reported in either the etanercept or conventional therapy cohorts. In the BSRBR registry protocol B1801309, there were 4 events of central demyelination among etanercept treated patients, with an estimated incidence rate of 0.01 per 100 PYs. As of 15 August 2024, there have been 1876 cases received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 PYs (estimated reporting rate of 0.022 per 100 PYs). Although demyelinating events can be serious, sometimes even fatal, given the rarity of the events, it is not expected to have a significant impact on public health.

SVII.3.1.2. Important Potential Risks

SVII.3.1.2.1. Important Potential Risk: Encephalitis/Leukoencephalomyelitis

SVII.3.1.2.1.1. Potential Mechanisms

The prime immunologic defect caused by TNFα inhibitors is in the cell-mediated immune response. Patients have an increased susceptibility to certain infections, which may include infectious encephalitis.[179]

SVII.3.1.2.1.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.2.1.3. Characterisation of the Risk

Frequency

In the clinical database, there were no cases of encephalitis/leukoencephalomyelitis in subjects receiving at least one dose of etanercept in the above noted clinical trials.

Seriousness/Outcomes

Clinical Trials:

In the clinical database, there were no cases of encephalitis/leukoencephalomyelitis in subjects receiving at least one dose of etanercept in the above noted clinical trials.

There were no cases reporting encephalitis/leukoencephalomyelitis events with a fatal outcome originating from clinical trials in the safety database.

Post-Marketing:

In the post-marketing experience, since first approval through 15 August 2024, there have been 131 cases received by the MAH reporting 134 relevant AEs.

Table 27. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Encephalitis/Leukoencephalomyelitis

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Encephalitis	95	95	63	8	26	4	16	41
Encephalomyelitis	9	9	7	2	4	0	1	2
Acute disseminated encephalomyelitis	7	7	6	0	2	1	2	2
Encephalitis autoimmune	7	7	6	0	3	1	2	1
Noninfective encephalitis	7	7	4	1	0	0	1	5
Encephalitis brain stem	4	4	4	2	2	0	0	0
Myelin oligodendrocyte glycoprotein antibody-associated disease	2	2	0	0	1	0	0	1
Acute haemorrhagic leukoencephalitis	1	1	1	0	0	0	1	0
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	1	1		1	0	0	0	0
Encephalitis allergic	1	1	1	0	1	0	0	0
Total	134	134	92	14	39	6	23	52

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

In the clinical database, there were no cases of encephalitis/ leukoencephalomyelitis in subjects receiving at least one dose of etanercept.

SVII.3.1.2.1.4. Risk Factors and Risk Groups

Subjects on concomitant immunosuppressive therapy, or with medical conditions that cause immunosuppression that, in addition to their underlying disease, could predispose them to infections.

SVII.3.1.2.1.5. Preventability

Prescribers should exercise caution in considering the use of etanercept in patients with pre-existing or recent-onset encephalitis/leukoencephalomyelitis.

SVII.3.1.2.1.6. Impact on the Risk-Benefit Balance of the Product

Encephalitis/leukoencephalomyelitis could have a significant impact on a patient's quality of life given the co-morbidities associated with these central nervous system inflammatory conditions.

SVII.3.1.2.1.7. Public Health Impact

In the etanercept clinical database, there were no cases of encephalitis/leukoencephalomyelitis reported out of 29,504.36 PYs of exposure. As of 15 August 2024, there have been 131 cases received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 PYs (estimated reporting rate of 0.0015 per 100 PYs). Although encephalitis/leukoencephalomyelitis can be serious, sometimes even fatal, given the rarity of the events, it is not expected to have a significant impact on public health.

SVII.3.1.2.2. Important Potential Risk: Progressive Multifocal Leukoencephalopathy

SVII.3.1.2.2.1. Potential Mechanisms

Increased risk for opportunistic infection with JC virus in patients with autoimmune diseases on immunosuppressive therapies.[180]

SVII.3.1.2.2.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.2.2.3. Characterisation of the Risk

Frequency

In the clinical database, there were no cases of PML in subjects receiving at least one dose of etanercept in the above noted clinical trials.

Seriousness/Outcomes

Clinical Trials:

In the clinical database, there were no cases of PML in subjects receiving at least one dose of etanercept in the above noted clinical trials.

There were no cases of PML originating from clinical trials in the safety database.

Post-Marketing:

In the post-marketing experience, since first approval through 15 August 2024, there have been 49 cases received by the MAH reporting 50 relevant AEs.

