EU Risk Management Plan

for

Usymro (Ustekinumab)

Usymro 130 mg concentrate for solution for infusion

Usymro 45 mg solution for injection

Usymro 45 mg solution for injection in pre-filled syringe

Usymro 90 mg solution for injection in pre-filled syringe

RMP version to be assessed as part of this application:	
RMP Version number	0.3
Data lock point for this RMP	23-Apr-2025
Date of final sign off	14-May-2025
Rationale for submitting an updated RMP	Not applicable
Summary of significant changes in this RMP	Not applicable
Other RMP versions under evaluation	
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP	
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable
QPPV name	Prashanth Belathur
QPPV signature	

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Ustekinumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, interleukin inhibitors. (ATC code: L04AC05)
Marketing Authorisation Applicant	ELC Group s.r.o.
Medicinal products to which this RMP refers	Four (04)
Invented name(s) in the European Economic Area (EEA)	Usymro 45 mg solution for injection Usymro 45 mg solution for injection in pre-filled syringe Usymro 90 mg solution for injection in pre-filled syringe Usymro 130 mg concentrate for solution for infusion
Marketing authorisation procedure	Centralized Procedure
Brief description of the product	**Chemical class :** Monoclonal antibody
	Summary of mode of action: Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL-12 and IL-23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis and Crohn's disease. By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis and Crohn's disease through interruption of the Th1 and

	Th17 cytokine pathways, which are central to the pathology of these diseases.
	Important information about product composition: Usymro 45 mg solution for injection Each vial contains 45 mg ustekinumab in 0.5 mL. Usymro 45 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL. Usymro 90 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 90 mg ustekinumab in 1 mL. Usymro 130 mg concentrate for solution for infusion Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL). Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a Chinese hamster ovarian (CHO) cell line using recombinant DNA technology. List of excipients: ***Usymro 45 mg solution for injection; Usymro 45 mg solution for injection in pre-filled syringe; Usymro 90 mg solution for injection in pre-filled syringe*** L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injections ***Usymro 130 mg concentrate for solution for infusion*** EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-Methionine, Polysorbate 80, Sucrose, Water for injections
Hyperlink to the Product Information	Refer to Module-1, Section-1.3.1-spclabelpl
Indication(s) in the EEA	***Usymro 45 mg solution for injection; Usymro 45 mg solution for injection in pre-filled syringe; Usymro 90 mg solution for injection in pre-filled syringe*** Ustekinumab is indicated for: Plaque psoriasis Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or psoralen and ultraviolet A (PUVA).

	Paediatric plaque psoriasis Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis (PsA) Ustekinumab, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Adult Crohn's Disease Ustekinumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. Paediatric Crohn's disease Ustekinumab is indicated for the treatment of moderately to severely active CD in paediatric patients weighing at least 40 kg who have had an inadequate response to or were intolerant to either conventional or biologic therapy. ***Usymro 130 mg concentrate for solution for infusion*** Adult Crohn's Disease Ustekinumab is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies. Paediatric Crohn's disease Ustekinumab is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighting at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.
	Proposed: Not Applicable.
Dosage in the EEA	**Current:** Usymro is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which Usymro is indicated. **Posology:** Plaque psoriasis The recommended posology of Usymro is an initial dose of 45 mg

administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Patients with body weight > 100 kg

For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter.

Psoriatic arthritis

The recommended posology of Usymro is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Paediatric plaque psoriasis (6 years and older)

The recommended dose of Usymro is based on body weight as presented in the SmPC section 4.2 (Posology and Method of Administration). Usymro should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Adult Crohn's Disease

Usymro treatment is to be initiated with a single intravenous (IV) dose based on body weight, followed by subcutaneous (SC) doses.

The infusion solution for the IV dose is to be composed of the number of vials of Usymro 130 mg as specified in SmPC section 4.2 (Posology and Method of Administration).

The first SC dose should be given at Week 8 following the IV dose. For the posology of the subsequent SC dosing regimen, see section 4.2 of the Usymro solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

Paediatric Crohn's disease (patients weighing at least 40 kg)

Usymro 130 mg concentrate for solution for infusion

Usymro treatment is to be initiated with a single IV dose based on body weight. The infusion solution is to be composed of the number of vials of Usymro 130 mg as specified in the table below.

Body weight of patient at the time of dosing	**Recommended dose[a]**	**Number of 130 mg Usymro Vials**
⩾40 kg to ⩽55 kg	260 mg	2
>55 kg to ⩽85 kg	390 mg	3

	<table><tr><td>>85 kg</td><td>520 mg</td><td>4</td></tr></table> [a] Approximately 6 mg/kg *Usymro 45 mg solution for injection/ Usymro 45 mg solution for injection in pre-filled syringe/ Usymro 90 mg solution for injection in pre-filled syringe* The first SC dose should be given at Week 8 following the IV dose. For the posology of the subsequent SC dosing regimen, see section 4.2 of the Usymro solution for injection (vial) and solution for injection in pre-filled syringe SmPC.
	Proposed: Not Applicable.
Pharmaceutical form(s) and strengths	**Current:** 45 mg/0.5 mL, 90 mg/1.0mL, 45 mg/0.5 mL Solution for injection; 130 mg/26 mL concentrate for solution for infusion
	Proposed: Not Applicable.
Is the product subjected to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

Indication: Adult psoriasis

Incidence:

According to the global burden of disease (GBD) 2019 methodology, there were 4,622,594 (95% uncertainty interval or uncertainty intervals (UI) 4,458,904 - 4,780,771) incident cases of psoriasis worldwide in 2019. The age-standardized incidence rate in 2019 was 57.8 (95% UI 55.8–59.7) per 100,000 people.[1] A systematic review reported the incidence of psoriasis in adults ranged from 30.3 per 100,000 person years (PY) in Taiwan to 321.0 per 100,000 PY in Italy. The incidence of psoriasis in all ages in the United Kingdom (from 159.0 to 129.0 per 100 000 person years between 1999 and 2013). In China, the age-standardized incidence rate of psoriasis in 2019 was 50 to <60 per 100,000 people.[2]

Prevalence:

The global psoriasis prevalence rate is around 2–3% of the world population, reaching 8–11% in some Northern European countries. Worldwide, there were 40,805,386 (95% UI 39,421,384–42,076,746) prevalent cases of psoriasis in 2019. The age-standardized prevalence rate in 2019 was 503.6 (95% UI 486.9–519.2) per 100,000 people. With respect to 1990, this corresponded to a decrease of 23.7% (95% UI −24.0 to −23.5). By sex, the age-standardized prevalence rate was similar between men [510.7 (95% UI 493.4–526.4) per 100,000 people] and women [497.5 (95% UI 481.1–513.1) per 100,000 people]. In terms of GBD regions, the age-standardized prevalence rate was highest in Western Europe [1,884.1 (95% UI 1,817.4–1,948.3)], followed by Australasia [95% UI 1,506.1 (1,448.9–1,560.8)] and high-income North America [1,081.6 (95% UI 1,048.9–1,115.4)], whereas they were lowest in Southeast Asia [128.8 (95% UI 124.5–133.2)], followed by central Latin America [132.0 (95% UI 127.7–136.5)] and Eastern Sub-Saharan Africa [166.8 (95% UI 160.8–172.9)].[1] The large population of China results in 2.3 million people affected by psoriasis, and thus, China has the third highest estimated number of patients with psoriasis in the world.[2]

Demographics of the Population in the Adult Psoriasis Indication and Risk Factors for the Disease:

A review of 14 studies of psoriasis found a trend of increasing incidence with age up to 39 years. Incidence then decreased in patients 40 to 49 years of age before increasing again, with a second peak around 50 to 59 years of age. Age-specific estimates of incidence decreased toward the end of life. In the same analysis, prevalence also showed an increasing trend with age. Psoriasis was uncommon before 9 years of age, varying from 0% in Norway to 0.55% in the UK. Studies in Norway, Scotland, Spain, and Taiwan showed a first peak of the prevalence of psoriasis at either 20 to 29 or 30 to 39 years of age. Studies from the UK, Germany, and Russia showed an increasing trend for prevalence with age until around 60 years, after which it decreased. Studies of the prevalence of psoriasis males and females have reported varying results. There was no differences in the prevalence between sexes in Taiwanese children and across all patients in Norway, Spain, Scotland, and the UK. Studies in Sweden, Germany, and Norway reported a slightly higher prevalence of psoriasis in females. Studies in Denmark, Australia, and China reported a higher prevalence of psoriasis in males.[3]

Reports from nationally representative data in the US for patients between 20 and 59 years of age estimated the prevalence of psoriasis to be highest in the white population (3.6%), followed by African Americans (1.9%), Hispanics (1.6%), and other races (1.4%) from 2009 to 2010.[4]

The risk factors for psoriasis can be divided into two groups, namely, extrinsic and intrinsic risk factors. Extrinsic risk factors includes mechanical stress, air pollution, drugs, vaccination, infection, smoking and alcohol. Intrinsic risk factors includes metabolic syndrome, obesity, diabetes mellitus, dyslipidaemia, hypertension, and mental stress.[5]

The Main Existing Treatment Options:

Treatment for psoriasis is intended to interrupt the cycle that causes increased production of skin cells, which can lead to reduced inflammation, reduced plaque formation, scale removal, and smoother skin. Therapies used to treat psoriasis include the following:[6]

- Topical therapies (applied to the skin): These include creams and ointments, such as topical corticosteroids (the most frequently prescribed medication for psoriasis), vitamin D analogues, anthralin, topical retinoids, calcineurin inhibitors, salicylic acid, coal tar, and moisturizers. When the disease is severe, creams are likely to be combined with light therapy or oral medications.
- Light therapy (i.e., exposing the skin to natural or artificial ultraviolet [UV] light).
- Systemic medications (oral or injected): These are used in patients with moderate to severe psoriasis and include retinoids, methotrexate, hydroxyurea, immunomodulator drugs (including apremilast, azathioprine, cyclosporine, and leflunomide), biologies (including adalimumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, and secukinumab), thioguanine, brodalumab, and certolizumab pegol.
- Alternative medicine: Alternative therapies used by people with psoriasis include special diets, vitamins, acupuncture and herbal products applied to the skin (includes aloe extract cream, fish oil supplements, oregon grape).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

The most common form of psoriasis, plaque psoriasis, occurs in more than 80% of affected patients.[7] In the UK, a study reported that 51.8% of patients between 25 and 64 years of age with at least 1 psoriasis diagnosis in the previous 2 years had mild psoriasis (~2% BSA affected). Moderate (3%-10% BSA) and severe (> 10% BSA) psoriasis occurred in 35.8% and 12.4% of patients, respectively. Patients with severe psoriasis are more likely to have certain co-morbidities. For example, these patients are at greater risk of developing renal disease (odds ratio [OR] of 1.83 versus 0.97, respectively) and rheumatologic disease (OR of 2.89 versus 2.01, respectively) compared with patients with mild disease.[8]

If the disorder becomes pustular, then mortality rates are high. In addition, all treatments have major adverse effects including skin cancers, liver damage and susceptibility to infections. The biggest morbidity is from poor aesthetics which can cause depression, isolation, and withdrawal from society.[7]

A meta-analysis of 12 studies reporting all-cause or cause-specific mortality risk estimates in psoriasis patients compared with the general population or subjects free of psoriasis. The pooled relative risks for all-cause mortality were 1.21 (95% Cl 1.14 to 1.28) in psoriasis, 1.13 (95% Cl 1.09 to 1.16) in mild psoriasis, and 1.52 (95% Cl 1.35 to 1.71) in severe psoriasis. The pooled RRs for cardiovascular mortality were 1.15 (95% CI 1.09-1.21) in psoriasis, 1.05 (95% CI 0.92-1.20) in mild psoriasis, and 1.38 (95% CI 1.09-1.74) in severe psoriasis.[9]