Table 28. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – PML

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Leukoencephalopathy	27	27	14	1	11	0	7	8
Progressive multifocal leukoencephalopathy	17	17	5	3	1	0	3	10
Human polyomavirus infection	2	2	0	0	0	0	0	2
JC polyomavirus test positive	2	1	1	1	0	0	0	1
JC virus infection	1	1	0	0	0	0	0	1
Polyomavirus test positive	1	0	0	0	0	0	0	1
Total	50	48	20	5	12	0	10	23

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

In the clinical database, there were no cases of PML in subjects receiving at least one dose of etanercept.

SVII.3.1.2.2.4. Risk Factors and Risk Groups

Subjects on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to PML.

SVII.3.1.2.2.5. Preventability

No data are available to identify specific measures that can be used to prevent PML. There are no criteria that identify patients receiving etanercept who are at risk of developing PML.

SVII.3.1.2.2.6. Impact on the Risk-Benefit Balance of the Product

PML can have a significant impact on a patient's quality of life given the severity of this condition, its life-threatening and often fatal nature, and associated co-morbidities.

SVII.3.1.2.2.7. Public Health Impact

In the BADBIR study, no events of PML were reported. In the etanercept clinical database, no cases of PML have been reported out of 29,504.36 PYs of exposure. As of 15 August 2024, there have been 49 cases received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 PYs (estimated reporting rate of 0.0006 per 100 PYs). Although PML can be serious, sometimes even fatal, given the rarity of the events, it is not expected to have a significant impact on public health.

SVII.3.1.2.3. Important Potential Risk: Impaired Growth and Development in Juvenile Subjects

SVII.3.1.2.3.1. Potential Mechanisms

The potential mechanism is currently not well understood.

SVII.3.1.2.3.2. Evidence Source and Strength of Evidence

Clinical trial and post-marketing data.

SVII.3.1.2.3.3. Characterisation of the Risk

Frequency

In the clinical database, 3 (0.35%) juvenile subjects experienced 3 events of impaired growth and development. The exposure-adjusted event rates per 100 patient-years by indication are presented below. There were no events in eoJIA, AS, and paediatric PsA.

- JIA: 0.052 (0.001, 0.291)
- ERA: 0.503 (0.013, 2.805)
- Paediatric PsO: 0.239 (0.029, 0.862)
- All Indications: 0.108 (0.022, 0.317)

Seriousness/Outcomes

Clinical Trials:

There were 3 events of impaired growth and development in juvenile subjects. All events coded to the PT Weight decreased. None of the events were serious, 1 (33.33%) event resolved, and 2 (66.67%) events had an unknown outcome.

There were no events of impaired growth and development in juvenile subjects with a fatal outcome originating from clinical trials in the safety database.

Post-Marketing:

In the post-marketing experience, since first approval through 15 August 2024, there have been 92 cases received by the MAH reporting 93 relevant AEs.

Table 29. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Impaired Growth and Development in Juvenile Subjects

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Weight decreased	69	16	6	1	12	0	20	36
Growth retardation	9	8	0	0	1	0	1	7
Weight abnormal	4	0	0	0	0	0	1	3
Underweight	3	1	1	0	0	0	3	0
Weight gain poor	3	1	0	0	0	0	2	1
Body height abnormal	1	0	0	0	0	0	0	1
Body height below normal	1	0	0	0	0	0	1	0
Body mass index decreased	1	0	0	0	0	0	0	1
Cachexia	1	1	0	0	1	0	0	0
Failure to thrive	1	1	0	0	0	0	0	1
Total	93	28	7	1	14	0	28	50

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

Of the 3 events of impaired growth and development in juvenile subjects (PT Weight decreased) in the clinical database, 2 were mild and 1 was moderate.

SVII.3.1.2.3.4. Risk Factors and Risk Groups

There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.

SVII.3.1.2.3.5. Preventability

At present, an effect on growth and development following exposure to etanercept cannot be identified pre-emptively.

SVII.3.1.2.3.6. Impact on the Risk-Benefit Balance of the Product

The potential impact of impaired growth and development in a juvenile subject could be significant given the nature of this condition and the impact it can have on the patient's psycho-social development.

SVII.3.1.2.3.7. Public Health Impact

In the etanercept clinical database, 3 (0.35%) juvenile subjects experienced 3 events of impaired growth and development, with an estimated incidence rate of 0.108 per 100 PYs. As of 15 August 2024, there have been 92 cases received by MAH in the post-marketing dataset with an estimated cumulative worldwide post-marketing exposure to etanercept of 8,601,385 PYs (estimated reporting rate of 0.0011 per 100 PYs). Although the event may potentially have significant impact on individual subjects depending on the degree of impaired growth. Given the overall low incidence rate and small number of cases reported in post-marketing, it is not expected to have a significant impact on public health.

SVII.3.2. Presentation of the Missing Information

There is none.