Important Co-morbidities:

Almost 80% of patients with psoriasis present with mild to moderate severity. Metabolic comorbidities are seen in association with psoriasis, leading to significant morbidity including type-2 diabetes mellitus, cardiovascular disease, hypertension, and metabolic syndrome. Erythrodermic, generalized pustular and arthropathic variants of psoriasis represent severe forms of psoriasis.[7]

Indication: Pediatric psoriasis

Incidence:

A population-based study in the US over a 30-year period reported the overall age- and sex-adjusted annual incidence of pediatric psoriasis as 40.8 per 100,000 (95% Cl 36.6 to 45.1) from 1970 to 1999. Incidence of psoriasis in children increased significantly over time from 29.6 per 100,000 in 1970-1974 to 62.7 per 100,000 in 1995-1999 ($p<0.001$).[10] The incidence of psoriasis in children increased with age from 13.5 per 100 000 person years (0-3 years old) to 53.1 per 100 000 person years (14-18 years old).[2]

Prevalence:

The prevalence of psoriasis in children varied from 0.02% (95% uncertainty interval 0.01% to 0.04%) in east Asia to 0.22% (0.06% to 0.81%) in Australasia and 0.21% (0.11% to 0.41%) in western Europe.[2] The highest values are from European studies, especially Italy (2.1 %), Germany (1.3%), and the UK (1.3% for patients from 10-19 years of age).[11]

Demographics of the Population in the Pediatric Psoriasis Indication and Risk Factors for the Disease:

In a US population-based cohort study in children diagnosed with psoriasis between 1970 and 1999, Tollefson (2010) found a rapid increase in the incidence of psoriasis in both sexes up to 7 years of age, with incidence remaining relatively flat thereafter.[10] According to a systematic review, psoriasis was rare in children younger than 9 years, varying between 0% in Norway to 0.55% in the UK.[3]

Many of the risk factors for psoriasis in adults also apply to the paediatric population. In a Turkish case-control study of environmental risk factors, high body mass index (BMI), environmental tobacco smoke exposure at home, and stressful life events appeared to be associated with pediatric psoriasis.[12] Other identified risk factors include infection, stress (usually emotional or psychological) and a history of trauma.[11]

The Main Existing Treatment Options:

For the treatment for psoriasis in children doctor may recommend an antihistamine to help with itching. They may suggest petroleum jelly to lock in moisture. Salicylic acid and urea cream may also be an option for thick plaques, but it should not be used on children under 6 years old.[13]

- Topical treatments: Most children have mild psoriasis which can be treated with a cream, lotion, or ointment that's spread onto the skin. These includes anthralin, calcipotriene (a form of vitamin D), coal tar and corticosteroids.
- Light therapy: Types include artificial light (UV light) and laser therapy.
- Systemic medications includes etanercept, ixekizumab, or ustekinumab.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Psoriasis begins in childhood in almost one-third of cases. Lesions may differ in distribution and morphology, and clinical symptoms at presentation may vary from those reported by adults. Compared with adults, typical plaques with overlying white scale are often thinner and smaller in children, and psoriasis lesions tend to develop more often on the face and flexural areas. Lesions in children are characterized by maceration and a less prominent scale than in adults. Up to 75% of older children manifest with chronic plaque psoriasis, which is characterized by well-defined plaques with overlying silvery-white scale. The lesions vary in size and develop primarily on the scalp (which is most frequently involved and often the site of first presentation in children), face, and extensor surfaces of the elbow and knee.[14] Patients with childhood-onset psoriasis are more likely to have significant disease and flares compared with those with adult-onset psoriasis.[11] Mortality data relating to psoriasis in the pediatric population is not available.

Important Co-morbidities:

Co-morbidities that occur in pediatric patients with psoriasis include increased rates of hyperlipidaemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis and Crohn's disease.[15]

<u>Indication: Psoriatic arthritis</u>

Incidence:

Psoriatic arthritis (PsA) is a chronic and multisystem osteoarticular disease that affects 0.1 to 1% of the world's population and 6 to 41% of individuals diagnosed with psoriasis.[16] The reported incidence of PsA in recent publications ranges from 3.6–7.2 per 100,000 person years. The cumulative incidence of PsA over time in patients with psoriasis and reported 1.7%, 3.1% and 5.1% respectively had developed PsA at 5, 10, and 20 years after their diagnosis of psoriasis.[17] Psoriatic arthritis was observed in 5% of the patients with psoriasis in China.[56]

Prevalence:

A meta-analysis of 28 population studies reported a pooled prevalence of Psoriatic arthritis (PsA) rates are 133 every 100,000 subjects (95% CI, 107–164 every 100,000 subjects) of the global population.[18] A cross-sectional study using data from The Health Improvement Network (THIN), a large UK-based medical record database, reported that among 4.8 million patients in the THIN database between 18 and 90 years of age, 9,045 patients had at least 1 medical code for PsA between 1994 and 2010, for an overall prevalence of 0.19% (95% Cl 0.185 to 0.193).[19] A meta-analysis of 266 studies reported a pooled prevalence of 19.7% (95% Cl 18.5 to 20.9) among psoriasis patients. The PsA prevalence was 22.7% (95% CI, 20.6%-25.0%) in European patients with psoriasis, 21.5% (95% CI, 15.4%-28.2%) in South American patients with psoriasis, 19.5% (95% CI, 17.1%-22.1%) in North American patients with psoriasis, 15.5% (95% CI, 0.009%-51.5%) in African patients with psoriasis, and 14.0% (95% CI, 95% CI, 11.7%-16.3%) in Asian patients with psoriasis.[20] From population-based surveys in China, the prevalence of Psoriatic arthritis (PsA) appeared to be similar to the rest of the world, ranging from 10 to 100 per 100 000 population.[56]

Demographics of the Population in the Psoriatic arthritis Indication and Risk Factors for the Disease:

The demographic profile of PsA is consistent with that of psoriasis. Overall, men and women are affected by PsA with equal frequency.[19] The analysis of data from 40,009 patients, most of them were female (54.38%). The mean age was 51.79 years.[10]

Various genetic risk factors predispose patients to develop psoriatic arthritis and psoriasis. In these patients, an environmental trigger such as infection or mechanical stress initiates a chronic inflammatory process primarily involving the joints and skin, resulting in the production of IL-23, which is a central cytokine in the pathogenesis of psoriatic arthritis and psoriasis. Macrophages and dendritic cells produce IL-23. In fact, the gastrointestinal tract may be the source of IL-23 due to disturbed barrier function or changes in the microbiota. Enthesitis, which is inflammation at the site where ligaments, tendons, and joint capsules attach to the bone, is the prominent pathologic lesion in psoriatic arthritis in contrast to synovitis in rheumatoid arthritis.[21]

The main existing treatment options:

Treatment recommendations for PsA were developed by a task force of the European League Against Rheumatism, as well as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. Initial therapy for musculoskeletal manifestations of PsA includes non-steroidal antiinflammatory drugs (NSAIDs). Traditional disease-modifying anti rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, and leflunomide are used when poor prognostic indicators are present. Finally, biologics such as TNFa inhibitor and anti-IL-17 therapies should be considered when inflammation persists despite traditional treatment.[22]

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Approximately 30% of patients with psoriasis develop PsA.[23] Spondylitis (inflammation of the vertebra) has been reported in 40% of PsA patients. Eighty-seven percent of PsA patients have psoriatic lesions of the nail. In patients followed for more than 10 years, 55% had 5 or more deformed joints [24] In a study that identified 8,706 patients from THIN, the overall mortality rate of PsA patients was 10.37 deaths per 1,000 Person-Years (PY). The same study reported a mortality rate of 7.80 deaths per 1,000 PY in PsA patients prescribed DMARDs and a mortality rate of 12.46 deaths per 1,000 PY in PsA patients who were not prescribed DMARDs. Compared with population controls, patients with PsA did not have an increased risk of all-cause mortality or cause-specific mortality after adjusting for age and sex.[25,26]

Important co-morbidities:

Co-morbidities that occur in PsA patients include diabetes mellitus, obesity, metabolic syndrome (or components thereof), CV disease, IBD, uveitis, depression, and osteoporosis.[27]

<u>Indication: Adult Crohn's disease</u>

Incidence:

In 2019, there were approximately 4.9 million cases of IBD worldwide, with China and the USA having the highest number of cases [911 405 and 762 890 (66.9 and 245.3 cases per 100 000 people, respectively)].[28] In a systematic review, the highest annual incidence of Crohn's disease (CD) was 12.7 per 100,000 person-years in Europe, 5.0 person-years in Asia and the

Middle East, and 20.2 per 100,000 person-years in North America.[29] A Danish study from 1997 found that the mean incidence rate for men per 100 000 person years increased from 3.3 in 1981-1984 to 4.1 in 1989-1992. For women in the same area and in the same time intervals, the incidence rate increased from 4.6 to 6.2. A peak incidence rate was found among 15-29-year-olds, with an incidence rate among men and women of 5.3 and 9.1, respectively. A recent study in which all new CD cases in Finland between 2000 and 2007 were included revealed an overall incidence rate of 9.2 per 100,000 inhabitants. The incidence rate in Olmsted County, Minnesota, United States was 5.7 cases per 100,000 person years between 1940 and 1993.[30] In China, the incidence rate of Crohn's disease is $0.848/10^5$.[57]

Prevalence:

In a systematic review, the highest reported prevalence values for CD in Europe was (322 per 100,000 persons) and North America (319 per 100,000 persons). In time-trend analyses, 75% of CD studies had an increasing incidence of statistical significance ($P < .05$).[24] An adjusted prevalence of 133 per 100 000 was found in Minnesota, United States in 1991. One study from South Korea indicated prevalence of 11.2.[25] In the US, the prevalence of CD in adults (age over 17 years) was reported as 197.7 per 100,000 population (95% Cl 195.8 to 199.6).[31] In china, the prevalence rate of Crohn's disease is 2.29/105 person/year.[57]

Demographics of the Population in the Crohn's disease Indication and Risk Factors for the Disease:

In a study of hospital statistics from 1994 to 2007 from 9 European countries, the age distribution of hospitalization related to CD showed a large peak in younger patients (before 30-35 years of age), followed by a small peak in older patients.[32] A pooled analysis of studies conducted in Europe, North America, Australia, and New Zealand reported that the incidence rate of CD is lower in females than in males during childhood, but then increases in females compared with males in the 10- to 14-year age group; thereafter, it generally remains higher in females than in males.[33] For example, 1 study in the UK from 1986 to 2003 found that 62% of CD patients were female; another study in Denmark showed that 54% of CD patients were female. In addition, Hispanics in the US are less prone to develop IBD than the non-Hispanic population. Occurrence of CD seems to vary according to geographical location. A north-south axis has been found in both Europe and the US, with higher incidence and prevalence in the northern regions.[25] Risk factors for CD include age around 30 years old, ethnicity being whites have the highest risk, especially people of Eastern European (Ashkenazi) Jewish descent, family history, medications (such as nonsteroidal anti-inflammatory medications).[34] Appendectomy and smoking is associated with an increased risk of developing CD.[25] In China, data of the study demonstrated a male predominance in CD, with a male vs. female ratio of 2.30:1. The peak incidence of CD observed in this study was in the fourth decade of life (32.3 years), consistent with previous reports from China.[58]

The main existing treatment options:

The goal of medical treatment of CD is to reduce the inflammation that triggers signs and symptoms of the condition and that may lead to long-term damage. It is also to improve long-term prognosis by limiting complications. In the best cases, treatment may lead to long-term remission. Drugs used to treat CD include:

- Anti-inflammatory drugs: These are often used as a first step in the treatment of CD. Examples include sulfasalazine, mesalamine, and corticosteroids.