Module SVIII. Summary of the Safety Concerns

Table 30. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Malignancy (including lymphoma and leukaemia)
	Serious and Opportunistic Infections (including tuberculosis, *Legionella*, *Listeria*, and parasitic infections)
	Demyelinating Disorders
Important potential risks	Encephalitis/Leukoencephalomyelitis
	Progressive Multifocal Leukoencephalopathy
	Impaired Growth and Development in Juvenile Subjects

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

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse drug reactions (ADRs) reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**
    - Per requests from regulatory agencies, data capture aids (DCAs) are used to collect supplemental information beyond the standard follow-up activities for specific adverse events or populations (e.g., demyelinating disorders, lymphoma, mycosis fungoides/cutaneous t-cell lymphoma, PML, JIA, paediatrics) to assist in understanding the medical aspects of the event and performing the causality assessment.
- **Other forms of routine pharmacovigilance activities for safety concerns:**
    - None.

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 31. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not applicable.

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

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 32. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Malignancy (including lymphoma and leukaemia)	Routine risk communication: SmPC Section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Package Leaflet (PL) Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes text recommending periodic skin examinations for all patients, particularly those with risk factors for skin cancer. Other routine risk minimisation measures beyond the Product Information: None.
Serious and Opportunistic Infections (including tuberculosis, *Legionella*, *Listeria*, and parasitic infections)	Routine risk communication: SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Contraindication for use in patients with sepsis or risk of sepsis and in patients with active infections, including chronic or localized infections is included in SmPC Section 4.3. SmPC Section 4.4 includes text to evaluate patients for infections before, during, and after treatment with etanercept, to monitor patients who develop a new infection while undergoing treatment, and to discontinue therapy if a patient develops a serious infection. It also includes text stating that appropriate screening tests for tuberculosis should be performed for all patients and if active tuberculosis is diagnosed, etanercept therapy must not be initiated. If inactive tuberculosis is diagnosed, treatment must be started with anti-tuberculosis therapy before initiation of etanercept.

Table 32. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None.
Demyelinating Disorders	Routine risk communication: SmPC Section 4.4 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes text recommending a careful risk/benefit evaluation, including a neurologic assessment, when prescribing etanercept to patients with pre-existing or recent onset of demyelinating disease or those considered to have an increased risk of developing demyelinating disease. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential Risks	
Encephalitis/Leukoencephalomyelitis	Routine risk communication: None proposed.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Progressive Multifocal Leukoencephalopathy	Routine risk communication: None proposed.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Impaired Growth and Development in Juvenile Subjects	Routine risk communication:

Table 32. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	None proposed.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

PL = package leaflet; SmPC = summary of product characteristics

V.2. Additional Risk Minimisation Measures

Patient Card

Proposed updates to the patient card:

The MAH is proposing the removal of the Important identified risks Congestive Heart Failure in Adult Subjects and of the Missing information Immunogenicity Profile and Related Clinical Outcomes of Etanercept Manufactured using the SFPHC Process in a Real-life Post-marketing Setting from the list of addressed safety concerns by the patient card. However, the batch number in the Patient card will remain for traceability purposes.

Rational for the updates to the patient card:

No new safety information regarding immunogenicity for etanercept using the SFPHC Process have emerged during the extension study of BSR Register of Anti-TNF Treated Patients and Prospective Surveillance Study for Adverse Events Enbrel study. Also, in the post-marketing experience, no new safety trends were observed during routine pharmacovigilance for etanercept due to SFPHC changes. The patient card does not provide additional information to that which is already included in the PL for the important identified risk of “Congestive Heart Failure in Adult Subjects”.

Objectives for the updated patient card:

The proposed additional risk minimisation measures in the Patient Card are designed to enhance patients’ awareness and knowledge surrounding the following safety concern and optimal use of etanercept.

- Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)

- Traceability of etanercept

Rationale for the additional risk minimisation activity:

To reduce risk and provide relevant information to mitigate the consequences of the "Serious and Opportunistic Infections (including tuberculosis, Legionella, Listeria, and parasitic infections)" and for traceability purpose.

Target audience and planned distribution path:

Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept.

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

Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends. Risk minimization measures are judged effective if no negative trends or worsening outcomes over time are identified.