- Immune system suppressors: These drugs reduce inflammation by suppressing the immune response. Sometimes, these drugs are used in combination. Examples include AZA, 6-mercaptopurine (6-MP), MTX, cyclosporin, infliximab, adalimumab, and vedolizumab.
- Biologics: This class of therapies targets proteins made by the immune system. Types of biologics used to treat Crohn's disease include vedolizumab, infliximab, adalimumab, certolizumab pegol, ustekinumab, and Risankizumab.
- Antibiotics: These drugs can reduce the amount of drainage and sometimes heal fistulas and abscesses in patients with CD. It is also believed that antibiotics reduce harmful intestinal bacteria that might suppress the intestine's immune system, triggering symptoms. Examples include metronidazole and ciprofloxacin.
- In addition to controlling inflammation, some medications may help to relieve signs and symptoms of the disease. Examples include antidiarrheals, laxatives, pain relievers, iron supplements, vitamin B-12 injections, and calcium and vitamin D supplements.

If lifestyle changes, drug therapy, or other treatments do not relieve signs and symptoms of CD, surgery may be required to remove the damaged portion of the digestive tract, close fistulas, and drain abscesses.[35] Rates of bowel resection procedures range from 12% within 1 year of diagnosis in Denmark to 35% within 5 years in the UK.[25]

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Crohn's disease most often begins gradually and can become worse over time with periods of remission that can last for weeks or years. Possible complications of the disease include intestinal obstruction, fistulas, abscesses, anal fissures, ulcers, malnutrition, and inflammation in other parts of the body. Patients with CD in the large intestine are more likely to develop colon cancer.[36] Approximately 25% to 46% of patients with CD experience extra-intestinal manifestations. Extra-intestinal manifestations of CD include musculoskeletal, dermatologic, ocular, hepatobiliary, vascular and renal complications. In the earlier period, as many as 35% of the CD patients underwent bowel resection performed within the first year of diagnosis. In the IBSEN study, the cumulative probability of surgery was 13.6%, 27.0% and 37.9% at one, five, and ten years after diagnosis, respectively.[25]

A meta-analysis from 2007 identified 13 papers that reported standardized mortality ratios (SMR). Most of these papers included patients diagnosed in the 1950s to the 1970s, although four of them included patients diagnosed from 1980 to 1985. In this study, an age-adjusted mortality risk in CD patients was more than 50% greater than in the general population, but three of the studies actually reported an SMR below 1.0. A meta-analysis from 2010 also confirmed slightly increased mortality in CD patients (SMR 1.39, 95% CI: 1.30-1.50). In a recent report, a complete 10-year follow-up was achieved in 197 of 237 patients. Two deaths during follow-up were probably CD-related. Another study did not show any decrease in survival curves for the total group of 373 CD patients followed for five years compared to the background population, although a small subgroup of patients diagnosed at the age of 20-29 and a subgroup with extensive small bowel disease displayed slightly increased mortality.[25]

Important co-morbidities:

Co-morbidities that occur in CD patients include uveitis; episcleritis; arthritis; hepatobiliary disorders; nephrolithiasis; fat malabsorption; pancreatic disease; obesity; Cardiovascular

conditions, including venous thromboembolism (VTE) and atherosclerosis; depression; anxiety.[37]

Indication: Pediatric Crohn's Disease

Incidence:

A systematic review of pediatric-onset CD found that the incidence and prevalence of pediatric CD have been increasing over recent decades. A total of 131 studies from 48 countries were included. Among studies reporting incidence (n=37), 31 studies reported significant increases, and among studies reporting prevalence (n=7), all 7 studies reported significant increases[59]. Trends in incidence are likely multifactorial and include changing environmental exposures, access to specialist care, and improved imaging[60]. Rates of pediatric CD are highest in Northern Europe and North America, while the lowest rates are reported in Southern Europe, Asia, and the Middle East[59]. The most recent regional incidence rates of pediatric CD per 100,000 PY in Europe ranged from 0 to 6.1 in Southern Europe to 2.1 to 15.3 in Western Europe. In North America, incidence rates of pediatric CD were 4.3 to 11.2 per 100,000 PY in Canada and 1.3 to 15.3 in the US[59].

The most marked increases in the incidence of CD in Europe have been among adolescent age groups rather than among infants and younger children[61], with similar findings in the US[62]. In Canada, the incidence of very early onset CD is increasing faster than the incidence of CD in other age groups[60].

Prevalence:

Prevalence rates of pediatric CD per 100,000 range from 15.5 to 39.5 in Europe, 17.8 to 47.5 in Canada [59], and 45.9 in the US[62]. Using US insurance claims data, Lewis (2023)[63] estimated the prevalence rates of pediatric CD per 100,000 population as 14.1 in females and 15.6 in males less than 10 years of age, and 105.2 in females and 136.9 in males 10 to 19 years of age.

Demographics of the Population in the Pediatric Crohn's Disease Indication and Risk Factors for the Disease:

The incidence of CD in children less than 6 years of age (very early onset IBD) is lower than in older children. Given that onset in older children may be more influenced by environmental factors, differences in the incidence among older children are likely associated with environmental exposures[60].

Gender distribution in pediatric CD also appears to be influenced by age. Whereas there is an equal ratio of males to females with adult IBD, with perhaps slightly more affected females with disease, in pediatric CD, prepubertal males seem to be more affected[64]. In a study of children with IBD diagnosed before their seventeenth birthday from all pediatric gastroenterology centers in Scotland, Van Limbergen (2008)[65] found a strong trend toward higher prevalence in males in pediatric CD, with a male-to-female ratio of 1.5:1. Vernier-Massouille (2008)[66] also confirmed a male predilection, with a similar ratio of 1.4:1 in children younger than 15 years. This figure compares with a ratio nearing 1:1 in patients older than 15 years in the same population[67].

Risk Factors

Risk factors for pediatric CD include family history, prenatal exposure to antibiotics and tobacco smoke, and early-life otitis media. Breastfeeding has been shown to be a protective factor[68].

The Main Existing Treatment Options:

Treatment and treatment targets for pediatric CD are similar to those for adults. Medications are used off-label by pediatric prescribers where available and are recommended for use in pediatric treatment guidelines[69,70]. Treatments include corticosteroids, immune system suppressors, and antibiotics. Biologic therapies with regulatory approval for pediatric CD include infliximab and adalimumab. The use of exclusive enteral nutrition is also recommended for pediatric CD patients with purely inflammatory disease[71].

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

CD is a chronic inflammatory condition with a relapsing and remitting course characterized by asymmetric, transmural, and granulomatous inflammation which can affect any portion of the intestinal tract. The majority of children have inflammatory behavior at the time of diagnosis, with up to 38% having had complicated, stricturing, and/or penetrating disease[72]. Children may present with a range of symptoms, including abdominal pain, diarrhea, short stature, and weight loss. The most common extraintestinal manifestations in children are arthritis, cutaneous changes, eye disease, and liver disease[73]. It is believed that the increased use of more advanced therapies, such as biologics, has impacted the natural history of disease in children, resulting in a decreased risk of intestinal resections and stricturing complications[74].

Mortality

Studies conducted in Danish[75] and Swedish[76] cohorts identified an increased risk of death when patients with pediatric onset CD were followed into adulthood; however, death in pediatric patients due to CD is very rare. The increased mortality in adulthood may be due to the longer duration of disease, with more time to accrue cumulative inflammatory damage[76].

Important Co-morbidities:

Pediatric patients with CD often experience growth impairment and may experience pubertal delay[71]. Other common comorbidities include arthritis, thyroid disease, atopic dermatitis, autoimmune hepatitis, nephrolithiasis, and pancreatitis[77,78].

Module SII - Non-Clinical Part of the Safety Specification

To support the safety comparability of BAT2206 and Stelara®, the following non-clinical safety studies were conducted. BAT2206 is a recombinant human anti-interleukin (IL)-12/23 monoclonal antibody injection, which is a biological product. According to relevant guidelines, genotoxicity, carcinogenicity, and reproductive toxicity tests were not separately conducted.

Overview of Toxicology Studies:

Study type	Species/Strain	Route of administration	Duration	Dose
Single-dose pharmacokinetic test (including toxicity and immunogenicity)	Cynomolgus monkey	Subcutaneous	Single dose	BAT2206 low (1 mg/kg) and high (10 mg/kg) dose; EU-Stelara® low (1 mg/kg) and high (10 mg/kg) dose;

Study type	Species/Strain	Route of administration	Duration	Dose
				US-Stelara® low (1 mg/kg) and high (10 mg/kg) dose
Repeat-dose toxicity (accompanied by toxicokinetic, immunogenicity, and safety pharmacology)	Cynomolgus monkey	Subcutaneous	Repeated doses	BAT2206 low (3 mg/kg), medium (15 mg/kg), and high (45 mg/kg) dose groups; and EU-Stelara® (15 mg/kg) group
Repeat-dose toxicity (accompanied by toxicokinetic, immunogenicity, and safety pharmacology)	Cynomolgus monkey	Intravenous	Repeated doses	BAT2206 low (3 mg/kg), medium (15 mg/kg), and high (45 mg/kg) dose groups; and EU-Stelara® (45 mg/kg) group

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

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single-dose toxicity **Single Subcutaneous Dose Toxicity Study in Cynomolgus Monkeys** A single-dose PK study of BAT2206 was performed in 48 cynomolgus monkeys randomized into 6 groups and each group received a single subcutaneous (SC) injection: BAT2206 low (1 mg/kg) and high (10 mg/kg) dose groups; EU-Stelara® low (1 mg/kg) and high (10 mg/kg) dose groups; and US-Stelara® low (1 mg/kg) and high (10 mg/kg) dose groups. In the single-dose PK study, it was observed that 4 animals in each low dose groups of BAT2206, EU-Stelara®, and the US-Stelara® produced anti-drug antibodies with the lowest antibody titer being < 1 and highest 1:16. No animals in the high dose groups produced antibodies. No abnormal clinical manifestations were observed in any of the animals during the test.	No abnormal clinical manifestations were observed in any of the animals during the test; hence, no relevance for human use could be found.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Repeat-Dose Toxicity **4-week repeated-dose toxicity study of BAT2206 administered by SC injection with a 5-week recovery** A 4-week repeated-dose toxicity study of BAT2206 administered by SC injection with a 5-week recovery period was conducted in 50 cynomolgus monkeys. The animals were divided into 5 groups each (negative control group; BAT2206 low [3 mg/kg], medium [15 mg/kg], and high [45 mg/kg] dose groups; and EU-Stelara® [15 mg/kg] group). No animal died or was moribund during the test. At doses ⩽ 45 mg/kg, no systemic toxicity or toxic target organs were observed in the animals, and the no-observed-adverse-effect level was 45 mg/kg. No drug-associated abnormal changes were found in terms of the clinical observations, body weight, food consumption, body temperature, 12-lead electrocardiogram (ECG) parameters, blood pressure, oxygen saturation, ophthalmological examination, blood count, coagulation function, blood biochemistry, urinalysis, lymphocyte immunophenotyping, cytokines, immunoglobulin, and serum complements in the BAT2206 dose groups (3, 15, and 45 mg/kg) and the EU-Stelara® dose group (15 mg/kg). No changes in organ weight, gross lesions, or microscopic lesions associated with BAT2206 or EU-Stelara® were found. No local irritation in the injection area or systemic toxicity was observed.	No significant difference in systemic exposure was observed between BAT2206 and Stelara®. The no-observed-adverse-effect-level in this study was 45 mg/kg. At the same dose (15 mg/kg), BAT2206 had consistent systemic toxicity, local irritative reaction at the administration site and immunotoxicity, and similar toxicokinetic profile and immunogenicity with STELARA® (commercially available in EU).
4-week repeated-dose toxicity study of BAT2206-IV administered by IV injection with a 5-week recovery A 4-week repeated-dose toxicity study of 130mg/26mL Vial of BAT2206 (BAT2206-IV) administered by intravenous injection (IV) with a 5-week recovery period was conducted in 50 cynomolgus monkeys. The animals were divided into 5 groups each negative control group; BAT2206 low [3 mg/kg], medium [15 mg/kg], and	No significant difference in systemic exposure was observed between BAT2206 and Stelara®. The no-observed-adverse-effect-level in this study was 45 mg/kg. At the same dose (45 mg/kg), BAT2206 had consistent systemic toxicity, local irritative reaction at the administration site and immunotoxicity, and similar toxicokinetic profile and immunogenicity with STELARA® (commercially available in EU).