V.3. Summary of Risk Minimisation Measures

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Malignancy (including lymphoma and leukaemia)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions; SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • DCA Additional pharmacovigilance activities: None
Serious and Opportunistic Infections (including tuberculosis, *Legionella*, *Listeria*, and parasitic infections)	Routine risk minimisation measures: SmPC Section 4.3 Contraindications; SmPC Section 4.4 Special warnings and precautions; SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Table 33. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Demyelinating Disorders	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions; SmPC Section 4.8 Undesirable effects PL Section 2 and 4 Additional risk minimisation measures: None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • DCA Additional pharmacovigilance activities: None
Important Potential Risks		
Encephalitis/ Leukoencephalomyelitis	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Progressive Multifocal Leukoencephalopathy	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • DCA Additional pharmacovigilance activities: None
Impaired Growth and Development in Juvenile Subjects	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • DCA Additional pharmacovigilance activities: None

AE = adverse event; BADBIR = British Association of Dermatologists Biologics Interventions Registry; DCA = data capture aid; PL = package leaflet; PURPOSE = Paediatric Registry of Psoriasis and Enbrel; SmPC = Summary of Product Characteristics

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Enbrel (etanercept)

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

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

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

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

I. The Medicine and What It Is Used For

ENBREL is authorised for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis, and paediatric plaque psoriasis (see SmPC for the full list of indications). It contains etanercept as the active substance and it is given by injection.

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

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

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

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

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

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

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

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

II.A. List of Important Risks and Missing Information

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

Table 34. List of important risks and missing information

Important identified risks	Malignancy (including lymphoma and leukaemia)
	Serious and Opportunistic Infections (including tuberculosis, *Legionella*, *Listeria*, and parasitic infections)
	Demyelinating Disorders
Important potential risks	Encephalitis/Leukoencephalomyelitis
	Progressive Multifocal Leukoencephalopathy
	Impaired Growth and Development in Juvenile Subjects

II.B. Summary of Important Risks

Table 35. Important Identified Risk – Malignancy (including lymphoma and leukaemia)

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Overall risk of malignancy including cutaneous and non-cutaneous cancers in subjects with RA and PsO has been reported to be higher than that observed in healthy subjects.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects PL Sections 2 and 4 <u>Additional risk minimisation measures:</u> None proposed.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> None proposed.

PL = package leaflet; PsO = psoriasis; RA = rheumatoid arthritis; SmPC = summary of product characteristics

Table 36. Important Identified Risk – Serious and Opportunistic Infections (Including Tuberculosis, *Legionella*, *Listeria*, and Parasitic Infections)

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy, in addition to their underlying disease, could be predisposed to infections. Treatment of moderate to severe PsO has typically involved conventional systemic therapies such as MTX, cyclosporine, and oral retinoids, or phototherapy,[174] which may increase the incidence of infections. Studies have shown that cyclosporine can be associated with influenza-like symptoms (9.9%) and upper respiratory tract infections (7.7%) when administered to subjects with PsO.[175]
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Sections 2 and 4 Additional risk minimisation measures: Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed.

MTX = methotrexate; PL = package leaflet; PsO = psoriasis; SmPC = summary of product characteristics

Table 37. Important Identified Risk – Demyelinating Disorders

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	In RA, the primary autoimmune condition may be a contributing factor to the development of demyelinating disorders, other inflammatory rheumatic disorders, particularly SpAs, are not classically associated with immune neurological disorders. Potential risk factors for central demyelinating disorders include vitamin D deficiency and certain childhood infections including Epstein-Barr virus.[177,178]
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions SmPC Section 4.8 Undesirable effects PL Section 2 and 4 Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed.

PL = package leaflet; RA = rheumatoid arthritis; SmPC = summary of product characteristics; SpA = spondyloarthritis

Table 38. Important Potential Risk – Encephalitis/Leukoencephalomyelitis

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy, or with medical conditions that cause immunosuppression that, in addition to their underlying disease, could predispose them to infections.
Risk minimisation measures	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed.

Table 39. Important Potential Risk – Progressive Multifocal Leukoencephalopathy

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	Subjects on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to PML.
Risk minimisation measures	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed.

PML = progressive multifocal leukoencephalopathy

Table 40. Important Potential Risk – Impaired Growth and Development in Juvenile Subjects

Evidence for linking the risk to the medicine	Clinical trial and post-marketing data.
Risk factors and risk groups	There are currently no known risk groups or risk factors in patients following the administration of etanercept for events in growth and development.
Risk minimisation measures	Routine risk minimisation measures: None proposed. Additional risk minimisation measures: None proposed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None proposed.

II.C. Post-Authorisation Development Plan

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

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

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

There are no studies required for etanercept.

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

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As part of routine pharmacovigilance, the MAH, including any licensing partner with marketing authorisation for Enbrel, must meet the regulatory requirement of submitting Data Capture Aids (DCAs) to enhance the capture of supplemental information regarding specific drug-event pairs as an adjunct to standard information gathering. The capture of supplemental information on the drug-event pairs assists in understanding the medical aspects of the event and performing a meaningful causality assessment. However, the DCAs are not for the collection of structured information, since responses are entered in the case narrative. The data collected are incorporated into the case and processed as follow up and included in routine signal detection. The DCAs for etanercept are included below.

As requested by the CHMP (following review of Variation EMEA/H/C/000262/II/0184, Opinion adopted on 19 November 2015), the criteria for the Pediatric DCA are presented herewith: If the patient's age is reported as under 18 years of age (or where a pediatric age group is provided [e.g., child, adolescent, neonate, or infant]), targeted follow-up must be actively pursued using the Pediatrics DCA.

AMYOTROPHIC LATERAL SCLEROSIS DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Amyotrophic Lateral Sclerosis (ALS) Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Was genetic testing performed?

☐ Unknown
☐ No
☐ Yes *(If yes, please answer the remaining questions)*

2. Was SOD1 (Cu / Zn superoxide dismutase type 1) mutation included in the testing?

☐ Unknown
☐ No
☐ Yes

3. Was another type of genetic testing performed?

☐ Unknown
☐ No
☐ Yes *(please specify type of testing and results)*

4. Date of genetic testing:

5. Was the SOD1 mutation present?

☐ Unknown
☐ No
☐ Yes

6. Were any other abnormalities discovered?

☐ Unknown
☐ No
☐ Yes *(please specify)*

ALS Follow-up Questions for Enbrel

Please provide additional details on a separate page if needed, and reference the question number.

Enbrel Daily Dose: *(please specify)* _____

Route of Administration: *(please specify)*_____

Therapy Dates (from/to) *(please specify)*_____/_____

DEMYELINATION DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Demyelination Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Does the patient have a history of Multiple Sclerosis?

☐ No ☐ Yes

If Yes, please provide the following details:

- Diagnosis date: _____
- Method of Diagnosis: _____
- Specific diagnosis: ☐ Primary progressive ☐ Secondary progressive ☐ Relapsing remitting

Does the patient have a history of relapse?

☐ No ☐ Yes *(please specify frequency)*

Has the frequency of relapse changed since starting the product?

☐ No ☐ Yes *(please provide details)*

2. Did the patient ever experience neurologic symptoms prior to starting the product?

☐ No ☐ Yes *(please provide details)*

3. Did the patient ever have a brain or spinal MRI scan prior to starting the product?

☐ No ☐ Yes *(please provide findings and reason for scan)*

4. Did the patient have a history of brain injury or lesions prior to starting the product?

☐ No ☐ Yes *(please provide details)*

5. Does the patient have a history of optic neuritis?

☐ No ☐ Yes *(please provide date and method of diagnosis)*

6. Does the patient have a history of other demyelinating neurologic disorders?

☐ No ☐ Yes *(specify condition and provide date and method of diagnosis)*

7. Does the patient have a family history of demyelinating neurologic disorders?

☐ No ☐ Yes *(please specify the condition and family relationship)*

8. Did the patient have any of the following risk factors?

☐ Drug treatment associated with demyelinating neurologic disorders *(please provide product name and dates / duration of therapy)*
☐ Radiation therapy *(please provide dates)*
☐ Occupational exposure *(please provide details)*
☐ Environmental exposure *(please provide details)*
☐ Other *(please specify)*

Details:

9. **Were any of the following laboratory tests/procedures performed?** *Please attach results or summary of results*		
Diagnostic Test	**Date Performed (DD-MMM-YYYY)**	**Check if test results attached or summarized**
☐ MRI		☐
☐ Lumbar puncture		☐
☐ Cerebrospinal fluid analysis		☐
☐ Visual evoked potential		☐
☐ Other *(specify)*		☐

Additional Demyelination Questions for Enbrel

Please provide additional details on a separate page if needed, and reference the question number.

[1. Enbrel] Was Enbrel discontinued? ☐ No ☐ Yes → *If Yes, did the patient's neurologic condition improve, worsen, or remain stable? Please provide details.*		**[2. Enbrel] Was Enbrel restarted?** ☐ No ☐ Yes → *If Yes, what was the result to the patient's neurologic condition?*
[3. Enbrel] Was the patient treated for the neurologic condition? ☐ No ☐ Yes → *If Yes, please specify.*		**[4. Enbrel] What is the patient's current status?** *Please specify.*

GUILLAIN-BARRÉ SYNDROME DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Guillain-Barré Syndrome Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Did the patient have any of the following risk factors?