Key Safety findings (from non-clinical studies)	Relevance to human usage
high [45 mg/kg] dose groups; and EU-Stelara® [45 mg/kg] group). The following parameters were examined during the study: mortality/moribundity, clinical observation, body weights, food consumption, ophthalmology examination, body temperature, ECG, clinical pathology parameters, urine analysis, occult blood in feces, irritation observation of injection sites. The first 3 animals/sex/group were euthanized after 4 weeks of administration, and the remaining 2 animals/sex/group were euthanized after 5 weeks of recovery and observation. In the 4-week repeat dose toxicity study in cynomolgus monkeys intravenously administered 3, 15, 45mg/kg/week BAT2206 or EU-Stelara at 45mg/kg/week, no unscheduled deaths occurred. At doses $\leqslant$ 45 mg/kg, no systemic toxicity or toxic target organs were observed in the animals, and the NOAEL was 45 mg/kg. At the same dose level (45mg/kg), the exposure levels (AUC_{0-t} and C_{max}), immunogenicity and toxic effect with treatment of BAT2206 were similar to those of EU-Stelara.	
Genotoxicity Studies As a monoclonal antibody, ustekinumab is a biological product and is not expected to interact with DNA or other chromosomal substances. According to relevant guidelines, the general genotoxicity test used for drug evaluation is not applicable to biological products. In addition, no special safety concern has been shown in the completed general toxicological study.	Not applicable
Carcinogenicity Studies According to relevant guidelines, the conventional carcinogenicity test method is unsuitable for most biological products; meanwhile, no relevant carcinogenicity study has been submitted for Stelara® in the FDA and EMA review, so no carcinogenicity-related test has been conducted for BAT2206.	Not applicable
Reproductive and Development Toxicity Studies Considering that BAT2206 is highly similar to the	Not applicable

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
marketed Stelara® in the comparative study of structure, function, and general toxicological tests, reproductive toxicity tests have not been conducted for BAT2206. According to the package insert of Stelara®, there is no data on the use of marketed Stelara® in pregnant women. It is unknown whether the use of this product in pregnant women will cause foetal harm or affect fertility. It is clearly stated in the package insert that it should not be used in pregnant women unless the expected benefits outweigh the potential risks to the foetus.	
Other toxicity-related information or data	
Immunotoxicity and Immunogenicity Immunotoxicity and immunogenicity studies were conducted together with single-dose PK and repeat-dose toxicity studies in cynomolgus monkeys to compare BAT2206 with Stelara®. In the single-dose PK study, it was observed that 4 animals in each low dose groups of BAT2206, EU-Stelara®, and the US-Stelara® produced antibodies with the lowest antibody titer being < 1 and highest 1:16. No animals in the high dose groups produced antibodies. In the 4-week repeated-dose toxicity study of BAT2206 administered by SC injection with a 5-week recovery, there was no immunotoxicity in cynomolgus monkeys after subcutaneous administration of BAT2206 low [3 mg/kg], medium [15 mg/kg], and high [45 mg/kg] dose groups; and EU-Stelara® [15 mg/kg] group) under the conditions of the study. In this study, anti-drug antibodies (ADAs) was detected in one male animal on Days 15, 50 and 65 at the BAT2206 low group with titer dilution 1:1-1:8; and in one female animal on Day 65 at BAT2206 low group with titer dilution <1 (titer dilution of the ADA was lower the titer point). The TK results indicated that there were no apparent differences in TK parameters of C_{max} and AUC_{last} between the two animals with positive ADA and other animals in the same group. Other animals were not detected Anti BAT2206 antibody through the study.	There was no immunotoxicity seen in this non-clinical study; hence, no relevance for human use could be found. The immunogenicity of BAT2206 was comparable with that of Stelara®.

Key Safety findings (from non-clinical studies)	Relevance to human usage
In the 4-week repeated-dose toxicity study of BAT2206-IV administered by IV injection with a 5-week recovery, there was no immunotoxicity in cynomolgus monkeys after intravenous administration of BAT2206-IV low [3 mg/kg], medium [15 mg/kg], and high [45 mg/kg] dose groups; and EU-Stelara® [45 mg/kg] group) under the conditions of the study. In this study, no ADAs were found..	

In conclusion, BAT2206 showed consistent reaction characteristics with the reference medicine Stelara® in the single-dose toxicity study, repeat-dose toxicity studies, and the accompanied safety pharmacology, toxicokinetics, immunogenicity, and immunotoxicity study. In combination with the toxicology study data published by Stelara® and clinical experience and adverse reactions of Stelara®, it was considered that BAT2206 has similar efficacy and safety in clinical trials and clinical application. The dosage, route, frequency, and duration of BAT2206 can be determined by referring to the administration of Stelara® and clinical requirements. In summary, the presented nonclinical development of BAT2206 is considered adequate to demonstrate its biosimilarity with the approved and licensed Stelara® and to support the safe clinical use of BAT2206 for the proposed indications.

Module SIII - Clinical Trial Exposure

Phase I

A randomized, double-blind, single-dose, parallel three-arm study to compare the pharmacokinetics and safety of BAT2206 injection with ustekinumab injection (Stelara®) in Chinese healthy male subjects. A total of 270 subjects were enrolled and randomized at a ratio of 1:1:1 to receive 45 mg BAT2206 injection or Stelara® (EU and US-sourced) after a subcutaneous single dose. A total of 269 subjects were administered, including 90 subjects in the BAT2206 injection group and 89 subjects in the Stelara® (EU-sourced) group and 90 subjects in the Stelara® (US-sourced) group. A total of 266 subjects completed the trial, including 90 subjects in the BAT2206 injection group, 88 subjects in the Stelara® (EU-sourced) group and 88 subjects in the Stelara® (US-sourced) group.

	Experimental group	Control group
Drug	BAT2206 injection, 45mg, subcutaneous injection	Stelara® (EU or US-sourced), 45mg, subcutaneous injection
Dose	45mg/0.5mL/injection, subcutaneous injection at abdominal site which should be at least 5 cm away from navel (single dose on Day 1)	45mg/0.5mL/injection, subcutaneous injection at abdominal site which should be at least 5 cm away from navel (single dose on Day 1)
Number of patients received drug	90	89 in Stelara® (EU-sourced), 90 in Stelara® (US-sourced)

Phase III

A clinical development program included a multicenter, randomized, double-blind, parallel-arm, phase 3 study to compare efficacy and safety of BAT2206 with Stelara® in patients with moderate to severe plaque psoriasis. A total of 556 patients with moderate to severe plaque psoriasis were enrolled and randomly assigned to one of the 2 treatment groups in a 1:1 ratio (278 patients in the BAT2206 group and 278 patients in the EU-sourced Stelara® group).

	Experimental group	**Control group**
Drug	BAT2206	Stelara® (EU-sourced)
Dose	The study is composed of a 28-week initial treatment period (Treatment Period 1 [TP1]), and a 24-week secondary treatment period (Treatment Period 2 [TP2]). The study will be a maximum of 56 weeks. During TP1 and TP2, patients will receive either 45 mg or 90 mg of BAT2206 by subcutaneous (SC) injection via prefilled syringe (PFS) based on patient's baseline body weight.	The study is composed of a 28-week initial treatment period (Treatment Period 1 [TP1]), and a 24-week secondary treatment period (Treatment Period 2 [TP2]). The study will be a maximum of 56 weeks. During TP1 and TP2, patients will receive either 45 mg or 90 mg of European Union (EU)-sourced Stelara® by subcutaneous (SC) injection via prefilled syringe (PFS) based on patient's baseline body weight.
Number of patients enrolled	278	278

Clinical trial exposure data has been presented as per gender, geographical region, country, race, and ethnicity in below tables.

Table SIII.1: Gender

Gender	**Stelara**	**BAT2206**	**Total**
Male	192	182	374
Female	86	96	182
Total	**278**	**278**	**556**

Table SIII.2: Geographical Region and Country

	Stelara	**BAT2206**	**Total**
Geographical Region			
Central Europe	185	184	369
Asia Pacific	93	94	187

Country			
Bulgaria	37	36	73
China	93	94	187
Georgia	25	33	58
Poland	91	93	184
Russia	32	22	54
Total	**278**	**278**	**556**

Table SIII.3: Race and Ethnicity

	Stelara	**BAT2206**	**Total**
Race			
White	185	183	368
Asian	93	95	188
Ethnicity			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	278	277	555
Total	**278**	**278**	**556**

Module SIV - Populations Not Studied in Clinical Trials

A clinical development program included a multicenter, randomized, double-blind, parallel-arm, phase 3 study to compare efficacy and safety of BAT2206 with Stelara® in patients with moderate to severe plaque psoriasis. Patient selection was done using inclusion and exclusion criteria. Male or female ⩾18 years old with a diagnosis of plaque psoriasis for at least 24 weeks before screening, moderate to severe plaque psoriasis, patients failed to respond or have a contraindication to, or is intolerant to other systemic therapies including cyclosporine, methotrexate or PUVA (psoralen and ultraviolet A), female patients of childbearing potential and male patients with a female partner of childbearing potential must be willing to use a highly effective contraceptive precaution throughout the study period and continuing for at least 15 weeks after the last dose of study drug were eligible for inclusion in the study.

However, the patients were excluded based on the exclusion criteria presented in table below.

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

Important exclusion criteria

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Any forms of psoriasis at the time of the screening visit other than plaque-type such as erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis or other skin conditions (e.g., eczema)	Other forms of psoriasis would interfere with evaluations of the effect of investigational product on psoriasis.	No	Not to include patients with other forms of psoriasis than plaque-type that would make the results difficult to interpret.
Have previously received ustekinumab, a biosimilar of ustekinumab, or any drug that targets IL-12, IL-17, or IL-23	Use of these agents could interfere with interpretation of the clinical outcomes.	No	Aim of study is to include the patients previously untreated with the medicines with same target or directly related targets of the product.
Weight > 120 kg	An upper limit of 120 kg of body weight to increase homogeneity of enrolled patient population and reduce potential variations in the response to study drug as recommended by the EMA.	No	Not to include patient with body weight that would make the results difficult to interpret.
Have received any monoclonal antibody-based biologic drugs for the treatment of psoriasis or psoriatic arthritis other than those prohibited within 5 half-lives of the drugs before the screening visit.	Use of these agents could interfere with interpretation of the clinical outcomes	No	Aim of study is to include previously untreated patients with the mentioned products within a certain period.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Have received non-monoclonal antibody biological drugs (eg, etanercept) for the treatment of psoriasis or psoriatic arthritis within 12 weeks or 5 half-lives (whichever is longer) before the screening visit.			
Have received topical therapies for the treatment of psoriasis (such as corticosteroids, vitamin D analogs, or retinoids) within 2 weeks before baseline visit			
Have received ultraviolet (UV) A phototherapy (with or without oral psoralen), UVB phototherapy, any systemic steroids, or nonbiological drugs (such as methotrexate, apremilast, sulfasalazine, azathioprine, JAK inhibitors, or other immunosuppressive agents) for the treatment of psoriasis or psoriatic arthritis within 4 weeks before baseline visit.			
Have received any investigational drug within 8 weeks or 5 half-lives (whichever is longer) before the screening visit	Possible interaction/ complications with ustekinumab. Use of any other investigational drug could interfere with interpretation of the clinical outcomes	No	Standard exclusion criteria in clinical trials

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
	and may confound with study results.		
Have received any herbal remedies or traditional medicines used to treat psoriasis or psoriatic arthritis within 4 weeks before baseline visit.	Possible interaction/ complications with ustekinumab.	No	Use of any herbal remedies or traditional medicines could interfere with interpretation of the clinical outcomes and may confound with study results.
Have current or chronic inflammatory or autoimmune disease other than plaque psoriasis that may confound the evaluation of the effect of the study treatment. Patients with concurrent psoriatic arthritis will be allowed to participate.	Other conditions could interfere with interpretation of the clinical outcomes.	No	Not to include patient with current or chronic conditions that may confound the evaluation of the effect of the study treatment.
History of allergy to the active substance or any of the excipients of study drugs, or of hypersensitivity to latex	Caution should be used in patients with history of allergy to active substance, excipients or latex in order to avoid potentially life-threatening hypersensitivity reactions.	No	It is a known precautionary measure as mentioned in the SmPC (Section 4.3).
Have received a live vaccination within 4 weeks before the baseline visit (1 year before initiating treatment for Bacillus Calmette–Guérin [BCG] vaccines). (Patient must agree not to receive a live vaccination during the study and up to 15	Administration of live vaccines during immunomodulatory therapy may increase the risk of active infection following vaccination.	No	SmPC recommends that before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
weeks [1 year for BCG vaccines] after the last dose of the study drug). COVID-19 vaccination will not be allowed for 4 weeks before randomization or for 2 weeks before each dosing (Week 4, Week 16, Week 28, and Week 40) during the study.			weeks after vaccination (SmPC section 4.4).
Have clinical signs or symptoms consistent with coronavirus disease 2019 (COVID-19) infection, e.g., fever, dry cough, dyspnea, sore throat, fatigue, or confirmed infection by appropriate laboratory test (done at the discretion of investigator or per local regulation) within the last 4 weeks before screening or during screening. In case of confirmed COVID-19 infection before screening, documentation of resolution of infection by appropriate laboratory test is required.	Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab.	No	It is a known precautionary measure as mentioned in the SmPC (Section 4.3 and 4.4). Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.
History of invasive infection (e.g., histoplasmosis, coccidioidomycosis, blastomycosis).			
Presence of active infection at screening, history of infection requiring intravenous			

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
antibiotics and/or hospitalization ⩽ 8 weeks before baseline visit, or oral antibiotics ⩽ 2 weeks before baseline visit. Minor fungal infections may be allowed.			
Any recurrent bacterial, fungal, or viral infection that (based on the investigator's clinical assessment) makes the patient unsuitable for the study, including recurrent/disseminated herpes zoster.			
Latent or active TB infection			
Abnormal laboratory test results at screening	Ustekinumab is likely to worsen condition of patient. Other conditions could interfere with interpretation of the clinical outcomes. A 'stable' selected population was required for the clinical trials at baseline so a subject with uncontrolled medical problem was excluded.	No	This is a precautionary measure. There is a potential for immunogenicity with ustekinumab, which in turn may cause inflammation in the body organs. Not to include patient with disease that would make the results difficult to interpret.
Positive HIV, hepatitis B, or hepatitis C serological result			
Evidence of malignancy, lung infection, or abnormalities suggestive of active TB on chest radiography (x-ray or computed tomography) performed within 12 weeks before the screening visit or during the screening period.			
Significant medical problems, including (but not limited to) uncontrolled hypertension (systolic pressure ⩾ 160			

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
mm Hg and/or diastolic pressure ⩾ 100 mm Hg), congestive heart failure (New York Heart Association status of class III or IV), history of unstable angina pectoris, myocardial infarction, or cerebrovascular accident within the past 12 months, uncontrolled diabetes, or renal or liver disease.			
Any history of malignancy or lymphoproliferative disease at any time, except curative treatment for non-melanoma skin cancer or resected carcinoma in situ of the cervix	Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies. Therefore, patients with malignancy were excluded. Other immunosuppressive biologics have been associated with lymphoma. Therefore, patients with lymphoma were excluded.	No	It is a known precautionary measure as mentioned in the SmPC (Section 4.4).
Transplanted organ/tissue or stem cell transplantation	This is typical, prudent, precautionary position when a drug has not been widely used in humans.	No	Transplant patients generally receive immunosuppressive therapy to prevent rejection of the transplanted organ. Exposure to

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
	Most patients who have undergone organ transplant require immunosuppressant medications that preclude inclusion in clinical trials.		ustekinumab might increase the risk of complications from concomitant immunosuppression.
An underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious, or gastrointestinal condition, which in the opinion of the investigator places the patient at unacceptable risk.	This is typical, precautionary position, applied to clinical trial subjects when a drug has not been widely used in humans. The patient would be at unacceptable risk.	No	To avoid the unacceptable risks that may occur due to the underlying conditions.
History of demyelinating diseases (including myelitis) or neurologic symptoms suggestive of demyelinating disease	Other conditions could interfere with interpretation of the clinical outcomes.	No	Introduction of confounding factors may result in possible interaction/ complications with ustekinumab.
Any major surgical procedure within 12 weeks of the baseline visit or planned during the study.			
Patient is not willing to limit UV light exposure (eg, sunbathing and/or the use of tanning devices) during the study			
History of clinically significant drug or alcohol abuse within the last 12 months as judged by the investigator.			

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
Pregnant or breastfeeding (lactating) women.	Per ICH guidance, pregnant women are generally excluded from clinical trials. Data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts.	No	SmPC section 4.6 notes lack of adequate data regarding the use of ustekinumab in pregnant women, advises against use during pregnancy, and advises for the use of effective methods of contraception during treatment and up to 15 weeks after treatment. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision must be made on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy.
Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study. Patients participating in another investigational drug or device (a device is an instrument, apparatus, implement, machine, contrivance, or implant, including a component part or accessory intended for use in the diagnosis of disease or other conditions, or in the cure,	Possible interaction/ complications with ustekinumab. Use of any other investigational drug or device could interfere with interpretation of the clinical outcomes and may confound with study results.	No	Standard exclusion criteria in clinical trials.

Criteria	Reason for exclusion	Is it considered to be included as missing information? YES/NO	Rationale
mitigation, treatment, or prevention of disease) trial or planning on participating in another clinical trial during the course of the study.			

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breast-feeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other: Paediatric Patients	Only patient's aged ⩾ 18 years were included in the study. Hence, no paediatric population were included in the clinical development program.

Type of special population	Exposure
Other: Patients with different type of psoriasis (psoriasis other than plaque-type that were listed in exclusion criteria 1) in clinical trials	Not included in the clinical development program

Module SV - Post-Authorisation Experience

Not applicable as the product is not marketed yet.

Module SVI - Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The Summary of Product Characteristics and package insert provides detailed information to the prescribers and users on the appropriate use of the ustekinumab which includes proper method of administration as well as number of doses and dosing. No trials have been conducted to evaluate the dependence potential of ustekinumab. The available data suggest that ustekinumab is unlikely to cause dependence. As a class, therapeutic mAbs are not associated with dependence, and the chemical structure of ustekinumab differs from central nervous system-active drugs associated with dependence. The pharmaceutical and pharmacokinetic/pharmacodynamic characteristics of ustekinumab are not characteristic of drugs with high dependence potential (e.g., rapid onset/short-acting active substances). In repeated dose toxicology studies, no abnormal behavior or withdrawal symptoms were observed following cessation of dosing in recovery periods. Further, ustekinumab is a prescription drug and misuse for illegal purpose is unlikely.

Module SVII - Identified and Potential Risks

This is an application submitted under the legal basis article 10(4) bio-similar application. The list of safety concerns considered for this Usymro RMP is in line with the reference product Stelara® RMP (https://www.ema.europa.eu/en/documents/rmp-summary/stelara-epar-risk-management-plan-summary_en.pdf).

SVII.1 Identification of safety concerns in the initial RMP submission

Important Identified Risks	• None
Important Potential Risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing Information	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease • Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks	**Listed in Section**	**Reason for not including an identified or potential risk in the list of safety concerns in the RMP**
Infusion-related reactions / Injection site reactions	Listed under SmPC Sections 4.4 'Special warnings and precautions for use' and 4.8 'Undesirable effects'.	Infusion-related reactions / Injection site reactions are already well known to health care professionals (HCPs). The HCPs have appropriate measures in place as part of routine clinical practice for prevention and treatment of these infusion-related reactions / Injection site reactions.
Serious skin conditions	Listed under SmPC Section 4.4 'Special warnings and precautions for use' and 4.8 'Undesirable effects'.	These are known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk

Risks	Listed in Section	Reason for not including an identified or potential risk in the list of safety concerns in the RMP
		minimisation messages in the product information are adhered by prescribers.
Lupus-related conditions	Listed under SmPC Section 4.4 'Special warnings and precautions for use' and 4.8 'Undesirable effects'.	These are known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.
Concomitant use of live vaccines	Listed under SmPC Section 4.3 'Contraindications', 4.4 'Special warnings and precautions for use', 4.5 'Interaction with other medicinal products and other forms of interaction' and 4.6 'Fertility, pregnancy and lactation'.	This has been specified as a precautionary measure. Concurrent use of ustekinumab with live vaccines should be avoided.
Overdose	Listed under SmPC Section 4.9 'Overdose'.	This is a common special situation observed with ustekinumab which may have clinical consequences, even serious.

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

Safety Concerns	Risk-benefit impact
Important identified risk	
None	
Important potential risk	
Serious infections (including mycobacterial and salmonella infections)	In this multi-database cohort study, the primary outcome measure was hospitalizations due to serious infections, which included bacterial, viral, or opportunistic infections. The incidence rates of serious infection

Safety Concerns	Risk-benefit impact
	among ustekinumab initiators ranged from 0.59 to 0.95 per 100 person-years.[38] As per Ustekinumab SmPC section 4.8, in the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up). As per Ustekinumab SmPC section 4.4, Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab. Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab. The frequency of infections with ustekinumab is Common (≥ 1/100 to < 1/10) for upper respiratory tract infection, nasopharyngitis, sinusitis and Uncommon (≥ 1/1,000 to < 1/100) for herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, and vulvovaginal mycotic infection.
Malignancy	Pooled analyses of clinical trials and long-term extension studies involving 3117 patients with follow-up time up to 5 years have malignancy risk incidence rates of 0.60 (0.45-0.78) per 100 patient years and post-marketing cohort study involving 4364 patients with follow-up time up to 7 years have malignancy risk incidence rates of 0.48 per 100 patient years.[39] As per Ustekinumab SmPC section 4.4, Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received ustekinumab in clinical studies developed cutaneous and non-cutaneous malignancies. The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

Safety Concerns	Risk-benefit impact
	As per Ustekinumab SmPC section 4.8, In the controlled and non-controlled periods of psoriasis, psoriatic arthritis and Crohn's disease and ulcerative colitis clinical studies, malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.540 per 100 patient- years of follow-up for ustekinumab-treated patients). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population.
Cardiovascular events	Incidence rates of severe cardiovascular event were estimated every 2 months in the 12 months following ustekinumab initiation. The risk of acute coronary syndrome, unstable angina and stroke in the 6 months following ustekinumab initiation was estimated according to the cardiovascular risk of the individuals. Among patients with high cardiovascular risk, the risk was 1.03%, 95%CI (0.60-1.46). For patients with low cardiovascular risk, the risk was 0.14%, 95%CI (0.05-0.23).[40] As per Ustekinumab SmPC section 4.4, Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab.
Serious depression including suicidality	There was one randomized controlled trial in which 131 participants were exposed to ustekinumab over 28 weeks. The most common adverse psychiatric events was anxiety (N = 4; 3.10%), followed by depression (N = 2; 1.53%). In the other randomized controlled trial involving ustekinumab, there were 394 participants exposed to ustekinumab over 8 weeks. The most frequent adverse psychiatric event was suicide or suicide attempt (N = 2; 1.53%).[41] Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. Depression has been identified as an ADR with uncommon (≥ 1/1,000

Safety Concerns	Risk-benefit impact
	to < 1/100) frequency as per Ustekinumab SmPC section 4.8 'Undesirable effects'.
Venous thromboembolism	There are no specific studies evaluating the risk of venous thromboembolism (VTE) and ustekinumab in inflammatory bowel diseases (IBD) patients, a recent meta-analysis including 13 studies and 1450 patients only reported one incidence of a deep venous thrombosis (DVT). In psoriasis patients, data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) also did not report any findings of increased VTE risk.[42]
Missing information	
Long-term safety in pediatric psoriasis patients 6 years and older	As per Ustekinumab SmPC section 4.8, the safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. No data available on long-term safety in pediatric psoriasis patients of 6 years and older.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	As per Ustekinumab SmPC section 4.8, the safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. No data available on long-term impact on growth and development in pediatric psoriasis patients of 6 years and older.
Long-term safety in adult patients with moderately to severely active Crohn's disease	No data available on long-term safety in adult patients with moderately to severely active Crohn's disease.
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn’s disease	No long-term safety data in pediatric patients weighing at least 40 kg with moderately to severely active CD have been obtained in clinical trials to date.