- ☐ Previous history of Guillain-Barré
- ☐ Recent surgery
- ☐ Recent vaccination *(please specify type)*
- ☐ Connective tissue disease *(please specify type)*
- ☐ Malignancy *(please specify type)*
- ☐ Pregnancy *(please specify EDC)*
- ☐ Recent infection *(please specify type of infection, infection onset date, and the time interval between infection and Guillain-Barré Syndrome symptoms)*

2. Did the patient experience any of the following clinical manifestations? ***(Check all that apply)***

2a. ☐ **Weakness**
- ☐ Symmetrical
- ☐ Trunk muscles
- ☐ Lower limbs (specify manual muscle test grade)
  Right: _____ Left: _____
- ☐ Upper limbs (specify manual muscle test grade)
  Right: _____ Left: _____

2e. ☐ **Paralysis** (specify type and all areas)

2f. ☐ **Sensory Changes**
- ☐ Paraesthesia
- ☐ Numbness or similar sensory changes *(please specify)*

2b. ☐ **Autonomic changes**
- ☐ Tachycardia
- ☐ Paroxysmal hypertension
- ☐ Anhidrosis and/or diaphoresis
- ☐ Bradycardia
- ☐ Orthostatic hypotension
- ☐ Facial flushing

2g. ☐ **Cranial nerve involvement**
- ☐ Facial weakness
- ☐ Dysphasia
- ☐ Dysarthrias
- ☐ Slurred speech
- ☐ Oropharyngeal weakness
- ☐ Difficulty swallowing

2c. ☐ **Respiratory involvement**
- ☐ Respiratory weakness
- ☐ Dyspnea on exertion
- ☐ Shortness of breath
- ☐ Other *(please specify)*

2h. ☐ **Pain**
- ☐ Severe
- ☐ Throbbing
- ☐ Aching
- ☐ Other *(please specify)*

2d☐ **Papilledema**
- ☐ Increased CSF pressure
- ☐ Headache
- ☐ Pseudotumor cerebri syndrome

2i. ☐ **Dysreflexia**
- ☐ Reflexes decreased
- ☐ Reflexes absent
- ☐ Hypotonia

3. Is there any other explanation for the adverse event?

☐ **No** ☐ **Yes** *(please specify)*

Details:

4. Were any of the following laboratory tests/procedures performed? (Check all that apply) *Please attach results or summary of results*

Laboratory Test	Date Performed (DD-MMM-YYYY)	Test Results or Summary Attached
☐ Electrodiagnostic test		☐
☐ Cerebrospinal fluid analysis		
☐ Other *(specify)*		

JUVENILE IDIOPATHIC ARTHRITIS DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Juvenile Idiopathic Arthritis Subtype Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. **At what age did JIA begin?:** _____	2. **What Subtype of JIA was the patient diagnosed with?**

3. **Were any of the following laboratory tests or diagnostic studies performed?** *Please specify laboratory data with units, date of test, and reference ranges; and please provide printouts and photographs if available*:

Laboratory Test	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ Rheumatoid Factor			
☐ HLA-B27 antigen			

LYMPHOMA DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Lymphoma Questionnaire

Please provide additional details on a separate page if needed, and reference the question number.

1. Is there a family history of cancer?

☐ Unknown ☐ No ☐ Yes

If Yes, mark all of the following that apply and specify the cancer type**:**

☐ Maternal: _____

☐ Paternal: _____

☐ Sibling: _____

☐ Other:: _____

2. Please mark whether the patient had a history of any of the following:

☐ Immune deficiency (*please specify Type*)

☐ HIV

☐ Prior organ transplant

- Date of transplant *(DD-MMM-YYYY)*: _____
- Type of organ transplant: _____

☐ Any chronic inflammatory disease (*please specify Type*)

☐ Any other chronic diseases (*please specify Type)*

☐ Cirrhosis

☐ Hepatitis B

☐ Hepatitis C

☐ Helicobacter Pylori

☐ Occupational exposures (*please specify*)

☐ Environmental exposures (*please specify*)

☐ Other (*please specify*)

4. Was the patient diagnosed with lymphoma or other malignancy <u>prior to</u> receiving the product?

☐ Unknown ☐ No ☐ Yes

Details (including type of lymphoma and dates of diagnosis):

5. What was the type of lymphoma was newly diagnosed?

☐ Hodgkin's

☐ Non-Hodgkin's

☐ T-cell

☐ B-cell

☐ Other (*please specify*)

Stage of lymphoma at time of diagnosis:

_____

Date of diagnosis *(DD-MMM-YYYY)***:**

_____

6. What treatments were initiated after diagnosis?

☐ Chemotherapy (*please specify type*)

☐ Radiation

☐ Rituxan

☐ Bone Marrow Transplant

→ Epstein Barr Virus (EBV) status of donor: _____

☐ Other (*please specify*) _____

7. Please mark whether the patient received any of the following immunosuppressive medications *(please specify dates and dosing / frequency)*

☐ Adalimumab:
_____

☐ Azathioprine:
_____

☐ Cyclophosphamide:
_____

☐ Cyclosporine:
_____

☐ Etanercept (Enbrel)_____

☐ Gold:
_____

☐ Infliximab:
_____

☐ Leflunomide :_____

☐ Methotrexate:
_____

☐ 6-Mercaptopurine:
_____

☐ Other (*please specify*)
_____

Details:

8. Was the patient tested for Epstein Barr Virus (EBV)?

☐ Unknown ☐ No ☐ Yes

If Yes, please specify:

- Type of EBV Test ☐ Blood test ☐ In situ hydridization ☐ Immunohistologic analysis ☐ Other (*please specify*)
- Date of EBV testing *(DD-MMM-YYYY)*: _____
- EBV Test Result: ☐ Positive ☐ Negative

9. Please provide pathology report results, including immunotype, cytogenic, and histologic subtype if available *(please attach report if available)*

MYCOSIS FUNGOIDES CUTANEOUS T-CELL LYMPHOMA DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Mycosis Fungoides/Cutaneous T-Cell Lymphoma Questionnaire

Please provide additional details on a separate page if needed, and reference the question number.

1. Was the patient diagnosed with lymphoma prior to receiving the product?

☐ Unknown ☐ No ☐ Yes

Details:

2. What is the patient's primary occupation? *(please specify the duration)*

3. Please specify relative to the history of the skin disorder:

Chronic dermatitis? ☐ Yes ☐ No ☐ Unknown

Features of rash ☐ Morbiliform ☐ Flaking/peeling ☐ Plaques ☐ Ulcers/exfoliation

Site of rash: ☐ Extremities ☐ Flexor surfaces ☐ Trunk ☐ Extensor surfaces

Clinical progression ☐ None ☐ Slow ☐ Rapid

Change in skin disorder presentation after initiation of the product? ☐ Yes ☐ No ☐ Unknown

If yes please describe:

4. Please mark if the patient had a history of any of the following:

☐ Immune deficiency *(please specify type)*
☐ HIV
☐ Lyme Disease
☐ Tobacco use *(please estimate use/duration)*
☐ Alcohol use *(please estimate use/duration)*
☐ Organ transplant → Specify type of organ:
Date of transplant *(DD-MMM-YYYY)*: _____
☐ Chronic diseases *(please specify)*
☐ Exposure to solvents *(specify duration & most recent exposure)*

5. Is there a family history of cancer?

☐ Unknown ☐ No ☐ Yes

If Yes, mark all of the following that apply and specify the cancer type:

☐ Maternal: _____
☐ Paternal: _____
☐ Sibling: _____
☐ Other: _____

6. Which of the following applies to the current skin disorder?

☐ Mycosis fungoides
☐ Sezary Syndrome
☐ Primary cutaneous anaplastic large cell lymphoma
☐ Lymphomatoid papulosis
☐ Other *(please specify)*

Date of symptom onset *(DD-MMM-YYYY)***:**

_____

Date of diagnosis *(DD-MMM-YYYY)***:**

_____

Clinical appearance:

_____

Stage of lymphoma at time of diagnosis:

_____

Current stage of lymphoma:

_____

7. Was the patient tested for Epstein Barr Virus (EBV)?

☐ Unknown ☐ No ☐ Yes

If Yes, please specify:

Type of EBV Test ☐ Blood test ☐ In situ hybridization ☐ Immunohistologic analysis ☐ Other *(please specify)*

Date of EBV testing *(DD-MMM-YYYY)*:

_____

EBV Test Result ☐ Positive ☐ Negative

☐ Exposure to pesticides *(specify duration &most recent exposure)*
☐ Exposure to publishing/printing *(specify duration & most recent exposure)*
☐ Exposure to paper/wood industry *(specify duration & most recent exposure)*
☐ Other *(please specify)*

8. Please provide pathology report results, including histopathology, immunohistology, flow cytometry, immunogenotype (TCR-rearrangement), and lymph node analysis if available *(please attach report if available)*

9. Please mark whether the patient received any of the following immunosuppressive medications *(specify dates, dosing / frequency)*

☐ Adalimumab
☐ 6-Mercaptopurine
☐ Cyclophosphamide
☐ Azathioprine
☐ Etanercept
☐ Cyclosporine
☐ Gold
☐ Infliximab
☐ Leflunomide
☐ Methotrexate
☐ Other *(please specify)*

Details:

10. Please mark if the patient received any of the following treatments for Cutaneous T-Cell Lymphoma

☐ Topical therapy *(please specify)*
☐ Phototherapy
☐ Extracorporeal photophoresis
☐ Radiation therapy
☐ Systemic treatments *(please specify)*
☐ Bone marrow transplant
☐ Chemotherapy *(please specify)*
☐ Bone marrow transplant
☐ Other *(please specify)*

Details:

PEDIATRICS DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Pediatrics Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported adverse event a:

☐ New event

☐ Recurrence *(Please specify details of the prior events)*

2. Please specify any relevant prenatal / perinatal or medical history (e.g., maternal / paternal age of parents at delivery, complications during delivery, complications after delivery)