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

Not applicable.

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

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

Important Identified Risk: None

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
Potential mechanisms:	Studies suggest that IL-12 may contribute to protective immune responses to intracellular protozoa, bacteria, and fungal pathogens[43], and IL-23 may contribute to immunity to Klebsiella pneumonia[44], Mycobacterium tuberculosis[45], and Candida albicans[46].
Evidence source(s) and strength of evidence:	Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. As per Ustekinumab SmPC section 4.4, in clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab. In clinical Phase 3 study (BAT-2206-002-CR), 365 treatment-emergent adverse events (TEAEs) of infections were reported in 231 subjects (41.6%). During the TP1, the proportion of subjects experiencing infections was higher in the Stelara group (5 subjects [35.7%]) than the BAT2206 group (2 subjects [15.4%]). During the TP2, 49 subjects [36.8%] in Stelara-Stelara group, 58 subjects [44.3%] in Stelara-BAT2206 group, and 117 subjects [44.3%] in BAT2206-BAT2206 group experienced TEAE of infections.
Characterisation of the risk:	As per Ustekinumab SmPC section 4.8, In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of exposure in 6,710 patients, the rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections. The impact of serious infection on the individual patient may be significant. Patients with a history

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
	of latent TB will require additional therapy prior to using ustekinumab or will have to choose a medication other than ustekinumab. Patients with active infections will have to choose an alternative medication and discontinue use of ustekinumab until the infection is cleared.
Risk factors and risk groups:	Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics.
Preventability:	Ustekinumab is contraindicated in patients with a clinically important, active infection (e.g., active tuberculosis) (ustekinumab SmPC section 4.3 'Contraindications'). To prevent serious infections, it is recommended that live vaccines not be given concurrently with ustekinumab (ustekinumab SmPC sections 4.4 'Special Warnings and Precautions for Use' and 4.5 'Interaction with Other Medicinal Products' and other Forms of Interaction'). For infants exposed to ustekinumab in utero, administration of live vaccines is not recommended for 6 months following birth or until ustekinumab infant serum levels are undetectable (SmPC sections 4.4 'Special Warnings and Precautions for Use', 4.5 'Interaction with Other Medicinal Products and other Forms of Interaction', and 4.6 'Fertility, Pregnancy and Lactation'). Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection (Stelara SmPC section 4.4 'Special Warnings and Precautions for Use'). Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and ustekinumab should not be administered until the infection resolves.
Impact on the risk-benefit balance of the product:	The available cumulative information does not provide evidence for an increased risk of serious infections in patients treated with ustekinumab and therefore a negative impact on the risk-benefit balance of the product is not evident.

Important Potential Risk: Serious infections (including mycobacterial and salmonella infections)	
	Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for serious infections is conducted through routine pharmacovigilance activities.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the product information.

Important Potential Risk: Malignancy	
Potential mechanisms:	Scientific literature suggests that IL-12 can contribute to tumour immunosurveillance and exogenous IL-12 can promote tumour-directed cytotoxic T cell responses in tumour vaccine strategies.[47] In contrast, IL-23 has been reported to promote tumour growth in animal models.
Evidence source(s) and strength of evidence:	There is a theoretical risk of malignancy associated with administration of Ustekinumab based on scientific literature pertaining to inhibition of lL12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer was low and was balanced between the ustekinumab and comparator groups. In clinical Phase 3 study (BAT-2206-002-CR), 01 TEAE of malignancy (breast cancer) was reported in 1 subject (7.1%) of the Stelara group during the TP1.
Characterisation of the risk:	As per Ustekinumab SmPC section 4.8, In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.540 per 100 patient- years of follow-up for ustekinumab-treated patients). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1)

Important Potential Risk: Malignancy	
	is comparable with the ratio expected in the general population.
Risk factors and risk groups:	The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Preventability:	As indicated in the Ustekinumab SmPC section 4.4 'Special Warnings and Precautions of Use', caution should be exercised when considering the use of ustekinumab in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy, or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer.
Impact on the risk-benefit balance of the product:	Although malignancies have been reported in patients treated with ustekinumab in clinical trials, available cumulative information does not suggest an increased risk of malignancy in patients treated with ustekinumab. Therefore, no negative impact on the risk-benefit balance of the product is evident. Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for malignancy is conducted through routine pharmacovigilance activities.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the product information.

Important Potential Risk: Cardiovascular events	
Potential mechanisms:	Ustekinumab inhibits the p40 subunit shared by IL-12, a helper T cell subtype 1 (TH1) inducer, and IL-23, which maintains TH17 cell homeostasis. The anti–IL-12/23p40 antibody ustekinumab, by the inhibition of the TH17 pathway, may therefore induce atherosclerotic plaque rupture and atherothrombotic events, including stroke and acute coronary syndrome.[48]
Evidence source(s) and strength of evidence:	The risk of developing cardiovascular events in subjects on ustekinumab is currently unknown. Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study of Ustekinumab. In clinical Phase 3 study (BAT-2206-002-CR), 20 TEAEs of cardiovascular events were reported in 15 subjects (2.7%). During the TP1, the proportion of subjects experiencing cardiac events was 1 subject (7.1%) in the Stelara group and 1 subject (7.7%) in the BAT2206 group. During the TP2, 2 subjects (1.5%) in Stelara-Stelara group, 4 subjects (3.1%) in Stelara-BAT2206 group, and 7 subjects (2.7%) in BAT2206-BAT2206 group experienced TEAE of cardiac disorders.
Characterisation of the risk:	There is evidence for an increased background risk of cardiovascular disease in patients with psoriasis and IBD, and patients may experience debilitating MI, stroke, or death. Patients are not considered at further cardiovascular risk from use of ustekinumab beyond that related to the psoriasis or IBD population risk. Patients with psoriasis and IBD require vigilance and adequate treatment of cardiovascular risk factors including hypertension, hypercholesterolemia, and diabetes. Major adverse cardiovascular events may result in fatal outcome.
Risk factors and risk groups:	Risk factors for the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, unhealthy diet, physical inactivity, obesity, and family history.[49]
Preventability:	Risk factors for cardiovascular disease should be regularly assessed during treatment with ustekinumab. The preventability of cardiovascular

Important Potential Risk: Cardiovascular events	
	disease is based upon the modification of known risk factors.
Impact on the risk-benefit balance of the product:	Although cardiovascular events have been reported in patients treated with ustekinumab in studies, the available cumulative information does not provide evidence for an increased risk of cardiovascular events in patients treated with ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is expected.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the product information.

Important Potential Risk: Serious depression including suicidality	
Potential mechanisms:	Depression is a complex disease with a variety of biologic theories for the pathophysiology. The mechanism by which ustekinumab could cause depression is not known.
Evidence source(s) and strength of evidence:	In one randomized controlled trial in which 131 participants were exposed to ustekinumab over 28 weeks. The most common adverse psychiatric event was anxiety (N = 4; 3.10%), followed by depression (N = 2; 1.53%). In the other randomized controlled trial involving ustekinumab, there were 394 participants exposed to ustekinumab over 8 weeks. The most frequent adverse psychiatric event was suicide or suicide attempt (N = 2; 1.53%).[50] Depression has been identified as an ADR for Ustekinumab SmPC section 4.8 'Undesirable Effects' and Package Leaflet section 4. The frequency of depression with ustekinumab is uncommon (≥ 1/1,000 to < 1/100). In clinical Phase 3 study (BAT-2206-002-CR), no adverse events of serious depression including suicidality were reported.
Characterisation of the risk:	Psoriasis patients can have an increased risk for depression and, in rare cases, suicide. The impact of depression on the individual patient may be very significant, and patients with a history of untreated or inadequately treated depression should be treated for such. There may be psychosocial impact and possibility of death from suicide attempts.

Important Potential Risk: Serious depression including suicidality	
Risk factors and risk groups:	Risk factors for depression include sociodemographic factors (gender, marital status, age and unemployment), physical diseases (chronic diseases, medical comorbid conditions), hereditary (personal or family history), and adverse childhood experiences (emotional abuse, sexual, and physical neglect during childhood).[51]
Preventability:	There is no known means of preventing depression.
Impact on the risk-benefit balance of the product:	Although depression has been reported in patients treated with ustekinumab in clinical trials, available cumulative information does not provide evidence for an increased risk of depression in patients treated with ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is evident. Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for depression is conducted through routine pharmacovigilance activities.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the product information.

Important Potential Risk: Venous thromboembolism	
Potential mechanisms:	The mechanism by which ustekinumab could cause venous thromboembolism is not known.
Evidence source(s) and strength of evidence:	Patients with inflammatory bowel disease (IBD) have an increased risk of venous thromboembolism (VTE). As reported in the literature, overall IBD patients have a two to three-fold increased risk of venous thromboembolism. In patients with active IBD, additional risk factors including corticosteroid use, oral contraceptive use, IBD flare, and surgery confer an even higher risk of thromboembolic events compared with the overall IBD population.[52] The meta-analysis found that patients with psoriasis had a 1.26-fold risk for new-onset VTE compared with those without psoriasis.[53] In clinical Phase 3 study (BAT-2206-002-CR), no adverse events of venous thromboembolism were reported.

Important Potential Risk: Venous thromboembolism	
Characterisation of the risk:	The impact of VTE on the individual patient may be significant and may result in a fatal outcome or cause serious long-term complications. Patients with IBD may require prolonged or indefinite anticoagulant therapy. Patients may experience debilitating VTE events including events of deep vein thrombosis, pulmonary embolism, or splanchnic vein thrombosis with or without fatal outcome. The occurrence of VTE imparts a greater risk of in-hospital mortality among hospitalized IBD patients that is greater than the greater mortality risk imparted by VTE in the non-IBD population. Patients with IBD require vigilance in adequate treatment of VTE risk factors.[54]
Risk factors and risk groups:	Substantial data suggest that IBD is a risk factor for VTE, with a 3-fold higher risk compared with patients without IBD[54]. Risk factors for VTE include high cholesterol, hypertension, diabetes, smoking, obesity, stress and nutrition.[55]
Preventability:	Patients with risk factors for venous thrombosis may require prophylactic anticoagulation. The preventability is also aimed at reducing acquired risk factors through appropriate measures like reducing cholesterol level, control blood pressure and diabetes, weight loss, and proper nutrition.
Impact on the risk-benefit balance of the product:	Although VTE has been reported in patients treated with ustekinumab in clinical trials, available cumulative information does not provide evidence for causal association between VTE and the use of ustekinumab. Therefore, no significant negative impact on the risk-benefit balance of the product is evident. Further characterization of the incidence, risk factors, and potential relationships with the use of ustekinumab for VTE is conducted through routine pharmacovigilance activities.
Public health impact:	The public health impact of the risk is anticipated to be minimal if the drug is used in accordance with the product information.

SVII.3.2. Presentation of the missing information

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older	
Evidence source:	Population in need of further characterisation: As per Usymro (Ustekinumab) SmPC section 4.8, The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis. There are no data on long-term safety in pediatric psoriasis patients 6 years and older.

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Evidence source:	Population in need of further characterisation: As per Usymro (Ustekinumab) SmPC section 4.8, The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis. There are no data on long-term impact on growth and development in pediatric psoriasis patients 6 years and older.

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Evidence source:	Population in need of further characterisation: There are no adequate data available on long-term safety in adult patients with moderately to severely active Crohn's disease.

Missing information: Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn’s disease	
Evidence source:	Population in need of further characterisation: As per Usymro (Ustekinumab) SmPC section 4.8, the safety of ustekinumab has been studied in one phase 1 and one phase 3 study of paediatric patients with moderately to

	severely active Crohn’s disease up to week 240 and week 52, respectively. In general, the safety profile in this cohort (n = 71) was similar to that seen in previous studies in adults with Crohn’s disease. There are no adequate data available on long-term extension safety in pediatric patients with moderately to severely active Crohn's disease.

Module SVIII - Summary of the safety concerns

Summary of safety concerns	
Important Identified Risks	• None
Important Potential Risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing Information	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn's disease • Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn’s disease

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

III.1 Routine pharmacovigilance activities

The applicant employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline to further characterise all the safety concerns discussed in this EU RMP.

With regard to the collection and recording of reports of suspected adverse reactions, follow-up activities would be performed as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases, in consistent with GVP Module VI. In considering that this is a biological medicinal product, all appropriate measures will be taken to clearly identify the product brand name and batch number(s) that involved for suspected adverse reaction(s).

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed in order to provide further characterisation data for specific safety concerns:

Specific adverse reaction follow-up questionnaires for safety concerns: The Applicant has a standardised process for the use of follow-up questionnaires within the pharmacovigilance system as part of post-marketing surveillance. This process includes contact to the healthcare professional (HCP) or reporter using the questionnaire via phone or e-mail. The follow-up to consumer will include an attempt to obtain consent to contact the HCP. A minimum number of queries are made depending on the seriousness of the case; medical judgment or local regulations are applied to determine if further attempts (above the minimum) should be made.:

- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Tuberculosis (TB)
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)
- Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cardiovascular Events
- Topic of lnterest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

Other forms of routine pharmacovigilance activities for safety concerns: None

III.2 Additional pharmacovigilance activities

There is no additional pharmacovigilance activity planned or ongoing for this product.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

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

Safety concern	Routine risk minimisation activities
Important identified risk	
None	
Important potential risk	
Serious infections (including mycobacterial and Salmonella infections)	Routine risk communication: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8. Package Leaflet (PL) sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance regarding evaluation of patients for TB infection, treatment of latent TB, and administration of anti-TB therapy in patients with a history of latent or active TB prior to initiation of ustekinumab. • Recommendation to monitor patients for signs and symptoms of active TB during and after ustekinumab treatment. • Guidance for managing patients who develop a serious infection. • Recommendations regarding the administration of live vaccines to patients receiving ustekinumab and to infants exposed to ustekinumab in utero. (The same recommendations are included in SmPC section 4.5) SmPC section 4.6 (Fertility, Pregnancy and Lactation) • Recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. PL section 2 • Guidance for patients who have recently had or are going to have a vaccination.

Safety concern	**Routine risk minimisation activities**
	• Guidance for mothers who received ustekinumab while pregnant and recommendation regarding the administration of live vaccines to infants exposed to ustekinumab in utero. • Guidance for patients who have had a recent infection, have any abnormal skin openings (fistulae), are over 65 years of age, or have recently been exposed to someone who might have TB. PL section 4 • Guidance for patients who develop signs of an infection or have open cuts or sores while using ustekinumab. <u>Other routine risk minimisation measures beyond the Product Information</u>: Legal Status: Restricted medical prescription.
Malignancy	<u>Routine risk communication</u>: SmPC sections 4.4 and 4.8. PL sections 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: SmPC section 4.4 (Special Warnings and Precautions for Use) • Guidance for monitoring patients for the appearance of skin cancer. <u>Other routine risk minimisation measures beyond the Product Information</u>: Legal Status: Restricted medical prescription.
Cardiovascular events	<u>Routine risk communication</u>: None <u>Routine risk minimization activities recommending specific clinical measures to address the risk</u>: None. <u>Other routine risk minimisation measures beyond the Product Information</u>:

Safety concern	**Routine risk minimisation activities**
	Legal Status: Restricted medical prescription.
Serious depression including suicidality	Routine risk communication: SmPC sections 4.8. PL sections 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal Status: Restricted medical prescription.
Venous thromboembolism	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal Status: Restricted medical prescription.
Missing information	
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal Status: Restricted medical prescription.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal Status: Restricted medical prescription.
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal Status: Restricted medical prescription.
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: Restricted medical prescription.

V.2 Additional Risk Minimisation Measures

None.

V.3 Summary table of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections (including mycobacterial and salmonella infections)	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8. PL sections 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQs for serious infections and TB.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
		Additional pharmacovigilance activities: None.
Malignancy	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQ. Additional pharmacovigilance activities: None.
Cardiovascular events	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: TOI TFUQ. Additional pharmacovigilance activities: None.
Serious depression including suicidality	Routine risk minimisation measures: SmPC sections 4.8. PL sections 4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Venous thromboembolism	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	Additional risk minimisation measures: None	reactions reporting and signal detection: TOIQ. Additional pharmacovigilance activities: None.
Long-term safety in pediatric psoriasis patients 6 years and older	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety in adult patients with moderately to severely active Crohn's disease	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Usymro (Ustekinumab)

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

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

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

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

I. The medicine and what it is used for

Usymro is authorized for plaque psoriasis, psoriatic arthritis (PsA), pediatric plaque psoriasis, adult Crohn's disease (CD) and pediatric CD. (see SmPC for the full indication). It contains ustekinumab as the active substance and it is given by the intravenous (IV) or subcutaneous (SC) route of administration.

Further information about the evaluation of Usymro's benefits can be found in Usymro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Usymro, together with measures to minimise such risks, and the proposed studies for learning more about Usymro'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 reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 Usymro is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Usymro 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 Usymro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risk	• None
Important potential risks	• Serious infections (including mycobacterial and salmonella infections) • Malignancy • Cardiovascular events • Serious depression including suicidality • Venous thromboembolism
Missing information	• Long-term safety in pediatric psoriasis patients 6 years and older • Long-term impact on growth and development in pediatric psoriasis patients 6 years and older • Long-term safety in adult patients with moderately to severely active Crohn' s disease • Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease

II.B Summary of important risks

Important potential risk: Serious infections (including mycobacterial and Salmonella infections)	
Evidence for linking the risk to the medicine	Published nonclinical and medical literature suggest that inhibition of IL-12/23 may predispose patients to serious infections. As per Usymro SmPC section 4.4, in clinical

	studies, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab.
Risk factors and risk groups	Risk factors for the development of serious infections include diabetes and other comorbidities, as well as the concomitant use of steroids, anti-TNFs, other immunosuppressants, or other biologics.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.5, 4.6 and 4.8. PL sections 2 and 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	There is a theoretical risk of malignancy associated with administration of Usymro based on scientific literature pertaining to inhibition of lL-12/23. In the pooled controlled portion of clinical trials across indications, the rate of malignancy other than non-melanoma skin cancer was low and was balanced between the ustekinumab and comparator groups.
Risk factors and risk groups	The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease. General risk factors for malignancy include increasing age, lifestyle factors (such as use of alcohol and tobacco and obesity), family history of cancer, and certain environmental exposures. Risk factors for the development of malignancy can differ by cancer site. However, in general, factors that can increase risk of malignancies in IBD patients include but are not limited to smoking, ongoing inflammation, and carcinogenic effects of immunosuppressive drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	The risk of developing cardiovascular events in subjects on Usymro is currently unknown. Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study.
Risk factors and risk groups	Risk factors for the development of cardiovascular disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, age, unhealthy diet, physical inactivity, obesity, and family history.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	In one randomized controlled trial in which 131 participants were exposed to ustekinumab over 28 weeks. The most common adverse psychiatric event was anxiety (N = 4; 3.10%), followed by depression (N = 2; 1.53%). In the other randomized controlled trial involving ustekinumab, there were 394 participants exposed to ustekinumab over 8 weeks. The most frequent adverse psychiatric event was suicide or suicide attempt (N = 2; 1.53%). Depression has been identified as an ADR for Usymro SmPC section 4.8 'Undesirable Effects' and Package Leaflet section 4. The frequency of depression with ustekinumab is uncommon (≥ 1/1,000 to < 1/100).
Risk factors and risk groups	Risk factors for depression include sociodemographic factors (gender, marital status, age and unemployment), physical diseases (chronic diseases, medical comorbid conditions), hereditary (personal or family history), and adverse childhood experiences (emotional abuse, sexual, and physical neglect during childhood).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.8. PL sections 4.

Important potential risk: Serious depression including suicidality	
	Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important potential risk: Venous thromboembolism	
Evidence for linking the risk to the medicine	Patients with inflammatory bowel disease (IBD) have an increased risk of venous thromboembolism (VTE). Overall IBD patients have a two to three-fold increased risk of venous thromboembolism. In patients with active IBD, additional risk factors including corticosteroid use, oral contraceptive use, IBD flare, and surgery confer an even higher risk of thromboembolic events compared with the overall IBD population. The meta-analysis found that patients with psoriasis had a 1.26-fold risk for new-onset VTE compared with those without psoriasis.
Risk factors and risk groups	Substantial data suggest that IBD is a risk factor for VTE, with a 3-fold higher risk compared with patients without IBD. Risk factors for VTE include high cholesterol, hypertension, diabetes, smoking, obesity, stress and nutrition.
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Long-term safety in pediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Long-term impact on growth and development in pediatric psoriasis patients 6 years and older	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Long-term safety in adult patients with moderately to severely active Crohn's disease	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Long-term safety in pediatric patients weighing at least 40 kg with moderately to severely active Crohn's disease	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

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

There are no studies required for Usymro.

PART VII: ANNEXES

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Annex 4 - Specific adverse drug reaction follow-up forms

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Note: The above questionnaires are utilized in conjunction with standard case follow-up procedures to obtain complete case information.

Follow-up Forms

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections

Drug (TRADENAME):

Date of Report: [dd-MMM-yyyy]

1. Medical History and Concurrent Conditions

☐ Prior history of exposure to TB
Details:

☐ Prior history of exposure to Hepatitis B/C
Details:

Details of vaccination history:

☐ The patient was considered immunocompromised *(underlying diagnoses, immunosuppressive therapy etc)*
Details:

Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. Adverse Event Details

☐ The infection was present prior to starting the product

☐ There were unusual features of the patient's presentation or clinical course
Details:

Type of infection (e.g., pneumonia, endocarditis, etc.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Tuberculosis (TB)

Drug Name:
Date of Report: [dd-MMM-yyyy]

1. **Relevant medical/occupational history** *(Check all that apply and provide details below.)*

☐ Weight loss ≥ 10% of ideal body weight
☐ Diabetes
☐ Gastrectomy or jejunoileal bypass
☐ Organ/Tissue transplant
☐ Prior BCG vaccination
☐ Recent travel to endemic area
☐ Head/Neck carcinoma
☐ Leukemia/Lymphoma
☐ Household contact/Exposure to TB
☐ Prior/prolonged steroid use
☐ IV drug abuse
☐ Prior/prolonged immunosuppressant use
☐ Silicosis
☐ Positive HIV test
☐ Resident/employee at high risk setting (e.g., correctional institute, homeless shelter, nursing home, refugee camp, etc.)