3. Who administered the medication to the patient?

☐ Health care professional ☐ Parent ☐ Patient-self administered

☐ Other *(please specify)*

Details:

4. Was the medication stored as per Manufacturer's instructions?

☐ Yes ☐ Unknown ☐ No → *If No, please specify how it was stored*

Details:

5. Was the medication altered in any way to accommodate administration?

☐ Unknown ☐ No ☐ Yes → *If Yes, please specify how it was changed*

Details:

6. Please specify any risk factors (e.g., social, occupational, environmental) that may have contributed to the patient's adverse event(s) or any other explanation for the adverse event(s):

Details:

7. Please specify the following for the gestational age of the patient at delivery and vital statistics at birth:

Gestational age at delivery: _____weeks

Weight at birth: _____kg

Length at birth: _____cm

Head circumference at birth: _____cm

Head circumference at adverse event: _____cm

8. Has the child failed to meet any developmental milestones since starting the medication?

☐ No ☐ Yes → *If Yes, please specify the developmental milestones and how they were <u>not</u> met*

Details:

9. Please specify whether the following developmental milestones have been <u>within normal range</u>:

Language / Speech ☐ Yes ☐ No

Emotional / Social ☐ Yes ☐ No

Fine / Gross Motor Skills ☐ Yes ☐ No

Cognitive Thinking ☐ Yes ☐ No

→ *If the response was "No" to any of the above, please provide details as to how the developmental milestone was out of normal range*

Details:

10. Has the child's physical growth been normal?

☐ Yes ☐ No → *If No, please specify how the growth has been out of normal range*

Details:

11. Has the child's pubertal growth been normal? ☐ N/A ☐ Yes ☐ No → *If No, please specify how the growth has been out of normal range* *Details:*		**12. Were any relevant laboratory tests performed at the time of the event?** ☐ Unknown ☐ No ☐ Yes → *If Yes, please specify test results with units, and reference ranges* *Details:*

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY DATA CAPTURE AID

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Progressive Multifocal Leukoencephalopathy (PML) Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Does the patient have a history of any of the following?

(Please provide specific diagnoses and when the conditions were diagnosed in the details section below)

- ☐ Neurologic disorder(s)
- ☐ Cancer
- ☐ Diabetes
- ☐ HIV infection
- ☐ Risk factor(s) for HIV infection
- ☐ Immune deficiency disorder
- ☐ Blood transfusion

Details:

2. Does the patient have a progressive neurologic / neuropsychiatric syndrome?

☐ No ☐ Yes

If yes, which of the following symptoms or signs are present?

- ☐ Limb weakness / incoordination
- ☐ Gait disorder
- ☐ Cognitive impairment
- ☐ Memory loss
- ☐ Vision loss / Visual defects
- ☐ Seizure
- ☐ Speech deficits
- ☐ Headache
- ☐ Focal sensory deficit
- ☐ Dysesthesia
- ☐ Other *(specify)*

3. Does the patient have a family history of Neurologic Disease?

- ☐ No
- ☐ Yes *(please provide details):*

4. Did the patient receive any of the following immunosuppressive medications?

(Please specify therapy dates and dosage / frequency)

- ☐ Adalimumab
- ☐ Anakinra
- ☐ Azathioprine
- ☐ Certolizumab
- ☐ Corticosteroids
- ☐ Cyclophosphamide
- ☐ Cyclosporine
- ☐ Etanercept (Enbrel)
- ☐ Golimumab
- ☐ Infliximab
- ☐ Leflunomide
- ☐ Methotrexate
- ☐ Natalizumab
- ☐ Rituximab
- ☐ Tocilizumab
- ☐ Other *(specify)*

5. Were any of the following laboratory tests performed before, during or after treatment?		
Laboratory Test	**Date of Test (DD-MMM-YYYY)**	**Test Results**
☐ Cerebrospinal fluid (CSF) analysis		
☐ JC Virus PCR		
☐ Magnetic Resonance Imaging (MRI) Brain		
☐ Brain Tissue Evaluation (biopsy / autopsy)		
☐ Other *(specify)*		

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

Approved key messages of the additional risk minimisation measures

Prior to the use of etanercept in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reducing the risk of serious infections and ensuring the traceability of etanercept drug product.

The MAH shall ensure that in each Member State where etanercept is marketed, all healthcare professionals who are expected to prescribe etanercept and all patients who are expected to use etanercept have access to/are provided with the following educational materials:

- Patient card
    - Patient cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides the following important safety information for patients:
        - Etanercept treatment may increase the risk of infection
        - Signs or symptoms of this safety concern and when to seek attention from a healthcare professional
        - Instructions to record the brand name and batch number of the medication to ensure traceability
        - Contact details of the etanercept prescriber