Details:

2. **Diagnostics**

☐ Purified Protein Derivative (PPD) testing was performed. Indicate test used:
☐ lntradermal skin test
☐ Multipuncture skin test
Number of units administered:
PPD Result: mm of induration (0, if no induration)
Date of PPD: [dd-MMM-yyyy]

2nd PPD results (if applicable): mm of induration
Date of second PPD: [dd-MMM-yyyy]

☐ False negative test (e.g., time of injection to time of evaluation too long/short, evaluator of induration, etc.)? Explain reasons:

☐ The subject had active TB
☐ Prophylactic therapy was given
Time elapsed from onset of TB symptoms to institution of treatment:
Type of tuberculosis:
☐ Pulmonary
☐ Extrapulmonary; Location:
☐ Disseminated: Location:
☐ Multi-drug Resistant TB

Other laboratory results

Laboratory Test		**Test Result**	**Date: [dd·MMM-yyyy)**
AFB Smear	**Sputum**		
	Other (Specify)		
Culture	**Sputum**		
	Other (Specify)		

Laboratory Test		Test Result	Date: [dd·MMM-yyyy)
PCR MTb			
Quantiferon TB Gold			

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Drug Name:
Date of Report: [dd-MMM-yyyy]

1. Relevant Medical/Family History *(Provide prior diagnoses and details for checked items below)*

☐ Previous malignancy (Provide specific diagnosis):

☐ Occupational/Exposure history:

☐ Excessive sun exposure (Describe):

☐ History of PUVA (Psoralen +Ultraviolet-A rays)

☐ History of radiation

Dose of radiation:
Area treated
Age (or date of therapy) of the patient when they were treated with radiation:
Indication for radiation:
Any radiation induced changes?

☐ Pre-malignant lesions, e.g., Barret's oesophagus, Bowen's disease. Details:

Viral infections ☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV

☐ Other relevant risk factors for malignancy (Excluding medications):

☐ Family history of malignancy (Provide specific diagnoses for each)

☐ In first degree relatives:

☐ In more distant relatives:

☐ Previous history of tumour necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):
Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)

Include drug indication, dose levels, and treatment duration (e.g., methotrexate, cyclophosphamide, vincristine, doxorubicin, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Dose/ Stop Dose (dd-MMM-yyyy)

☐ Cytogenetic abnormalities detected at any point in time? (Include those relevant for any malignancy including myeloma -this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc, or cytogenetic abnormalities relevant to myeloma)

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):
Include malignancy stage, location of primary tumour, metastases, lymph node involvement and staging system used:
Additional diagnostic information, including finding that support specified staging; specialty consultations (Attach reports, if available): Final diagnosis:
☐ Lymphoma
☐ Non-Hodgkin's lymphoma
Histologic subtype: lmmunophenotype: Cytogenetics:
☐ Hodgkin's lymphoma

Histologic subtype:
Was the lymphoma tissue tested for Epstein-Barr virus (EBV) (e.g., by in situ hybridization and/or immunohistology analysis)? ☐ No ☐ Yes (Attach report)
If Yes, Test Result: ☐ EBV positive ☐ EBV negative.

☐ **Second malignancy** (A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) (List):

☐ **Secondary malignancy** (A cancer caused by treatment for a previous malignancy e.g., Treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) *(List):*

Malignancy screening/Preventive measures (Include those that are relevant to the specific malignancy that is being reported, e.g., recent mammography, breast exam, Pap smear, sigmoidoscopy or colonoscopy, faecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine etc.)

Screening Test/ Preventive Measure	Date (dd-MMM-yyyy)	Result (Including units and reference ranges where applicable)

3. Treatment

What was the response to the first treatment for malignancy?
☐ Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Cardiovascular Events

Drug Name:
Date of Report: [dd-MMM-yyyy]

1. **Drug Details:**
   Number of doses (e.g., injections, infusions) given prior to cardiovascular event
   Recent **dose change? Details:**
   When did the patient **last** receive the product **before the current dose?**
   Date: [dd-MMM-yyyy], Time:

   Date and time of dose (e.g., injections, infusions) **after which this** cardiovascular event occurred:
   [dd-M M M-yyyy], Time:

   Date and time of onset of cardiovascular event **reported now:** [dd-MMM-yyyy], Time:

2. **Relevant medical history** *(Provide prior diagnoses relevant laboratory data {including echo and ischemic evaluation], dates, etc. below.)*

   ☐ Hypertension
   ☐ Hyperlipidaemia/Hypercholesterolemia/Hypertriglyceridemia
   ☐ Obesity
   ☐ Coronary artery disease
   ☐ Myocardial infarction
   ☐ Valvular heart disease
   ☐ History of percutaneous coronary intervention
   ☐ Coronary artery bypass graft
   ☐ Congenital heart disease
   ☐ Arrhythmias
   ☐ Cardiomyopathy
   ☐ Pericarditis
   ☐ Congestive heart failure
   ☐ Peripheral artery disease
   ☐ Diabetes mellitus
   ☐ Renal impairment
   ☐ Liver disease
   ☐ Headaches
   ☐ Head trauma
   ☐ Transient ischemic attack
   ☐ Ischemic cerebrovascular accident
   ☐ Haemorrhagic cerebrovascular accident
   ☐ Other (Specify):

   Relevant family history:

   ☐ Coronary disease ☐ Stroke
   ☐ Hyperlipidaemia/ Hypercholesterolemia/ Hypertriglyceridemia
   ☐ Myocardial infarction
   ☐ Diabetes mellitus
   ☐ Family history of long QT syndrome

☐ Other (Specify)

3. **Adverse Event: Patient's symptoms/Signs** *(Check all that apply and provide details below)*

☐ Dizziness	☐ Exercise intolerance	☐ Chest discomfort
☐ Palpitations	☐ Dyspnea	☐ Hemoptysis
☐ Edema	☐ Cough	☐ General malaise
☐ Syncope	☐ Sudden death	☐ Aphasia
☐ Visual disturbance	☐ Transient weakness (i.e., slurred speech)	
☐ Sensory changes	☐ Sweating	☐ Nausea/Vomiting
☐ Jaw pain	☐ Left arm pain	☐ Ataxia
☐ Facial weakness	☐ Extremity paralysis	☐ Altered gait
☐ Other relevant details		

Topic of Interest Questionnaire (TOIQ) for Venous Thromboembolism (VTE)

Date of Report: [dd-MMM-yyyy]
Drug Name:

1. Adverse Event Description

Patient's clinical signs and symptoms

☐ Leg/Calf Oedema	☐ Pain in Leg/Calf	☐ Haemoptysis
☐ Dyspnoea	☐ Chest Pain/Discomfort	☐ Syncope
☐ Tachypnoea	☐ Tachycardia	☐ Cough
☐ Headache	☐ Blurred vision	☐ Abdominal pain
☐ Nausea	☐ Vomiting	☐ Other symptoms

Was patient on VTE prophylaxis? ☐ No ☐ Yes, details:

2. Medical History and Concurrent Conditions

Provide details:

Is the patient overweight or obese? If available, please provide height/weight and BMI:	☐ No	☐ Yes
Does the patient have a sedentary lifestyle?	☐ No	☐ Yes - details:
Has the subject been travelling and or sitting for long periods of time (> 4 hours) prior to the event?		
Is there a current history of smoking?	☐ No	☐ Yes - details:
Is there a prior history of smoking?	☐ No	☐ Yes - details:
Is there a history of cancer?	☐ No	☐ Yes - details:
Any past medical history of autoimmune disease (i.e., collagen-vascular disease, inflammatory bowel disease) or myeloproliferative disease?	☐ No	☐ Yes - details:
Does the subject have a history of a previous clotting disorder or a diagnosis of a hypercoagulable state?	☐ No	☐ Yes - details:
Is there a prior history of varicose veins, trauma to the involved leg or pelvis, DVT/PE/VTE?	☐ No	☐ Yes - details:
Is there a history of blood transfusion?	☐ No	☐ Yes - details:
Was the patient (female) pregnant at the time of event?	☐ No	☐ Yes - details:
Is there a history of cardiovascular disorder?	☐ No	☐ Yes - details:
Is there a history of organ transplantation?	☐ No	☐ Yes - details:

Genetic risk factors:

☐ Dysfibrinogenemia	☐ Antiphospholipid syndrome	☐ Factor V Leiden mutation
☐ Protein C or S deficiency	☐ Elevated factor VIII levels	☐ Anti-thrombin deficiency
☐ Hyperhomocysteinemia	☐ Prothrombin gene mutation	☐ Blood-clotting disorder
☐ Thrombophilia		

Acquired risk factors:

☐ Reduced mobility (paralysis, paresis, travel etc.)	☐ Recent surgery
☐ Indwelling central venous catheters	☐ Recent trauma
☐ Recent discontinuation of anticoagulants (e.g., heparin, warfarin, DOACs)	
☐ Hormone replacement therapy (HRT)	☐ Hormonal contraceptives

☐ Polycystic ovary syndrome (PCOS) ☐ Pregnancy
☐ Postpartum (up to 3 months after childbirth)
☐ Phlebitis ☐ Lupus
☐ Inflammatory bowel disease ☐ Myeloproliferative disorders
☐ Diabetes mellitus ☐ Hyperlipidemia
☐ Hypertension ☐ Dehydration
☐ Other significant medical co-morbidities or risk factors for DVT, specify:

If yes to any of the above, provide details:
Provide Well's score, if calculated:

3. **Relevant results of diagnostic tests including laboratory tests, imaging, biopsies, etc.** (Note the levels/conclusion, date performed, normal ranges as well as any other details. **Alternatively, attach full reports of the diagnostic tests**.)

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
CBC with smear (microscopic evaluation)		
ESR		
Platelet count		
Antibodies to platelet factor 4 (PF4)		
Fibrinogen levels		
Clauss fibrinogen assay		
D-Dimer		
Clotting Profile (PT, aPTT- prior to an anticoagulation treatment)		
Thrombin time (Bovine) Plasma		
Prothrombin		
Antithrombin activity		
Factor V Leiden		
Protein C activity		
Protein S activity		
C-reactive protein		
Homocystein levels		
Dilute Russells Viper Venom Time (DRVVT), Plasma		
Activated Protein C Resistance V (APCRV), Plasma		
Thrombophilia interpretation		

Diagnostic Test	Results at baseline or prior to use of product (Include date and value/details)	Test results after use of product (Include date and value/details)
Anticardiolipin antibodies (lgG and lgM) or beta-2 glycoproteins antibodies		
Antiphospholipid antibodies (lgG and lgM)		
Lupus anticoagulant		
Heparin antibodies		
ANAand ANCA		
IL6 levels		
ADAMTS13 Activity Assay		
Ceruloplasmin		
Direct Coombs test		
Complement C3, C4		
Methylene tetra hydro folate reductase gene mutation		
Prothrombin gene mutation (G20210A)		
Occult blood in stool		
COVID-19 test		
Troponins		
Brain Natriuretic Peptide		
Arterial Blood Gases		
Chest X-Ray		
Electrocardiography		
Echocardiography		
Duplex Ultrasonography		
MRI scan		
CT scan		
Contrast Venography		
Pulmonary Angiography		
Ventilation-Perfusion Scanning		

Provide details of any additional diagnostic results:

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.